Recent Developments in Medicine and Medical Research

Vol. 8

B P International

Recent Developments in Medicine and Medical Research

Vol. 8

Recent Developments in Medicine and Medical Research

Vol. 8

India ▪ United Kingdom

Editor(s)

Prof. Jaffu Othniel Chilongola

Department of Biochemistry and Molecular Biology, Kilimanjaro Christian Medical University College, Tumaini University, Tanzania.
Email: j.chilongola@kcri.ac.tz;

FIRST EDITION 2021

ISBN 978-93-5547-060-7 (Print)
ISBN 978-93-5547-068-3 (eBook)
DOI: 10.9734/bpi/rdmmr/v8

Contents

Preface

This book covers key areas of Medicine and Medical Research. The contributions by the authors include Cutaneous Rhinosporidiosis, Disseminated, Nodules, Gestational trophoblastic disease, gestational trophoblastic neoplasia, chemotherapy, methotrexate, Epidemiology of Hemodialysis, end-stage renal disease, Coil embolization, hemoptysis, multidetector computed tomography , pseudoaneurysm, Visual impairment, obstructions and dissatisfaction in services, eye care facilities, mortality, morbidity, Survival, Pectoral nerve, pectoralis major muscle, nerve compression, Woven bone, carotis artery plaques, Turner syndrome, adolescent, delayed diagnosis, short stature, Cavernous sinus thrombosis , orbital cellulitis, high index of suspicion, Vascular Rehabilitation, Veno-Arterial-Lymphatic Rehabilitation, Ocular prosthesis, iris positioning, graph grid, eyewear method, Wound healing, chemo-surveillance, abnormal methylation enzymes, differentiation inducers, differentiation helper inducers, Sugar chain, postmortem brain, apoptosis, dentate gyrus, hippocampus, schizophrenia, Cerebral cortex, locus coeruleus, medulla oblongata, prenatal stress, noradrenaline, immunohistochemistry, Yoga, anorexia, psychiatric disorders, osteoporosis, childhood, extra pulmonary tuberculosis, Serum fluorescence, advanced glycation end products, diabetes duration, glycemic control, microvascular complications, Antioxidant nutricosmetics, growth factors for treatment of alopecia, and injectables for alopecia. This book contains various materials suitable for students, researchers and academicians in the field of Medicine and Medical Research.

Chapter 1
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Disseminated Cutaneous Rhinosporidiosis : A Rare Case Presentation

Shyamala R.[1*], Gufran Ahmed[1], Hisham[1] and Leeja latiff[1]

DOI: 10.9734/bpi/rdmmr/v8/4405F

ABSTRACT

Rhinosporidiosis is a granulomatous illness of the mucous membranes of humans that causes polyposis in the nasal mucosa, conjunctiva, and other areas. Rhinosporidium seeberi causes the infection. We present the case of a 71-year-old man who has had several cutaneous painless nodular lesions over the right side of abdomen, left shoulder, back and over the medial aspect of right thigh since 5 years. He had previously undergone nasal surgery for nasal obstruction. The image of cutaneous rhinosporidiosis was revealed by a potassium hydroxide mount and histological testing. This case underscores that disseminated rhinosporidiosis has to be suspected with papillomatous lesions of skin associated with pharyngeal lesions.

Keywords: Cutaneous Rhinosporidiosis; Disseminated; Nodules.

1. INTRODUCTION

Rhinosporidiosis is a granulomatous illness of the mucous membranes of humans and animals that causes polyposis in the nasal mucosa, conjunctiva, and other areas. Rhinosporidiosis is caused by Rhinosporidium seeberi, a hydrophilic pathogen classified with Mesomycetozoea [1] .The disease is widespread over the Indian subcontinent, Sri Lanka, South and East America. Infections are spread by coming into touch with polluted water. Polyps in the nasal mucosa, nasopharynx, and oropharynx are common signs of rhinosporidiosis. Rhinosporidiosis frequently involves the nasopharynx (70%) presenting as a painless, friable, polypoidal growth, which may hang anteriorly into the nares or posteriorly into the pharynx [2,3-6]. Cutaneous manifestations with or without mucosal involvement are extremely rare [1,7]. We hereby report a case of disseminated cutaneous rhinosporidiosis in an elderly male.

2. CASE HISTORY

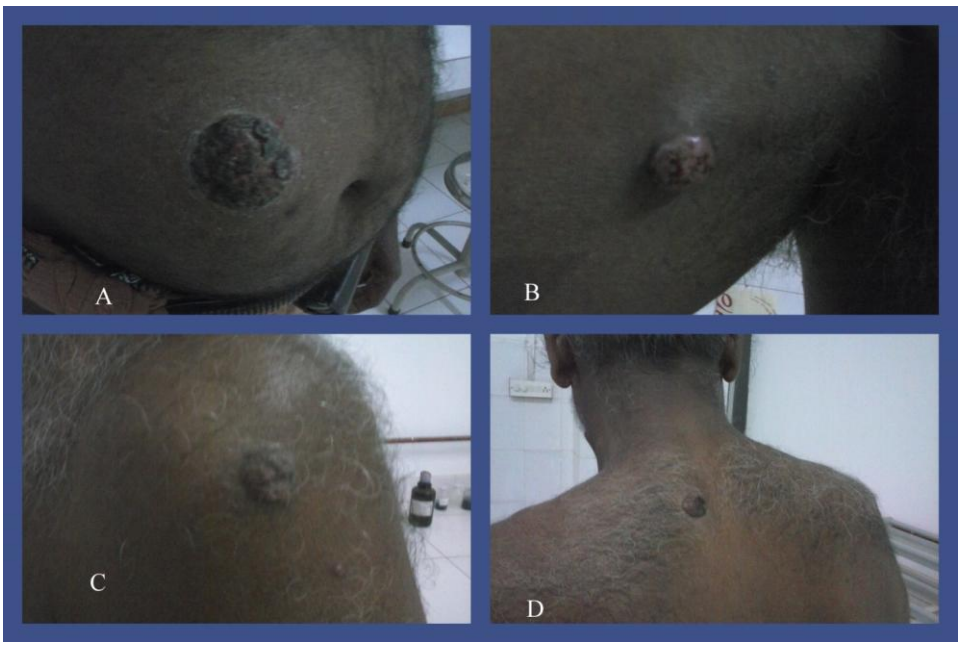
A 71-year old male presented with multiple cutaneous nodular lesions over the right side of abdomen, left shoulder, back and over the medial aspect of right thigh since 5 years. Lesions started with the abdominal cutaneous swelling; later he noticed it in other regions. Lesions were progressively increasing in size and were painless, nodular without discharge or ulceration. Hand lens was used for detailed examination. He gave past history of having nasal obstruction and difficulty in breathing due to swelling, for which he was operated 10 years ago.

Biopsy material was taken and sent for microbiological and pathological examination. Potassium hydroxide (KOH) mount showed multiple 5-8µm thin walled sporangia with endospores within. Histopathological sections showed hyperplastic epithelium with numerous globular cysts of varying sizes representing immature and few mature sporangia in the upper dermis.

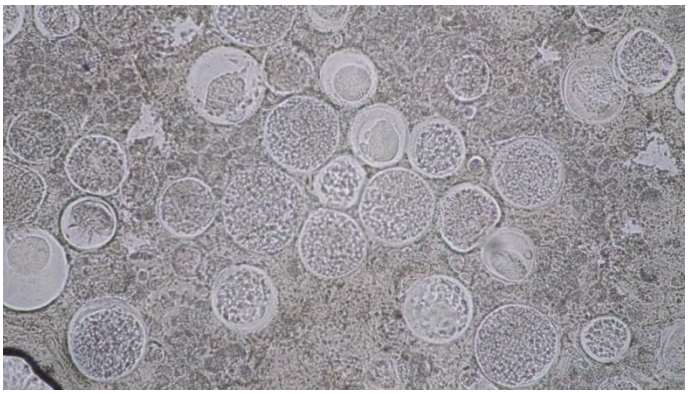
He was screened for involvement in other areas and proved negative; the otolaryngeal examination also turned out to be negative. His haemoglobin was 9.2mg/dl; testing for HIV and HbSAg was

[1]*Department of Microbiology, Kodagu Institute of Medical Sciences, India.*
**Corresponding author: E-mail: drshyamalar@gmail.com;*

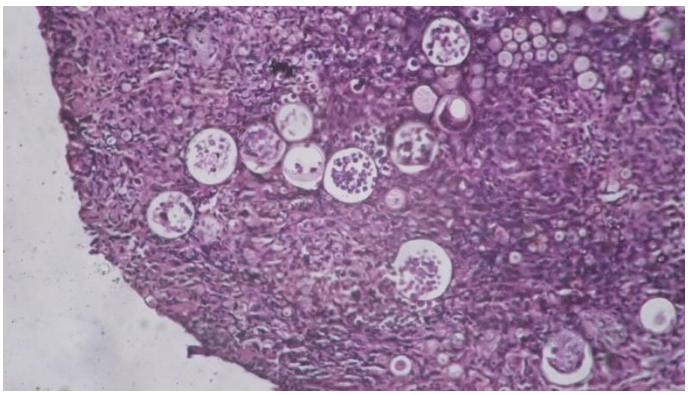
negative, RBS- 90mg/dl. Chest X-ray and abdominal sonography was normal. A final diagnosis of Disseminated Cutaneous Rhinosporidiosis was made and advised for Excision Diathermy.



Picture 1. Showing multiple lesions over A. abdomen, B. thigh, C. shoulder, D. back



Picture 2. KOH mount showing Sporangia (40 X)



Picture 3. HPE showing sporangia (40X)

3. DISCUSSION

Cutaneous lesions in Rhinosporidiosis are rare and usually present as papillomatous or sessile masses in areas adjoining to nose and face. In addition, there may be subcutaneous scattered nodules which may ulcerate and are seen fungating over the skin. Cutaneous lesions are rarely pedunculated [7] However, Tappa MD [8] has reported pedunculated lesions in 2009. The mode of infection may be direct inoculation to the local site or it may be through hematogenous route and present as extracutaneous lesions.

In rhinosporidiosis, papillomatous lesions in buccal cavity, vagina, vulva, urethra and over penis have been reported. Rhinosporidiosis has also been reported from scalp, tracheobronchial tree, larynx, lips, palate, rectum and anal canal. The differential diagnosis includes syphilis, cutaneous tuberculosis, rhinoscleroma, neoplastic lesions like hemangioma, angiofibroma or epithelioma. Others include polypoid tumors of *Cryptococcus neoformans*, Coccidioidomycosis and Adiaspiromycosis [7]. The diagnosis of Rhinosporidiosis mainly depends on the direct microscopy on histopathological section, scrape cytology and FNAC cytology, KOH mount. The organism can be observed with fungal stains e.g.,Gomori methenamine silver, periodic acid-Schiff , as well as with standard hematoxylin and eosin stain showing mature or immature sporangia with lymphocytic infiltration. Till now, *R. seeberi* has not been cultivated successfully on artificial culture media. However, it has been shown to grow in an epithelial carcinoma cell culture [7,2].

In our case, patient had nasal polyp without any cutaneous manifestations. After 5 years of surgery, he noticed cutaneous lesions at various sites which were gradually progressive. In this case, it may be due to hematogenous spread. [8] reported a similar case of disseminated cutaneous rhinosporidiosis with pharyngeal lesions. Our patient didn't have any systemic symptoms and did not reveal any systemic lesions.

Cutaneous lesions should be treated early to prevent extension of lesions or disseminations. Surgical removal and diathermy excision is the treatment of choice, but recurrences do occur. Drugs such as Dapsone, Ketoconazole, Amphotericin B have proved effective and has to be used with excision to prevent recurrence [9-10].

This case underscores that disseminated rhinosporidiosis has to be suspected with papillomatous lesions of skin associated with pharyngeal lesions.

4. CONCLUSION

Disseminated rhinosporidiosis has to be looked in.

ACKNOWLEDGEMENT

The skilled technical assistance by the technicians and staff of the pathology department is greatly acknowledged.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Kishan Prasad, Veena S, Permi HS, Teerthanath S, Padmaa Shetty K and Shetty JP. Disseminated Cutaneous Rhinosporidiosis, J Lab Physicians. 2010;2(1):44-46.
2. Kumari R, Nath AK, Rajalakshmi R, Adityan B, Thappa DM. Disseminated cutaneous rhinosporidiosis: Varied morphological appearances on the skin. Indian J Dermatol Venereol Leprol. 2009;75:68-71.

3. Verma R, Vasudevan B, Pragasam V, Deb P, Langer V, Rajagopalan S. A case of disseminated cutaneous rhinosporidiosis presenting with multiple subcutaneous nodules and a warty growth. Indian Journal of Dermatology, Venereology, and Leprology. 2012;78(4):520-.
4. Sen S, Agrawal W, Das S, Nayak PS. Disseminated cutaneous rhinosporidiosis: Revisited. Indian journal of dermatology. 2020;65(3):204.
5. Bansal R, Gupta M, Jain V. Cytodiagnosis of Disseminated Rhinosporidiosis-A Case Report. International Journal of Tropical Disease & Health. 2017;23:1-6.
6. Desai CA, Patil S. Disseminated cutaneous rhinosporidiosis. Indian journal of dermatology, venereology and leprology. 2020;20:1-2.
7. Jagadish Chander. Rhinosporidiosis. In: Text Book of Medical Mycology. 3rd ed. India: Mehta offset pvt. 2010;462-73.
8. Thappa DM, Venkatesan S, Sirka CS, Jaisankar TJ, Gopalkrishnan, Rathnakar C. Disseminated cutaneous rhinosporidiosis. J Dermatol. 1998;25:527-32.
9. Shailendra S, Prepageran N. Oropharyngeal Rhinosporidiosis in a Migrant Worker – A Delayed Presentation. Oropharyngeal Rhinosporidiosis in a Migrant Worker. Med J Malaysia. 2008; 63(1):65-70.
10. Shenoy MM, Girisha BS, Bhandari SK, Peter R. Cutaneous rhinospordiosis. Indian J Dermatol Venerol Leprol. 2007;73:179-8.

Biography of author(s)

Dr. Shyamala R., MD DNB CHIC FIID
Associate Professor, Department of Microbiology, Kodagu Institute of Medical Sciences, India.

Research and Academic Experiences: Completed projects on Candida, HIV.
Completed ICMR STS projects.

Academic experiences: 11 years

Research area: Research Interest Candida, HIV, Infection Control, Antimicrobial resistance.

Number of Published papers: 10

Special Award: Gold medal for a paper in National seminar on Nanoparticles.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
American Journal of Advances in Nursing Research. 2015; 2(2):70-72.

Chapter 2
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Gestational Trophoblastic Neoplasia: Brief Overview

Sanjivani Wanjari[1*]

DOI: 10.9734/bpi/rdmmr/v8/14038D

ABSTRACT

Gestational trophoblastic neoplasia is a unique neoplastic condition that arises from fetal trophoblastic tissues and can be considered as semi-allografts. Most of the gestational trophoblastic tumours are hydatidiform moles and are mostly benign. The malignant form of gestational trophoblastic disease is called Choriocarcinoma. The disease is common in Asian and African countries, incidence in India is about 1 in 400 pregnancies. Serum β-HCG assay is the main investigation for the diagnosis and management of GTN. This is important to detect persistent trophoblastic disease and hence follow up to two years is recommended. For complete and partial moles, surgical evacuation and follow up may be sufficient. Women with non-metastatic GTN and those with metastatic low-risk GTN can be treated with single-agent chemotherapy. Methotrexate is the drug of choice when single agent chemotherapy is used. Pre-treatment HCG levels more than 40,000 U/L are indicative of high risk GTN. They are treated with multi-agent chemotherapy. The most commonly used regimen is EMA-CO. After treatment the prognosis for GTN is now excellent, nearly 100% with low-risk disease and survival is nearly 86% in high-risk disease.

Keywords: Gestational trophoblastic disease; gestational trophoblastic neoplasia; chemotherapy; methotrexate; beta HCG.

1. INTRODUCTION

Various types of GTD gestational trophoblastic disease and Choriocarcinoma are a common occurrence in some Asian and African countries. They are also frequent in the Philippines and other south-east Asian countries like China, India, Japan, and also in Central and Latin America and Africa. In India the incidence is about 1 in 400 pregnancies. The incidence is 1-2 per 1000 pregnancies in US and Europe. It is highest in the Philippines and is about 1%

Gestational trophoblastic neoplasia is a unique neoplastic condition that arises from fetal trophoblastic tissues and can be considered as semi-allografts. Most of the gestational trophoblastic tumours are hydatidiform moles and are mostly benign. The malignant form of gestational trophoblastic disease is called Choriocarcinoma. Nearly 50% of gestational choriocarcinomas are seen after molar pregnancies. About 25% develop in after spontaneous or induced abortions or ectopic pregnancy. Another 25% may develop after a normal pregnancy [1]. GTN are the most curable of all cancers in women.

The term GTD gestational trophoblastic disease, refers to a group of disorders showing biologic behaviour that ranges from benign to potential for distant metastases. Gestational trophoblastic disease (GTD includes, complete and partial mole, and invasive mole, and choriocarcinoma.

The World Health Organization WHO has classified gestational trophoblastic disease as follows –

[1]Department of Obstetrics and Gynaecology, Mahatma Gandhi Institute of Health Sciences, Sewagram, Wardha. Maharashtra, India.
**Corresponding author: E-mail: sanjivaniwanjari@yahoo.com;*

Hydatidform moles –

1) Hydatidiform mole

- Complete and
- Partial

2) Invasive mole

Trophobastic tumours –

3) Choriocarcinoma
4) Placental site trophoblastic tumor (PSTT)
5) Epithelioid trophoblastic tumor (ETT)

Risk factors for the disease are –

Age- the risk is high at extremes of ages. It is twice higher, if age is more than 35 years.
Ethnicity- More common in Asians
Dietary factors-Decreased consumption of animal fat, carotene, vitamins and proteins
Past history of molar pregnancy and cytogenetic abnormality
Smoking
Previous miscarriage
Increased gamma globulin levels
AB blood group
Irradiation

Complete and partial hydatidiform mole are not tumours as such because they have uncertain neoplastic potential [2,3]. The others which include invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor form the spectrum of gestational trophoblastic neoplasia (GTN). Alternatively they are termed as malignant GTD gestational trophoblastic disease by the American College of Obstetricians and Gynaecologists (2004).

Complete mole -

A complete mole, in almost 90% cases develops when one haploid sperm fertilizes an empty ovum, which contains no nucleus or DNA. This then divides, resulting in a “complete” 46-XX chromosome set. All the genetic material comes from paternally derived chromosomes only. Complete hydatidiform moles are usually diploid and androgenetic in origin. Hydatidiform mole is mostly diploid with a 46, XX karyotype, but usually all molar chromosomes are paternal in origin. Homozygous 85%, Diandric diploidy/ Androgenesis.

About 10% have a 46, XY karyotype, because of fertilization of empty ovum by two spermatozoa. Heterozygous 15%, Dispermic diploidy. About 5-10% of complete hydatidiform mole are 46, XY, which results when there is fertilization of an ovum devoid of any chromosomes of its own, by two different sperms [4,5].

Partial mole -

A partial hydatidiform mole develops when a normal ovum is fertilized by two different sperms. Or by fertilization of a healthy ovum by one sperm which later duplicates itself, resulting in the genotypes 69 XXX, 69 XXY, or 69 XYY. Genetically, partial hydatidiform moles are always triploid in nature. It is associated with abnormal foetus or embryo which can be alive or dead.

The treatment for complete or partial hydatidiform mole is usually surgical with help of suction evacuation and dilation and curettage (D&C). In order to make the procedure safer, it can be done under ultrasound guidance. This also ensures that that the uterine cavity is empty and avoids

perforation of the uterus [4]. Surveillance or consistent follow-up is necessary for women in whom a molar pregnancy has been evacuated. Surveillance should be minimum 6 months for molar pregnancy, 1 year for GTN or gestational trophoblastic neoplasia and 2 years for metastatic disease. There is a need for follow up as the primary concern is of developing trophoblastic disease in a subsequent pregnancy [6]. This risk is approximately 2 percent.

Recommendations after evacuation of molar pregnancy –

1. Pregnancy should be avoided for a minimum of 6 months post-evacuation, by using contraception.
2. Baseline serum β-hCG levels are to be done within 48 hours of evacuation. Thereafter serum β-hCG levels are monitored every 1 to 2 weeks, till they progressively fall to undetectable levels. This is important to detect persistent trophoblastic disease.
3. Once the β-hCG level falls to a normal levels, the serum β-hCG levels can be done monthly for another 6 months. If undetectable, surveillance can then be discontinued, and pregnancy allowed.
4. If there is rise or plateau of serum β-hCG levels, thorough evaluation for persistent gestational trophoblastic disease becomes necessary. An increase signifies trophoblastic proliferation that can be a malignant change and will usually require treatment.

Diagnosis of GTN -

Serum β-HCG assay is the main investigation for the diagnosis and management of GTN. Serial measurements of β-hCG levels is used for follow-up of women diagnosed with GTN. β-hCG is a sensitive tumour marker for GTN and its level is directly related to the number of viable tumour cells. An increasing level of serum β-hCG is diagnostic of invasive disease which can be invasive mole or choriocarcinoma.

Ultra-sonography is the single most important diagnostic modality. It shows invasion of myometrium, nodules in the myometrium and hyper-vascularity. These findings can be used for prediction of gestational trophoblastic neoplasia or choriocarcinoma (Garavaglia and co-workers, 2009) [7].

CT & MRI are helpful for diagnosis of GTN especially Metastatic Disease.

Gestational Trophoblastic Neoplasia -

Invasive Mole (Chorioadenoma Destruens)

Invasive mole shows marked trophoblastic activity, invasion of myometrium and persistence of villous structures. It is not necessary to make histo-pathological diagnosis of invasive mole, as it is difficult to diagnose from curettings, and hysterectomy is rarely done for invasive mole. Invasive mole can be diagnosed because of post-molar bleeding, sub-involution of the uterus and rising HCG levels. Chemotherapy is main stay in management of invasive moles and it can be started on basis of rising HCG levels.

Choriocarcinoma

This can arise as malignant transformation of a molar pregnancy or can arise de novo after term pregnancy or abortion. The tumour demonstrates abnormality of syncytiotrophoblast and cytotrophoblasts, which lack chorionic villi. GTN have the potential of local invasion into pelvic structures and metastasis to distant organs like lungs, brain and other sites. It produces human chorionic gonadotropin (β-hCG) and hence can be diagnosed by increasing levels of serum β-hCG.

Non-gestational choriocarcinoma have a less favourable prognosis as compared to gestational choriocarcinoma. They are less responsive to chemotherapy.

Placental-site Trophoblastic Tumor (PSTT)

It is a rare form of GTN. This tumour can develop after a normal pregnancy or abortion, and also after evacuation of complete or partial mole. PSTT are locally invasive and have a tendency to invade the

myometrium of the uterus. Mostly they do not metastasise to other sites in the body. Placental-site trophoblastic tumours represent neoplastic proliferation of intermediate cytotrophoblasts. Hence they produce more of hPL as compared to HCG (as there are less number of syncitiotrophoblast) and hence HCG may not serve as a tumour marker for follow up of these tumours. PSTTs are not sensitive to chemotherapy drugs. Hence they are usually treated with surgery in the form of hysterectomy in order to completely remove the disease.

Epithelioid Trophoblastic Tumor (ETT)

It is an extremely rare type of GTN which is difficult to diagnose. Epithelioid trophoblastic tumours occur more commomnly after a full-term pregnancy. Epithelioid trophoblastic tumours, do not respond very well to chemotherapy. Hence the main treatment of the disease is surgery in the form of hysterectomy. Metastasis are common and hence ETT have a poor prognosis.

Signs and Symptoms of GTN -

Most of the times, GTN are diagnosed in patients who are being followed up after the diagnosis of hydatidiform mole, when the serum β-hCG levels rise or plateau.

The following signs and symptoms may indicate development of metastases. The common sites of metastases are the lower genital tract, the gastrointestinal tract and the lungs, brain, liver, kidney, etc.

Symptoms-

Poor health & malaise
Abnormal uterine bleeding
Symptoms due to metastasis
Cough with and without expectoration
Headache, blurring of vision, fits, unconsciousness or paralysis or hemiplagia /hemiperesis
Anorexia, weight loss, jaundice, epigastric pain
Irregular bleeding form vagina or small lump in vagina

Signs-

General condition- poor
Physical examination – shows gross Pallor, tachycardia, icterus and cachexia
Respiratory system examination – Crepitation may indicate lung metastasis
Per abdominal examination – Hepatomegaly
Vaginal examination – blue red sub urethral nodule in anterior vaginal wall or any other part of vagina.
Uterus – normal size or bulky, bilateral ovaries may be palpable

Diagnosis –

Investigations –

To confirm diagnosis
To know the extent of disease
Pre-operative investigations

Women who develop GTN following a molar pregnancy, can be detected early with the help of β-hCG monitoring. Hence other costly investigations are not required. Treatment is usually decided on basis of information available from the history taking & examination, and from estimation of serum β-hCG levels and findings of pelvic ultrasound. Serum quantitative β-hCG levels help to assess the disease status and also the response to therapy. Pelvic ultrasonography is done mainly to rule out a pregnancy. It also helps measure the uterine size and volume and to assess the extent of spread of disease within the pelvis. The vascularity is assessed by the Doppler pulsatility index. Doppler studies

can predict resistance to single-agent methotrexate therapy and hence can serve as an independent prognostic factor [8].

Imaging studies are recommended for patients with persistent hydatidiform mole, choriocarcinoma, and when there are suspected metastasis. Chest radiograph is essential for detecting pulmonary metastases which are most common [9]. If the chest X-ray findings are normal, computed tomography (CT scan) of the chest is not required [10]. However, if lesions are noted on X-ray chest, then CT scan of the body and magnetic resonance imaging (MRI) of the brain and should be done. Presence of widespread disease involving metastasis to the brain or liver, will make a significant difference in management of the disease.

Staging and Prognostic Scoring

The Federation of Gynaecology and Obstetrics (FIGO) staging of gestational trophoblastic neoplasia is as follows [11].

Stage I – lesion confined to the uterus
Stage II – lesion limited to the genital structures (adnexa, vagina, and broad ligaments)
Stage III – Lung metastases
Stage IV – Other metastases

The currently used prognostic scoring index consists of 19 prognostic factors. This system is a modification of the World Health Organization (WHO) classification.
The scores are given, by adding up points from a list of 19 prognostic factors.

Table 1. FIGO prognostic scoring system

FIGO scoring	*0*	*1*	*2*	*4*
Age	< 40	> 40	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval months from index pregnancy	< 4	4- 7	7- 13	>13
Pretreatment serum hCG IU/L	$< 10^3$	10^3 -10^4	10^4 -10^5	10^5-10^6
Largest tumor size cm	< 3	3- 5	> 5	—
Site of metastasis	Lung	Spleen, kidney	GIT	Liver, brain
Number of metastasis	—	1- 4	5 - 8	>8
Previous failed chemotherapy	—	—	Single drug	2 or more drugs

Treatment of Low-risk disease - Patients with non-metastatic (stage I) and low-risk metastatic (stages II and III, score < 7) disease should be treated with single-agent therapy in the form of methotrexate or actinomycin D chemotherapy [12,13].

Stage IV and high risk (Stage II & III with risk score of >=7) GTN should be treated with multi-agent chemotherapy and/or adjuvant radiotherapy or surgery to achieve clinical response rate of 80-90 %.

Management

Women with GTN can be treated either with single-agent or multi-agent chemotherapy. The treatment depends on whether the patients belong to the low-risk or high-risk group according to the FIGO prognostic scoring system [14].

Patients with GTN are divided into 2 groups depending on the risk of treatment failure:

1) Low risk - Those with a WHO score of less than 7 and
2) High risk - those with a score of 7 or higher

Contraception –

The woman should not conceive until the follow up is complete. Barrier method can be used until β-hCG reverts to normal. Once β-hCG becomes normal, combined OC oral contraceptive pills can be used. IUCD should not be advised till the β-hCG levels come to normal.

Treatment for low risk GTN –

Women with non-metastatic GTN and those with metastatic low-risk GTN can be treated with single-agent chemotherapy [15-19]. Methotrexate is the drug of choice when single agent chemotherapy is used. Methotrexate can also be used in the managing women with malignant GTN. Li et al in 1956 reported the first and complete remission in a patient of metastatic choriocarcinoma using methotrexate [20].

Complete blood count CBC, liver and kidney function tests should be done as part of pre-treatment evaluation and also twice a week thereafter. Mild toxicity is reported in 20 -30 % patients. Presence of anaemia and infection increase the risk of toxicity. Toxicity can be in the form of GI tract ulcers, bone marrow depression, alopecia & photosensitivity of the skin.

Patients with low-risk GTN are usually treated with help of single-agent chemotherapy. Methotrexate in the dose of 0.4 mg/kg IM or IV daily for 5 days (maximum 25 mg) appears to be the most effective treatment regimen [21,22,23]. Another widely used regimen is using folinic acid along with methotrexate (Bagshawe & Wilde). The folinic acid rescue allows higher doses of methotrexate to be used [24]. This regimen includes giving injection Methotrexate 1mg/kg body weight on days 1, 3, 5 & 7 and injection Folinic acid 0.01mg/kg body weight in day 2, 4, 6 & 8. The cycle can be repeated if necessary in non-metastatic and low risk metastatic GTD in order to achieve complete remission [25]. Each cycle consists of eight days of chemotherapy, followed by rest period of even days and then the cycle is repeated again. Methotrexate cycles are continued until levels of serum β-hCG remain normal for a few weeks.

Another drug that can be used instead of methotrexate, is Actinomycin D (dactinomycin). Actinomycin D is recommended when serum β-hCG levels remain high or rise and the WHO score remains less than 7. Dactinomycin has a high primary cure rate of in women with low-risk GTN. Also treatment failures are less with dactinomycin as compared with methotrexate. Therefore actinomycin D is frequently used as secondary therapy when there is resistance to methotrexate or in patients with liver and renal compromise. Actinomycin D can be given 10-12 mg/kg intravenously, every day for 5 days, every alternate week. It can also be given as a larger single dose 1.25 mg/m² intravenously once every two weeks. This schedule seems to work well and has fewer side effects.

A randomized phase III trial, conducted by the Gynaecologic Oncology Group compared the two most commonly used single-drug drugs; intravenous methotrexate and pulsed Dactinomycin, to find out the complete response rate. In the trial included patients with a WHO risk score of 0 to 6; and women with local metastatsis (limited to lung lesions < 2 cm, adnexa, or vagina) or women with choriocarcinoma [26].

The study found that for low-risk GTN, twice a week dactinomycin regimen was better than the weekly IM methotrexate regimen. Dactinomycin showed a higher complete response rate. Also dactinomycin is easier to administer and toxicity is also less. The trial showed that methotrexate at the same dose and schedule, was not a very effective drug for patients with a WHO risk score > 4 or for patients with choriocarcinoma.

During theray, the serum β-hCG levels are checked weekly. Six weeks of maintenance chemotherapy is given even after the serum β-hCG levels have come to normal. And after 3-4 normal readings of serum β-hCG levels, monthly follow up is continued for another one year.

Treatment for high risk GTN –

Criteria for high risk

1. Duration of more than four months from antecedent pregnancy.
2. Pre-treatment HCG levels more than 40,000 U/L
3. Antecedent term pregnancy
4. Metastasis to sites other than lungs and vagina
5. Prior failed therapy

Chemotherapy - Combination or multi-agent chemotherapy is used in patients with WHO scores of 7 or higher.

Few of the commonly used chemotherapy combinations are –

1. MAC - Methotrexate/leucovorin,

Actinomycin-D, and
Cyclophosphamide or chlorambucil

2. EMA-CO - Etoposide,

Methotrexate/leucovorin, and
Actinomycin-D, followed a week later by
Cyclophosphamide and
Oncovin/vincristine

3. EMA-EP - Etoposide,

Methotrexate/leucovorin, and
Actinomycin-D, followed a week later by
Etoposide and
Cisplatin ("platinum")

4. VBP - Vinblastine,

Bleomycin, and
Cisplatin

5. BEP - Bleomycin,

Etoposide,
Cisplatin

Initially the MAC regimen was very popular and had cure rates ranging from 63 to 71 %. Later Bagshaw and colleagues at Charing Cross Hospital, London developed the seven drug regimem (the CHAMOCA protocol), which consisted of cyclophosphamide, hydroxyurea, actinomycin – D, methotrexate with folinic acid, vincristine and doxorubicin. This regimen gave a remission rate of 82%.

Following the discovery of Etoposide, Newlands from London formulated the EMA-CO regimen which had a complete clinical response rate of 80% [27]. EMA-CO regimen consists of combination of etoposide, methotrexate with folinic acid, and actinomycin D administered in the first week of a 2-week cycle, followed by cyclophosphamide and vincristine (Oncovin) administered in the second week. The EMA-CO regimen is effective when uninterrupted treatment is given at short intervals. Chemotherapy should be continued till one gets three consecutive normal HCG reports. Granulocyte Colony Stimulating Factor can be used in patients who develop neutropenia.

EMA-EP regimen is similar to EMA-CO regimen, only Cyclophosphamide & vincristine are replaced by Cisplatin and etoposide during the second week. This regimen is useful for patients in whom EMA-CO fails. Paclitaxel and alternating platinum and etopoide (TP/TE) has reported to have good efffcicy with less toxicity.

In recent years, large number of studies have demonstrated the benefits of using combination chemotherapy for high-risk metastatic GTN (such as the EMA-CO and EMA-EP regimens). Also newer chemotherapy drugs are been studied which include pemetrexed, paclitaxel, and gemcitabine. Some of these have already been used in women where the GTD did not respond to routine drugs.

Radiotherapy is not used very often to treat gestational trophoblastic neoplasia. It is used when the disease is wide spread and is not responding to chemotherapy. Radiation may then be used to treat sites inaccessible to surgery or where surgery is difficult and the cancer may be causing problems. For treating brain metastasis, external beam irradiation, is the type of radiation therapy most often used. Brain metastasis are usually treated with whole brain irradiation (3000 cGy) and this can be combined with chemotherapy when necessary. Patients with liver metastasis can be given liver irradiation (2000 cGy).

Stereotactic radiotherapy can be used for multiple lesions or for solitary metastasis in regions that can cause lot of surgical morbidity. This can be followed up with high to moderate dose of intravenous methotrexate. Also intra-thecal methotrexate approach has been used in some institutions. Dexamethasone can be administered to reduce brain edema.

Surgery for GTN –

Suction evacuation is done as a primary measure to remove the complete or partial mole. Repeat D&C dilatation and curettage can be done in women with persistent disease as found on pelvic ultrasonography. Repeat D&C helps reduce the number of chemotherapy cycles needed [28]. It was noted that in women with low-risk GTN who underwent a repeat dilatation and curettage, serum β-hCG levels came to normal in 30-40% of patients. However repeat dilatation and curettage can be associated with complications like haemorrhage, infection, perforation, intra-uterine adhesions or anaesthetic complications.

Hysterectomy

Hysterectomy can be done for several reasons. Hysterectomy reduces the dose of chemotherapy needed to achieve complete remission in women with low risk GTN [29]. The treatment of choice for PSTT is hysterectomy, but the ovaries should be preserved if the woman is premenopausal [30]. Also hysterectomy can be performed for epitheloid trophoblastic tumours ETT or other types of chemo-resistant disease. Hysterectomy may be needed as an emergency procedure, in the event of uncontrolled haemorrhage. Women need to be monitored post-operatively, even after hysterectomy as there can be a 3-5 % risk of persistent disease.

Resection of solitary metastasis - thoracotomy or craniotomy may be needed for removal of distant metastasis in exceptional cases.

Cure rates –

For low-risk Gestational trophoblastic disease, cure rates can be almost 100%. For high-risk Gestational trophoblastic disease, cure rates are good and can be as high as 80% to 90%. But high-risk GTD will probably require more aggressive treatment in the form of combination chemotherapy and sometimes radiotherapy and/or surgery. The key challenge is designing treatment protocols in those who develop drug resistance.

2. CONCLUSION

Gestational trophoblastic neoplasia is a neoplastic condition that is unique in many ways. Its origin is from fetal trophoblastic tissues. Hence can be detected by elevated levels of serum beta HCG. These tumours are extremely sensitive to chemotherapy and hence cure rates are very high almost 90%. Multi-agent chemotherapy, surgery wherever needed and radiotherapy are various treatment modalities. Follow up these cases is of utmost importance, to prevent recurrence of the condition.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet. 2010;376:717–729.
2. Altieri A, Franceschi S, Ferlay J, et al. Epidemiology and aetiology of gestational trophoblastic diseases. Lancet Oncol. 2003;4:670-678.
3. Ngan HY, Seckl MJ, Berkowitz RS et al.Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet. 2015;131(suppl 2):S123–S126. Crossref, Medline, and Google Scholar.
4. Lurain JR. Gestational trophoblastic disease. I. Epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol. 2010;203(6):531–539. Crossref, Medline, Google Scholar
5. Stevens FT, Katzorke N, Tempfer C et al. Gestational trophoblastic disorders: an update in 2015. Geburtshilfe Frauenheilkd. 2015;75(10):1043–1050. Crossref, Medline, Google Scholar
6. Garrett LA, Garner EIO, Feltmate CM, et al. Subsequent pregnancy outcomes in patients with molar pregnancy and persistent gestational trophoblastic neoplasia. J Reprod Med. 2008;53:481.
7. Garavaglia E, Gentile C, Cavoretto P, et al. Ultrasound imaging after evacuation as an adjunct to beta-hCG monitoring in posthydatidiform molar gestational trophoblastic neoplasia. Am J Obstet Gynecol. 2009;200(4):417.e1.
8. Agarwal R, Harding V, Short D, et al. Uterine artery pulsatility index: a predictor of methotrexate resistance in gestational trophoblastic neoplasia. Br J Cancer. 2012;106:1089–1094.
9. Berkowitz RS, Goldstein DP. Current management of gestational trophoblastic diseases. Gynecol Oncol. 2009;112:654–662.
10. Darby S, Jolley I, Pennington S, Hancock BW. Does chest CT matter in the staging of GTN? Gynecol Oncol. 2009;112:155–160.
11. FIGO Oncology CommitteeFIGO staging for gestational trophoblastic neoplasia, International Journal of Gynecology & Obstetrics. 2000;77:285-287.
12. Lurain JR. Pharmacotherapy of gestational trophoblastic disease. Expert Opin Pharmacother. 2003;4:1-13.
13. Alazzam M, Tidy J, Hancock BW, Osborne R. First line chemotherapy in low risk gestational trophoblastic neoplasia. Cochrane Database Syst Rev. 2009;1:CD007102.
14. RCOG -The management of gestational trophoblastic disease green–top guideline no. 38; 2010.
15. Foulmann K, Guastalla JP, Caminet N, et al. What is the best protocol of single-agent methotrexate chemotherapy in nonmetastatic or low-risk metastatic gestational trophoblastic tumors? A review of the evidence. Gynecol Oncol. 2006;102(1):103-10. [Medline].
16. Roberts JP, Lurain JR. Treatment of low-risk metastatic gestational trophoblastic tumors with single-agent chemotherapy. Am J Obstet Gynecol. 1996;174(6):1917-23. discussion 1923-4. [Medline].
17. Matsui H, Suzuka K, Yamazawa K, et al. Relapse rate of patients with low-risk gestational trophoblastic tumor initially treated with single-agent chemotherapy. Gynecol Oncol. 2005;96(3):616-20. [Medline].
18. Kohorn EI. Is lack of response to single-agent chemotherapy in gestational trophoblastic disease associated with dose scheduling or chemotherapy resistance. Gynecol Oncol. 2002;85(1):36-9. [Medline].
19. Ngan HY, Odicino F, Maisonneuve P, Creasman WT, Beller U, Quinn MA, et al. Gestational trophoblastic neoplasia. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95(Suppl 1):S193-203. [Medline].
20. Li MC, Hertz R, Spencer DB. Effect of methotrexate therapy on choriocarcinoma and chorioadinoma. Proc Soc Exp Biol Med. 1956;93:361.
21. Hammond CB, Hertz R, Ross GT, et al. Primary chemotherapy for nonmetastatic gestational trophoblastic neoplasms. Am J Obstet Gynecol. 1967;98:71-8.

22. Hammond CB, Borchert LG, Tyrey L, et al. Treatment of metastatic trophoblastic disease: good and poor prognosis. Am J Obstet Gynecol. 1973;115:451-7.
23. Lurain JR, Elfstrand EP. Single-agent methotrexate chemotherapy for the treatment of non-metastatic gestational trophoblastic tumors. Am J Obstet Gynecol. 1995;172:574-9.
24. Bagshawe KD1, Dent J, Newlands ES, Begent RH, Rustin GJ. The role of low-dose methotrexate and folinic acid in gestational trophoblastic tumours (GTT). Br J Obstet Gynaecol. 1989;96(7):795-802.
25. Berkowitz RS, Goldstein DP, Bernstein MR. Ten years' experience with methotrexate and folinic acid as primary therapy for gestational trophoblastic disease. Gynecol Oncol. 1986; 23(1):111-8.
26. Osborne RJ, Filiaci V, Schink JC, et al. Phase III trial of weekly methotrexate or pulsed dactinomycin for low-risk gestational trophoblastic neoplasia: A gynecologic oncology group study. J Clin Oncol. 2011;29(7):825-31.
27. Newlands ES, Mulholland PJ, Holden L, et al. Etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy and patients presenting with metastatic placental site trophoblastic tumors, J Clin Oncol. 2000;18:854-859.
28. Van Trommel NE, Massuger LF, Verheijen RH, et al. The curative effect of a second curettage in persistent trophoblastic disease: a retrospective cohort survey. Gynecol Oncol. 2005;99(1):6-13. [Medline].
29. Suzuka K, Matsui H, Iitsuka Y, et al. Adjuvant hysterectomy in low-risk gestational trophoblastic disease. Obstet Gynecol. 2001;97(3):431-4. [Medline].
30. Berkowitz BJ, Jones JG, Merkatz IR, et al. Ovarian conservation in placental site trophoblastic tumor. Gynecol Oncol. 1990;37(2):239-43. [Medline].

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Open Access Journal of Gynecology, 5(1), 2020.

Chapter 3
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Determination of Hemodialysis Status in an Egyptian Coastal City, Alexandria: An Epidemiological Study with a 3-year Prospective Mortality Observation

Abir Farouk Megahed[1*], Reem Mohamed Farouk Saleh[2], Afaf Mohamed Fahmy[3] and Nagy Sayed-Ahmed[4]

DOI: 10.9734/bpi/rdmmr/v8/2672E

ABSTRACT

Backgrounds: Hemodialysis (HD) represents the main modality of RRT in Egypt and it constitutes a burden on the health care budget. HD is a vital and lifesaving procedure so that many organizations, including governmental and non-governmental bodies, adopt it. In Alexandria province of Egypt, HD service is provided through fifty-seven HD units, which are categorized into twenty-one nonprofit units and thirty-six private for-profit HD units. Our objectives were to study epidemiology and to assess the three-year survival of ESRD patients treated by HD in governmental hospitals in Alexandria province.
Methods and Design: In the year 2016; the data of the patients were collected from all the governmental hospitals in Alexandria province, which comprised seven HD units containing 687 patients. In a cross-sectional arm of the study, demographic data, vascular access, HIV, HBV and HCV serology, the possible etiology of chronic kidney disease (CKD), associated comorbidities, and the routine laboratory variables were included. Furthermore, in a prospective phase of the study, a three-year-survival rate of the studied HD patients was recorded.
Results: The total number of HD patients in Alexandria province during 2019 was totaled to be 3552 in all HD units, so the estimated HD prevalence rate would be around 710 ppm. Demographic data of the surveyed 687 patients in the governmental HD units showed their mean age; 50.78 years with more males, and their mean duration of HD; 55 months. It was also noted that there was no positive seroconversion regarding HCV, HBV nor HIV. Sixteen HCV antibody-positive patients received direct-acting antiviral drugs and were converted to HCV PCR-negative. HTN was more common etiology of CKD in males, while DM and combined DM and HTN were more common in females. The target hemoglobin level was present in around 37% of the studied HD patients. Most of the studied patients had serum calcium ranged from 8-10 mg /dl and 53% of them had serum phosphorus ranged from 3-5.5 mg /dl. Para-thyroidectomy was done for 2% of the studied patients while 4% of cases received cinacalcet. The 3-year, 5-year and 7-year survival rates were 92.5%, 87%, and 82% respectively.
Conclusion: The epidemiology of hemodialysis patients in Alexandria province is not different in many aspects from other published data about some Egyptian governorates however there is no published new epidemiology about the whole country. 11.2% of HCV Abs positive became PCR negative after antiviral management protocol.

Keywords: Epidemiology of HD; Alexandria; Egypt; mortality.

[1]MOH Nephrology Administration, Mansoura Military Hospital, Department of Nephrology, Mansoura, Ministry of Health, Mansoura, Egypt.
[2]Alexandria University, Alexandria, Egypt.
[3]High Nurse and Supervisor on Nursing Staff in Hemodialysis in Alexandria, Egypt.
[4]Nephrology and Dialysis Unit (MNDU), Faculty of Medicine, Mansoura University, Mansoura, Egypt.
**Corresponding author: E-mail: dnps2016@gmail.com;*

1. INTRODUCTION

CKD is emerging as an essential non- communicable disease worldwide. The three crucial risk factors of CKD are diabetes mellitus (DM), hypertension (HTN), and obesity, which are highly prevalent in developing countries including Egypt. Before 1996, the epidemiology of the ESRD in Egypt was not examined on a national scale [1]. CKD is a major health problem that leads to ESRD requiring RRT.

Regular dialysis treatment has been available at a national level in Egypt for more than three decades [2]. HD is a vital and lifesaving procedure so that many organizations, including governmental and non-governmental bodies, adopt it. HD service is usually provided by either non-profit- or profit-based bodies. Non-profit HD centers are divided into HD units related to university hospitals, military hospitals, and police hospitals, or those related to the ministry of health. The latter is further divided into insurance hospitals, teaching hospitals, and government hospitals. Egyptian government usually subsidizes the cost of HD in almost all sectors.

Only a few studies have systematically examined the epidemiology of HD population in Egyptian provinces; namely, Sohag [3], El-Minia [4], Kafr El Sheikh [5], Dakahlia [6], Menoufia [7] and [8], Assiut [9], Sharkia [10] and El Beheira governorate [11]. An Annual Report of the Egyptian Renal Data System (ERDS 2018), representing seventy-four dialysis units from 17 Egyptian governorates (cities) who participated with their data with a total number of 6,757 patients, was declared recently [12]. However, nation-wide Egyptian epidemiological data are still incomplete and need further study and proper registration.

Alexandria city, the capital of Alexandria province, is the second-largest and populous city, and the most important port in Egypt. In this province, HD service is provided through fifty- seven HD units, which are categorized into twenty-one nonprofit units (five universities, nine insurances, and seven governmental) and thirty- six private for-profit HD units. The well-designed health care service structure and limited distance between the governmental units in Alexandria pave the way for a systematic epidemiological examination of the HD patients in this coastal region.

1.1 Aim of the Work

The present work aims to study epidemiology and assess the three-year survival of ESRD patients treated by HD in governmental hospitals in Alexandria province.

2. PATIENTS AND METHODS

The current work was instigated in the year 2016. The data of the patients were collected from all the governmental hospitals in Alexandria province of Egypt, which comprised seven HD units containing 687 patients. In a cross-sectional arm of the study, treating physicians and residents as well as qualified nurses collected the patients' data by a questionnaire form, which included demographic data, vascular access, HIV, HBV and HCV serology, associated comorbidities, possible etiology of CKD and the routine laboratory variables. All laboratory investigations were done through sample withdrawn pre-hemodialysis session. The possible etiological diagnosis of CKD was recorded subjectively according to the opinion of the treating consultants. Furthermore, in a prospective phase of the study, a three-year- survival rate of the studied HD patients was recorded. On the other hand, the total number of HD units and the total number of HD patients throughout the whole province was retrieved from the Alexandria Directory of health affairs in June 2019.

The seven governmental HD units surveyed included; Abo Keir Hospital (127 patients), El Gomhorya Hospital (109 patients), Alexandria Fever Hospital (114 patients), Borj El Arab Hospital (58 patients), El Agamy General Hospital (48 patients), Ras El Tin General Hospital (72 patients), El Amrya Hospital (159 patients).

2.1 Statistical Analysis and Data Interpretation

Data were collected, revised, verified then edited on a personal computer and analyzed using IBM SPSS software package version 22.0. Qualitative data were described using numbers and percentages. Quantitative data were described using mean ± standard deviation for parametric data, or median (minimum-maximum and/or interquartile range) for non-parametric data after testing for normality using the Kolmogorov- Smirnov test. The significance of the obtained results was judged at the (0.05) level. For qualitative data, the Chi-Square test with or without correction maneuvers was used for comparison of the distribution of observation(s) between 2 or more groups of patients. Kaplan- Meier test was used to calculate overall survival and disease-free survival by using log-rank 2 to detect the effect of risk factors affecting survival.

3. RESULTS

The number of HD patients in Alexandria province during 2019 was totaled to be 3552 in all HD units. Since the province has a population of around five-million individuals, then, the estimated HD prevalence rate would be around 710 ppm. The newly admitted patients over the three years of the study observation were found to be 473 patients, giving an estimated mean frequency of newly admitted cases of ~158 patients/year (data were not shown).

According to the regulations of the prevailing rules, all patients were offered regular HD sessions three times per week, four hours each, utilizing bicarbonate-based dialysate with a blood flow rate of 300 ml/min and a dialysate flow rate of 500 ml/min. Dialysis-related water treatment in all of the included HD units was carried out following the Egyptian MOH guidelines [13]. Dialysis adequacy was assessed utilizing the urea reduction ratio (URR); being targeted to be above 60%.

Demographic data of the surveyed 687 patients in the governmental HD units in Alexandria province are shown in Table 1. Their mean age was 50.78 years and around 63% of them were between 19-55 years of age, with more males than females, and their mean duration of HD was 55 months. The mean BMI of the total studied group was 27.5±5.3. Most of the HD patients received HD through arterio-venous (A-V) fistulae (92.1%) and only 1.2% of total patients had previous kidney transplantation.

Table 2 shows the status of seroreactivity to hepatitis C virus antibodies (HCV-Abs), hepatitis B surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV-Abs). During the period of the study, it was noticed that the frequency of HCV-antibody-positive patients and that of HBsAg changed from 142 and 19 out of the 687 patients (20.6% and 2.76%, respectively) to 129 and 30 out of the 801 patients (16.1% and 3.74%, respectively), in the years 2016 and 2019, respectively. Moreover, sixteen HCV antibody-positive patients received direct-acting antiviral drugs (Qurevo) and were converted to HCV PCR-negative. (data were not shown), In 2019, the study included three HIV antibody-positive cases who were dialyzed in the Fever Hospital; being the only place that accepts this type of patient in the province (data were not shown). It was also noted that there was no positive seroconversion regarding HCV, HBV nor HIV.

The routine Laboratory variables of the studied HD patients are shown in Table 3, while Table 4 shows the relation between one-year mortality and different variables denoting that males had statistically significantly higher mortality than females.

The distribution of possible etiologies of ESRD in both genders is illustrated in Graph 1, revealing that while HTN was more common in males, DM and combined DM and HTN were more common in females. While HTN represented the most common possible cause of CKD, followed by DM, pregnancy-related factors were the least cause for ESRD. However, in a significant proportion of cases, the cause of ESRD was unknown. Similarly, the frequency of commonly associated comorbidities is shown in Graph (2) denoting that the commonest comorbidities were HTN and Ischemic heart disease (IHD).

The type of HD vascular access in both genders is demonstrated in Graph 3, showing that permanent HD catheters were more commonly used in females, while the graphs for distribution of their hemoglobin level, corrected serum calcium, and serum phosphorous are depicted in Graphs 4 and 5a, b respectively. Graph 5c shows the frequency of distribution of the parathyroi*d hormo*ne levels in these patients. Thirteen patients (1.9%) were noticed to have had Para thyroidectomy performed before the study, whereas 4% of the cases were maintained on calcimimetics (data were not shown).

Graph 6 and Table 5 show that the median survival after initiation of HD among the studied cases was 17.67 months with a confidence interval ranging from 15.25 to 20.09, while the 3-year, 5-year, and 7-year survival rates were 92.5%, 87% and 82%, respectively.

4. DISCUSSION

The prevalence of ESRD requiring RRT is believed to be increasing in Egypt and it constitutes a burden on the health care budget in our country since all the health care needs of these patients are subsidized by the Egyptian ministry of health (MOH). It is well known that HD represents the main mode of RRT in Egypt, and Alexandria is not an exception. The epidemiology of ESRD in Alexandria has not been formally examined before 2016. Alexandria, a coastal city on the Mediterranean Sea in the north of Egypt, with a total area of 2833 km^2, has a population of around five million individuals (National institute of urban planning, [14,15], and [16]. As registered in the records of Alexandria's Directory of health affairs, the number of HD patients was known to be 3523, which means 710 pmp. Lack of data on the previous frequency of patients on HD in Alexandria province makes accurate identification of the changing prevalence of ESRD not feasible. Only eight cases out of 687 HD patients, who were treated in governmental hospitals, had had kidney transplants before the study.

Table 1. Demographic data of patients in Alexandria governmental hemodialysis units*

	Mean±SD
Age in years (N=687)	50.78±12.75
BMI in total population (N=302)kg/m^2	27.5±5.3
BMI in females (N=144)kg/m2	28.2±5.7
BMI in males (N=158) kg/m2	26.8±4.9
Duration of Dialysis (N=673) in months	55.06±50.76
Pre-sessional systolic blood pressure. (N=583)	129.7±18.5
Pre-sessional diastolic blood pressure (N=584)	81.09±10.05
Gender: Male/total [N (%)]	357/687 (52.0%)
Previous kidney transplantation [N (%)]	8/687 (1.2%)
Vascular access Fistula [N (%)]	606 (92.1%)
N=658	
Permanent catheter [N (%)]	
33 (5%)	
Graft [N (%)]	1 (0.15%)
Temporary Vascular access[N (%)]	
18 (2.7%)	

**N represents the number of available data*

Table 2. Frequency of viral serology in hemodialysis patients in Alexandria governorate*

Viral serology (N=687)	**N(%)**
Negative viral serology (HCV, Hepatitis B,HIV)	534(77.7)
HCV - antibody-positive	134(19.5)
HBs - antigen-positive	11(1.6)
Both HBs antigen and HCV-antibody-positive	8(1.16)

** N represents the number of available data*

Table 3. Laboratory variables in hemodialysis patients in Alexandria governorate*

	Mean ±SD
HB (N=585)	9.49±1.55
Albumin (N=133)	3.24±0.58
Urea reduction ratio(URR) (N=522)	0.59±0.11
pre-dialysis session blood-urea (N=591)	133.84±38.79
Serum creatinine (N=527)	7.76±5.1
Serum calcium (N=385)	5.05±1.12
Serum calcium (N=385)	8.58±1.22
Serum phosphorus(N=380)	5.3±1.5
Parathyroid hormone level (N=167)	560.86±566.8
Serum ferritin (N=79)	468.73±375.3

**N represents the number of available data*

Table 4. Relation between one-year mortality from June 2016 until May 2017 and different variables*

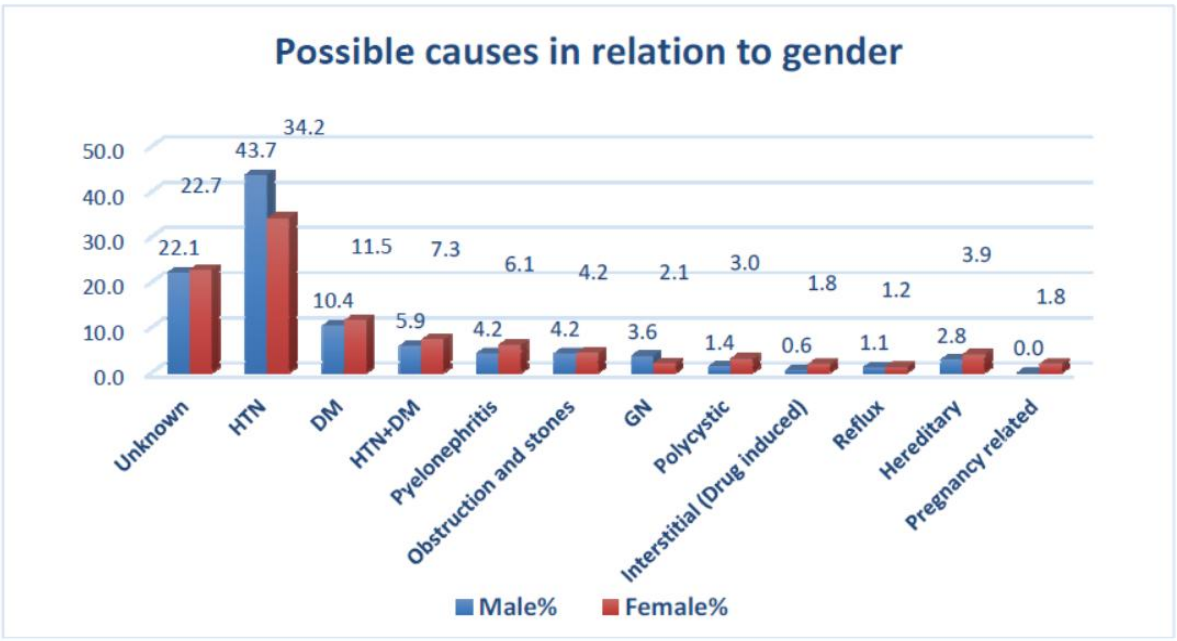
	Mortality		**Test of significance**
	Alive N (%)	**Dead N (%)**	
Sex	616(89.7%)	71(10.3%)	
Female (N=330)	305 (92.4)	25 (7.6)	x^2=5.22
Male (N=357)	311 (87.1)	46 (12.9)	P=0.02
Vascular access			
A-V Fistula (N=606)	545 /606(89.94)	61/606(10.06)	Monte Carlo test
Permanent catheter	28/33(84.8)	5/33(15.2)	P=0.57
Temporary catheter	16/18(88.9)	2/18(11.1)	
***Possible etiology**			
Unknown	144/155(92.9)	11/155(7.1)	χ^2=2.26 P=0.13
Hypertension(HTN)	245/269(91.1)	24/269(8.9)	χ^2=0.952 P=0.329
Diabetes (DM)	63/75(84)	12/75(16)	χ^2=2.92 P=0.087
Combined DM and HTN	32/45(71.12)	13/45(28.88)	χ^2=17.89 P<0.001*
Pyelonephritis	31/35(88.57)	4/35(11.43)	χ^2=0.047 P=0.83
Obstruction and stones	26/29(89.66)	3/29(10.34)	χ^2=0.0 P=1.0
Glomerulonephritis	18/20(90)	2/20(10)	χ^2=0.0025 P=0.96
Polycystic kidney disease	15(100)	0(0.0)	χ2=1.77 P=0.18
Interstitial nephritis (Drug induced)	7/8(87.5)	1/8(12.5)	χ2=0.041 P=0.84
Urinary Reflux	7/8(87.5)	1/8(12.5)	χ2=0.041 P=0.84
Hereditary	23/23(100)	0(0.0)	χ2=2.74 P=0.09
Pregnancy related	6/6(100)	0(0.0)	χ2=0.041 P=0.84

**N: represents the number of available data*
**Possible etiology: the suspected etiology according the treating team*

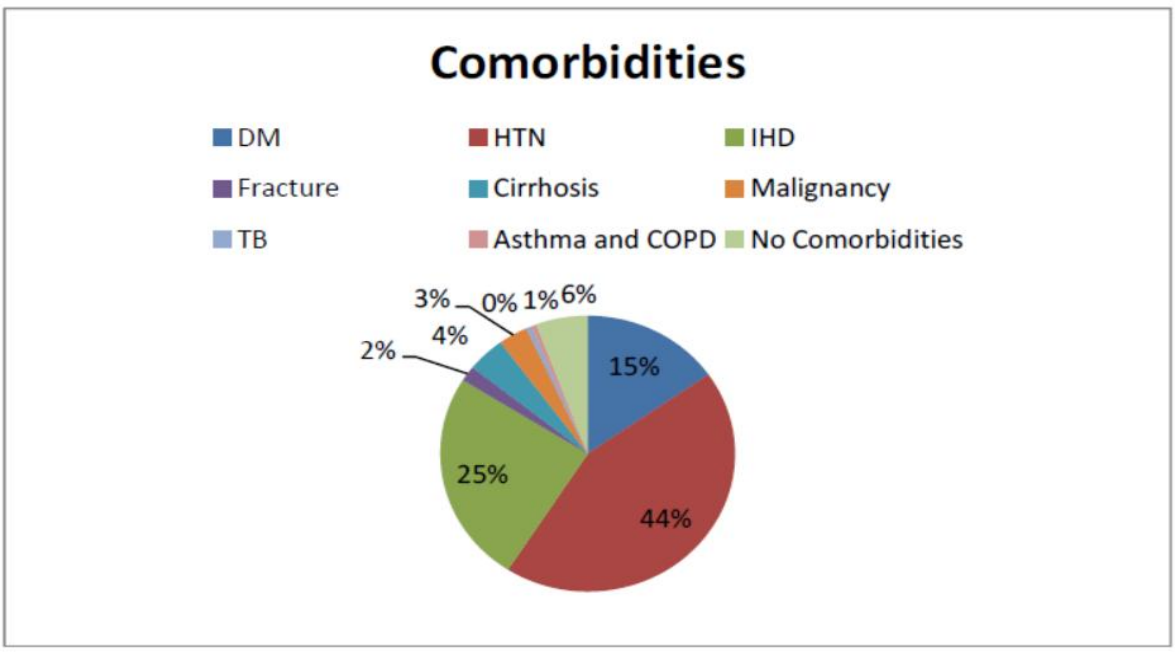
Table 5. Median overall survival time

Median overall survival time/years	**Std. error**	**95% confidence interval**	
		Lower bound	**Upper bound**
17.67	1.235	15.246	20.087

a. Estimation is limited to the largest survival time if it is censored

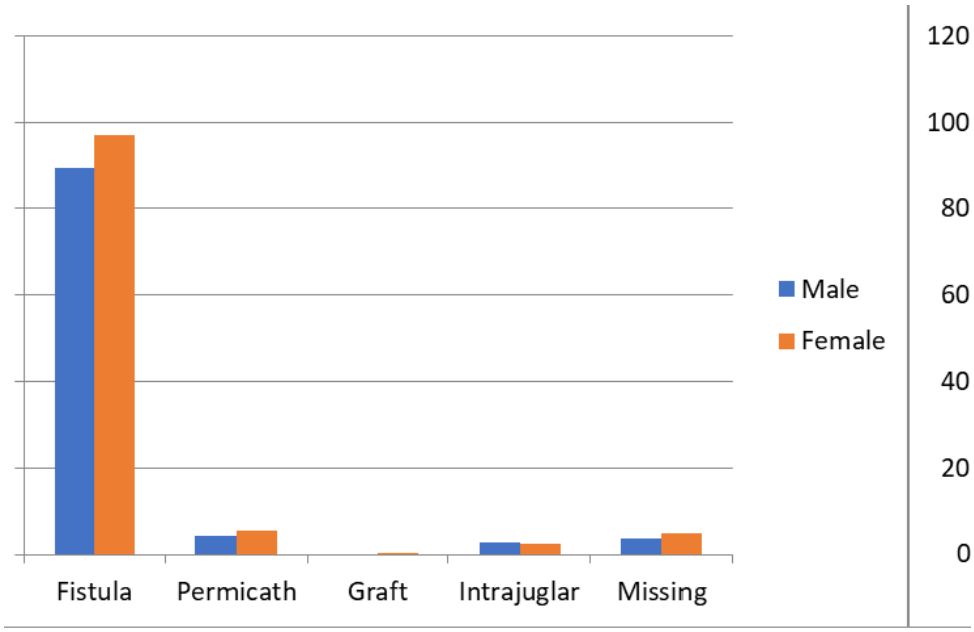


Graph 1. Relation between gender and possible etiology of CKD

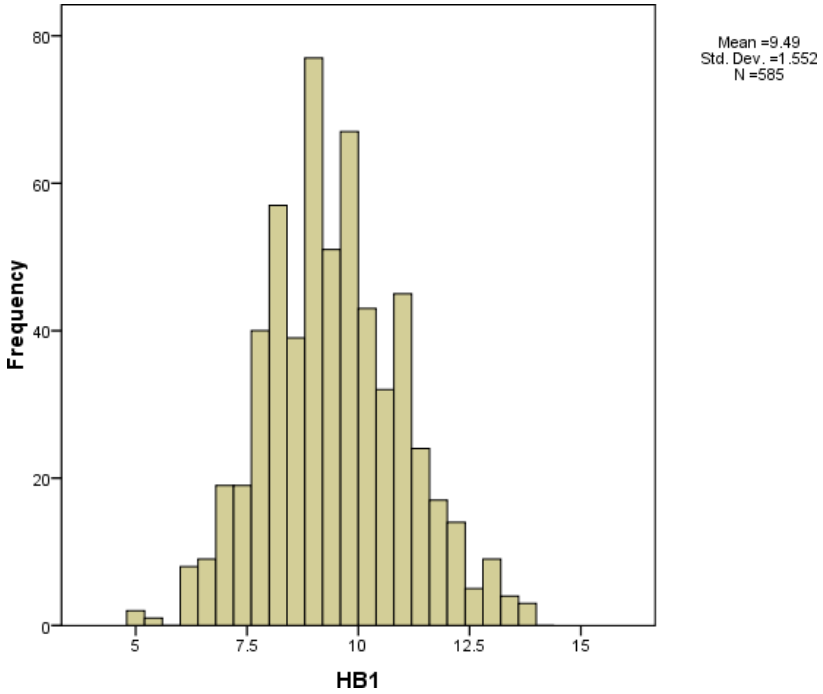


Graph 2. Associated comorbidities in the studied group

The prevalence of ESRD worldwide differs significantly; the highest prevalence was found in Taiwan (0.16%), [17], while the lowest prevalence was 230 pmp in the Philippines [18]. In the USA, the prevalence was; 2,160.7 pmp, during the year 2016 [19], while in Europe, the prevalence increased from 889 pmp in 2008 to 924 pmp in 2014 [20,21]. In Egypt, there have been no published studies, until now, that covers the prevalence of ESRD all over the country. Nevertheless, a Ministry of Health official stated that the total number of HD patients during the year 2016 was 56,000 from a total population of over ninety-four million; giving a prevalence rate of ~593 pmp [22,16].



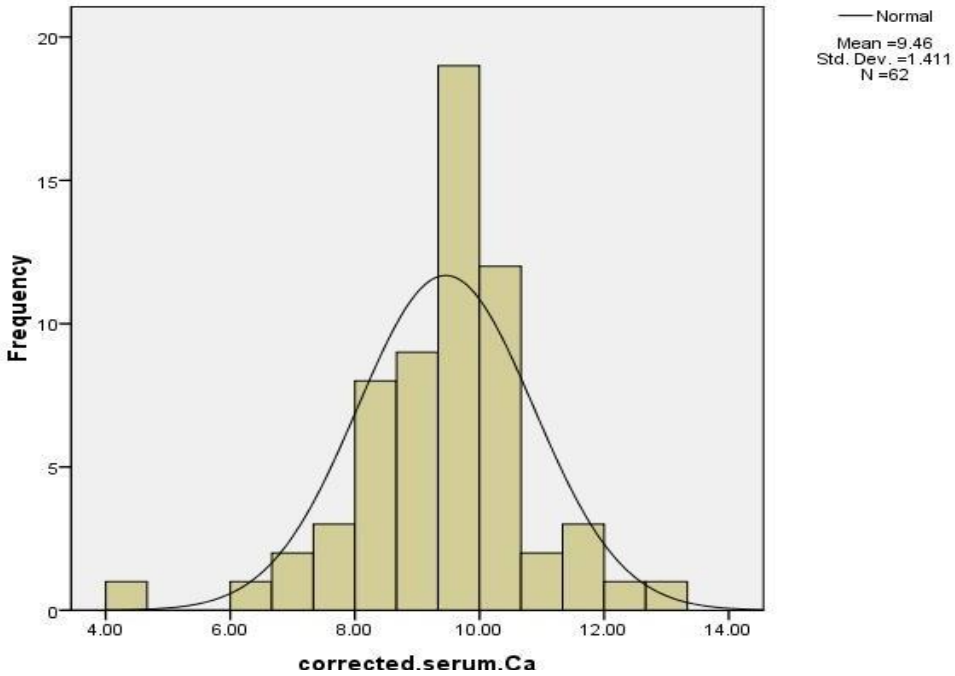
Graph 3. Relation between gender and vascular axis



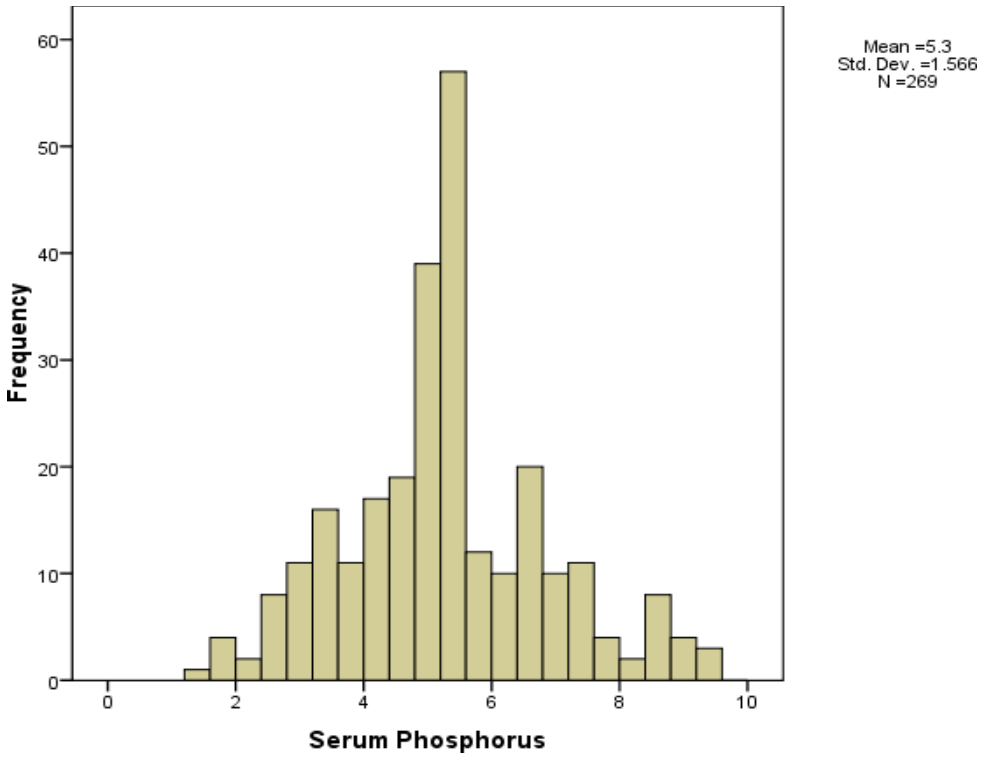
Graph 4. Histogram for hemoglobin

Additionally, few studies have been published tackling such an issue in some Egyptian localities. In Upper Egypt, several studies were published: A study in El-Minia governorate during the year 2006 reported a prevalence rate of 308 pmp [4]. In Sohag during the year 2010, the prevalence was 316 pmp [3], while in Assiut it was 366 pmp during the year 2014 [9]. On the other hand, in Lower Egypt, the prevalence in Kafer El Sheikh during the year 2012 was 283 pmp [5], in Menoufia during 2013 it was 330 and increased to 483 pmp during 2016 [7,8], while in Dakahlia governorate, the prevalence was 462 pmp and 503 pmp during the years 2013 and 2014, respectively [6]. In the El Beheira governorate, the prevalence during the year 2018 was 571 pmp [11]. This relatively low prevalence of

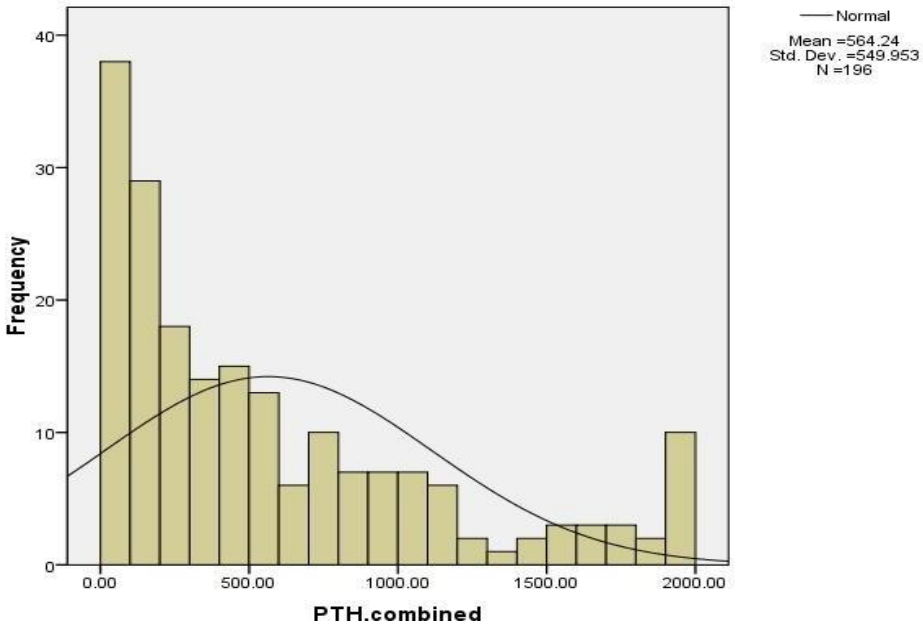
ESRD-HD in Egypt is felt to be an underestimation of the real problem taking into consideration relatively poor data registration and documentation in this respect. Another explanatory issue might be a possible relatively higher mortality of HD patients compared to the developed countries.



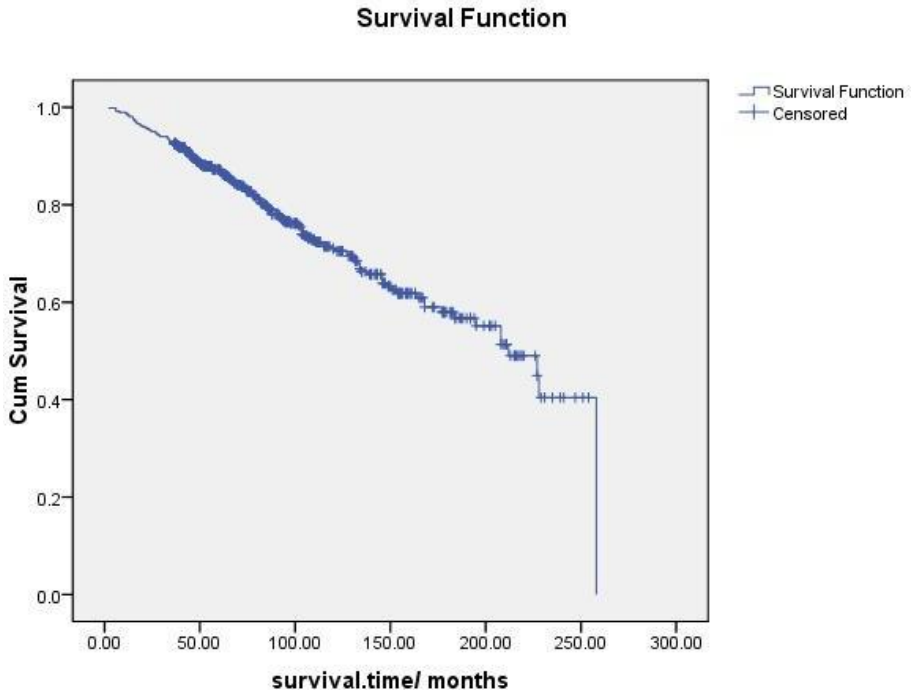
Graph 5a. Histograms of corrected serum calcium in the studied group



Graph 5b. Histograms of serum phosphorus in the studied group



Graph 5c. Histograms of parathyroid hormone in the studied group



Graph 6. Kaplan-meier curve for 3-year survival

In our study, the mean age of HD patients is 50.78 with male to female ratio 1.1:1 and the mean duration of HD is 55.06 months. In this respect, the mean duration of HD was previously reported to be 3.78±3.372 years in Menofia province during 2016 [8], while Afifi (2008) reported that the mean age in Egypt had increased from 45.6 years in 1996 to 49.8 years in 2008 [23]. The increasing mean age of ESRD patients on HD, together with the increase in the mean duration of HD, might reflect the potential progressive improvement in the healthcare services in Egypt in recent years. Recently, the Egyptian Ministry of Health has launched several steps and measures to increase the awareness of CKD, advising the treating medical practitioners on testing kidney function routinely, and early referral

to a nephrologist. However, there is still a window for improvement of health care service and prevention of CKD, as the mean age of the HD patients in our country is much lower than that in the USA (69.1 years; [24] and Europe (64.4 years; [23].

In this study, the prevalence of hepatitis C was 19.5% in the studied HD population in governmental HD units and showed a decreased prevalence of HCV Abs +ve from 20.6% in 2016 to 16.1 in 2019. This decrement in the prevalence of HCV might, at least partially, be in harmony with an overall significant reduction of 32 and 29% in the prevalence of HCV-antibody- and HCV-RNA-positive individuals, respectively, between the Egyptian Health Demographic Survey, carried out in 2008 and the Egyptian Health Issue Survey conducted during 2015, had been published [25]. The prevalence of HCV in Egyptian HD patients might have decreased, at least in part, due to the protocol of isolation of HCV patients and infection control programs that have been implemented in all HD units, as well as the initiation of the protocol of management of HCV in HD patients that was carried out all over the country. On the other hand, the worldwide prevalence of HCV in HD patients showed wide variations, with estimates ranging from 5% to approximately 60% depending on geographic location [26] [DOPPS in 3 continents], [27] [Italy], [28] [China] and [29] [Iran]). In 2002, the prevalence of HCV infection across HD centers of the United States was approximately 8%, nearly five times greater than that of the general population in that country [30].

The prevalence of HBsAg *s*eropositivity in the governmental hospitals was 2.76% in 2016 and increased to 3.7% in 2019 but without seroconversion. This prevalence was lower than that of most of the Arab countries: HBsAg was 5.88% among 81 Bahraini and 34 Saudi HD patients [31], 7.8%, in a Syrian study [32], and 8.1% in the Gaza Stripe [33]. There is a strict protocol for vaccination of HBV for all HD patients and staff in Egypt. Moreover, blood testing before transfusion for HBsAg-positive has been implemented as a strict routine rule since the last decade of the previous century. The rate of serum HBsAg seropositivity in patients on maintenance HD in the developed world is currently low (0–10%) while it appears higher (2– 20%) in developing countries based on relatively few reports [34,35].

In the current study, the main identifiable potential cause of ESRD on HD was HTN (39.2%), followed by DM (10.9%), while the leading cause was unknown in around 22%. This is similar to previous local epidemiological studies performed in. El Beheira [11] and Sharkia [10] governorates, while unknown causes exceeded 30% in the epidemiological studies conducted in Dakahlia [6] and Menoufia [8]. Notably, HTN is the commonest leading cause of ESRD on HD in nearly all epidemiological studies all over Egypt. In accordance with that, the Egyptian Annual Report of ERDS (2018) nominated HTN (38%) followed by DM (18%), as the most common causes of ESRD. Patients with ESRD of unknown etiology represented the third common presentation (12%). However, in a few studies considering patients treated by HD, DM was the leading cause of ESRD, followed by HTN (34.7% and 21.5% in one study and 46% and 19% in another one, respectively; [36,37]. In the current work, interstitial nephritis, hereditary nephritis, and pyelonephritis were more common in the female gender as a leading cause of ESRD on HD; a difference that could be explained by more tendency for female gender to urinary tract infection, and the possibility of them using more analgesics.

Treatment of CKD-MBD targeted at lowering high serum phosphate and maintaining serum calcium [38], and management of anemia is an essential part of the care of hemodialysis patients [39]. In Egypt, drugs controlling the calcium/phosphorus axis (calcium carbonate, alfacalcidol, cinacalcet) and the use of ESA therapy are offered for HD patients through a fund by the MOH. Most of the studied patients of the current study had serum calcium ranged from 8-10 mg/dl and 53% of them had serum phosphorus ranged from 3-5.5 mg /dl. Parathyroid hormone level ranges were less than 150 pg/ml in 30% of patients and more than 700 pg/ml in 32%, while 38% of them had a PTH range between 150 and 700 pg/ml. Para thyroidectomy had been performed for 2% of the studied patients while 4% of cases were receiving cinacalcet. These findings were similar to the Egyptian Annual Report [12] that declared that 2% of the Egyptian hemodialysis patients had para-thyroidectomy and 5% of them were receiving cinacalcet. The target hemoglobin level that set by KIDIGO guidelines, which ranged from 10 to above 11.5 g/dl, was present in around 37% of the studied HD patients [39]. This was nearly similar to the finding of a previous study that reported that 40% of the prevalent dialysis patients had a mean monthly target hemoglobin level of 11-12 g/dl, [40].

Mortality rates among HD patients vary greatly across regions and according to differences in age, gender, race, and comorbid conditions. The one-year mortality rate was 10.3% in the current study, while, according to the Dialysis Outcomes and Practice Patterns Study (DOPPS) the mortality rate was reported to be 6.6% in Japan, 15.6% in Europe, and 21.7% in the USA [41]. The median survival time among our studied cases was 17.67 months with a confidence interval ranging from 15.25 to 20.09. The 3-year, 5-year, and 7-year survival rates were 92.5%, 87% and 82%, respectively. Msaad et al. [42] reported that overall survival was 80.2% of their studied hemodialysis patients; their data were collected between January 2012 and January 2016.

5. CONCLUSION

The prevalence of ESRD on HD in Alexandria governorate, Egypt, was 710 ppm. Compared to previous Egyptian studies, there was an increasing age of HD patients and an increased duration of HD. HTN and DM were the most common possible etiologies of ESRD. Hepatitis C infection in dialysis patients have been decreasing and there was zero positive seroconversion as regard hepatitis B and C, while HCV Abs positive cases became PCR negative after antiviral management protocol in 11.2% of patients. The 3-, 5-, and 7-year survival rates, following hemodialysis initiation, were 92.5%, 87% and 82%, respectively. Future studies are recommended in other regions in Egypt to highlight the effect of different ecologic factors on the morbidity and mortality of hemodialysis patients.

CONSENT AND ETHICAL APPROVAL

Depending on Egyptian minister of health and population decree #95/year 2005 for Health Research and decree #539/year 2016 – ICH – Good Clinical Practice, Declaration of Helsinki and World Health Organization Guidelines, the Ethics Committee meet in the Central Directorate of Research and Health Development and review. The approval number is Com. No/Dec. No: 11-2017/ 27. Moreover, consent was taken from all the participants.

ACKNOWLEDGEMENTS

Authors are thankful to:

- Drs. Hassan El Azawy, Huda Ahmed, Emad Hamdy, Elzahraa Amar, Marwa AbdElhafiez, Nahed AbdelMonem, Abeer AbdelTawab, Aida Helmy, Lobna Elgamal, Eman Hussien, Tolba Elbasosy,
- Ms. Shaimaa Mustafa, Hanan Fawzi, Elham Hafez, Hagar Hassan, Wadida Aly, Maha Nassar, Doaa Elsayed, Heba Mahdy,
- Mr. Mohamed GamalDiab

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Afifi A, Kareem MA. Renal replacement therapy in Egypt: First annual report of the Egyptian society of nephrology, 1996. East Mediterranean Health Journal. 1999;5(5):1023-9.
2. Rashad S. Barsoum. Burden of chronic kidney disease: North Africa. International Society of Nephrology. 2013;3(2):164-66.
3. Hassan AT, Hamed AF, Waer SM. Epidemiology of end stage renal failure in Sohag Governorate, Upper Egypt, an update. JESN. 2011;12:54-63.
4. El Minshawy O. End-stage renal disease in the El-Minia Governorate, Upper Egypt: An epidemiological study. Saudi J Kidney Dis Transpl. 2011;22(5):1048-54.
5. Ahmed HA, Yassine YS, Tawafe AR, Ebazaway MM. Epidemiological study of patients on regular haemodialysis at the Kafer El-Shakh Governorate, Egypt, Menoufia. Med J. 2015;28:267-71.

6. Hamza AM. Epidemiology of end stage renal disease (ESRD) patients on hemodialysis in Dakahlia governorate [dissertation]. Supervised by: Prof Dr. Ali Elsayed Badr, Prof Dr. Nagy Abdel-Hay Sayed-Ahmed, and Prof Dr. Adel Elwehedy Ibrahem. Egypt: Mansoura University; 2015.
7. El-Arbagy AR, Kora MA, El-Barbary HS, Gabr HM, Selim AA, Kora El-A, et al. Prevalence of end stage renal disease in Menoufia Governorate. Nature and Science. 2015;13(6).
8. El-Zorkany KMA. Maintenance hemodialysis in Menoufia governorate, Egypt: Is there any progress? J Egypt Soc Nephrol Transplant. 2017;17(2):58-63.
9. El-Arbagy AR, Yassin YS, Boshra BN. Study of prevalence of end-stage renal disease in Assiut governorate, Upper Egypt. Menoufia Med J. 2016;29:222-27.
10. Ghonemy TA, Farag SE, Soliman SA, El- okely A, El-Hendy Y. Epidemiology and risk factors of chronic kidney disease in the El-Sharkia Governorate, Egypt. Saudi J Kidney Dis Transpl. 2016;27(1):111-17.
11. El-Ballat MA, El-Sayed MA, Kamel H, Emam A. Epidemiology of end stage renal disease patients on regular hemodialysis in El-Beheira Governorate, Egypt. The Egyptian Journal of Hospital Medicine. 2019;76(3):3618-25.
12. Egyptian Renal Data System (ERDS) 1st Annual Report of End Stage Renal Disease in Egypt; 2018.
Available:https://www.esnt-online.com/images/files/ERDS-2018-final.pdf?fbclid=IwAR1WaNZfjlUZnAMobM0NeMIeAi9xUwM3NOquesxSFxnTcpsqHFmYZZC0HQM
13. Available:https://manshurat.org/node/1454 4
14. National Institute of Urban Planning; 2017.
15. Central Agency for Public Mobilization and Statistics.
Available:https://www.capmas.gov.eg/Pag es/populationClock.aspx
16. World Meters. Population of Egypt (2019 and Historical).
Available:https://www.worldometers.info/w orld-population/egypt-population/
17. Tsai MH, Hsu CY, Lin MY, Yen MF, Chen HH, Chiu YH, et al. Incidence, prevalence, and duration of chronic kidney disease in Taiwan: Results from a community-based screening program of 106,094 individuals. Nephron. 2018;140:175-84.
18. Tang SCW. Chronic kidney disease in disadvantaged populations. ESRD in South-East Asia. 2017;149-56.
19. Saran R, Robinson B, Abbott KC, Agodoa LYC, Bragg-Gresham J, Balkrishnan R, et al. US Renal Data System 2018 Annual Data Report: Epidemiology of kidney disease in the United States. Am J Kidney Dis. 2019;73(3 Suppl 1):A7-A8.
DOI: 10.1053/j.ajkd.2019.01.001
20. Stel VS, van de Luijtgaarden MW, Wanner C, Jager K. Jon. Behalf of the European Renal Registry Investigators. The 2008 ERA-EDTA Registry Annual Report-a précis. NDT Plus. 2011;4:1-13.
21. Pippias M, Kramer A, Noordzij M, Afentakis N, de la Torre RA, Patrice M, et al. The European Renal Association – European Dialysis and Transplant Association Registry Annual Report 2014: A summary. Clinical Kidney Journal. 2017;10(2):154-69.
22. Megahed AF, Azzawi H. MOH hemodialysis Registry: Comparing Services 2016 VS 2017. 1st Acute Renal Dialysis Symposium, Baxter Company, 20th & 21st July. Alexandria, Egypt; 2017.
23. Afifi A. Annual reports of the Egyptian renal registry; 1996-2008.
Available:http://www.esnonline.net
24. Collins AJ, Foley RN, Gilbertson DT, Chen SC. United States renal data system public health surveillance of chronic kidney disease and end-stage renal disease. International Society of Nephrology. 2015;5(1):2-7.
25. Kandeel A, Genedy M, El-Refai S, Funk AL, Fontanet A, Talaat M. The prevalence of hepatitis C virus infection in Egypt 2015: Implications for future policy on prevention and treatment. Liver Int. 2017;37(1):45- 53.
26. Fissell RB, Bragg-Gresham JL, Woods JD, Jadoul M, Gillespie B, Hedderwick SA, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: The DOPPS. Kidney Int. 2004;65:2335-42.

27. Di Napoli A, Pezzotti P, Di Lallo D, Petrosillo N, Trivelloni C, Di Giulio S. Epidemiology of hepatitis C virus among long-term dialysis patients: A 9-year study in an Italian region. Am J Kidney Dis. 2006;48:629-37.
28. Sun J, Yu R, Zhu B, Wu J, Larsen S, Zhao W. Hepatitis C infection and related factors in hemodialysis patients in China: Systematic review and meta-analysis. Ren Fail. 2009; 31:610-20.
29. Alavian SM, Kabir A, Ahmadi AB, Lankarani KB, Shahbabaie MA, Ahmadzad-Asl M. Hepatitis C infection in hemodialysis patients in Iran: A systematic review. Hemodial Int. 2010;14:253-62.
30. Patel PR, Thompson ND, Kallen AJ, Arduino MJ. Epidemiology, surveillance, and prevention of hepatitis C virus infections in hemodialysis patients. Am J Kidney Dis. 2010;56:371-78.
31. Qadi AA, Tamim H, Ameen G, Bu-Ali A, Al- Arrayed S, Fawaz NA. Hepatitis B and hepatitis C virus prevalence among dialysis patients in Bahrain and Saudi Arabia: A survey by serologic and molecular methods Author links open overlay panel. American Journal of Infection Control. 2004;32(8):493-95.
32. Moukeh G, Yacoub R, Fahdi F, Rastam S, Albitar S. Epidemiology of hemodialysis patients in Aleppo City. Renal Data from the Arab World. 2009;20:140-46.
33. El-Ottol AY, Elmanama AA, Ayes BM. Prevalence and risk factors of hepatitis B and C viruses among haemodialysis patients in Gaza strip, Palestine. Virology Journal. 2010;7:210.
34. Fabrizi F, Messa P, Martin P. Hepatitis B virus infection and the dialysis patient. Seminars in Dialysis. 2008;21(5):440-6.
35. Al Hijazat M, Ajlouni YM. Hepatitis B infection among patients receiving chronic hemodialysis at the Royal Medical Services in Jordan. Renal Data from the Arab World. 2008;19:260-67.
36. Soliman AR, Fathy A, Roshd D. The growing burden of end-stage renal disease in Egypt. Renal Failure. 2012;34(4):425-8.
37. Al Alawi I, Al Salmi I, Al Mawali A, Al Maimani Y, Sayer JA. End-stage kidney failure in Oman: An analysis of registry data with an emphasis on congenital and inherited renal diseases. Int J Nephrol. 2017;6403985.
38. Ketteler M, Block GF, Evenepoel P, Fukagawa M, Herzog CA, McCann L. Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update: What's changed and why it matters. Kidney International. 2017;92:26-36.
39. Gregorio T. CKD-related Anemia Conclusion from Kdigo controversies Conference. Nefrologia; 2017.
40. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K, et al. US Renal Data System 2011 Annual Data Report. Am J Kidney Dis. 2012; 59(1 Suppl 1):A7,e1-420. DOI: 10.1053/j.ajkd.2011.11.015
41. Goodkin DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan and the United States: The Dialysis Outcomesand Practice Patterns Study (DOPPS). J Am Soc Nephrol. 2003;14(12):3270-7.
42. Msaad R, Essadik R, Mohtadi K, Meftah H, Lebrazi H, Taki H, et at. Predictors of mortality in hemodialysis patients. Pan African Medical Journal. 2019;33:61.

Biography of author(s)

Dr. Abir Farouk Megahed
MOH Nephrology Administration, Mansoura Military Hospital, Department of Nephrology, Mansoura, Ministry of Health, Mansoura, Egypt.

She was born on 1st September 1966, in Egypt .She is a Visiting Consultant and Head of Nephrology Department in King Salman Specialized Hospital, Hail, Saudi Arabia . She completed MBBCh, Mansoura University, 1989, Master Degree of Internal Medicine, Mansoura University, 1996, and MD in Internal Medicine, Menoufia University, 2009. She has Egyptian Fellowship of Nephrology, 2003. She is a Nephrology consultant in MOH and Visiting consultant in Mansoura military hospital, Coordinator and Supervisor of HD units in MOH , Management of training Nephrology programs for Nephrology doctors and nurses in MOH. She has 21 Published Papers in the national and international journals.

Prof. Nagy Sayed-Ahmed
Nephrology and Dialysis Unit (MNDU), Faculty of Medicine, Mansoura University, Mansoura, Egypt.

He was born in Mansoura Egypt on 19th February, 1959. He is a Professor of internal medicine and nephrology, Mansoura Nephrology and Dialysis Unit (MNDU), Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt. He completed MBBCh, Mansoura University, 1983, Master Degree of Internal Medicine, Mansoura University, 1989, and MD in Internal Medicine, Mansoura, 1994. He is Currently a Member of Nephrology Department of Mansoura university hospital, Currently Chief tutor of Nephrology MD degree in Mansoura University. He supervised many original articles, MD, and MSc thesis in different Nephrology aspects.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Asian Journal of Medicine and Health, 18(10): 52-64, 2020.

Chapter 4
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Characteristics of ESRD Patients who have been on Long-term Hemodialysis Therapy in Egypt: A Clinical Approach

Abir Farouk Megahed[1*] and Nagy Sayed-Ahmed[2]

DOI: 10.9734/bpi/rdmmr/v8/2671E

ABSTRACT

Background: It is well-known that hemodialysis extends the life of end-stage renal disease (ESRD) patients, who would have otherwise died. Hemodialysis is the commonest modality of renal replacement therapy (RRT) in Egypt and many other countries. The characteristics of long-term patients on hemodialysis (HD) were not evaluated before in Egypt. We aimed at identifying the specific characteristics of the patients who have survived on hemodialysis for more than 20 years in Egypt.
Subjects and Methods: During the years 2018 and 2019, the twenty-seven governorate health affairs Directories of the Egyptian Ministry of Health were contacted to participate in data collection. The dialysis physicians in each hemodialysis unit were sent a questionnaire form requesting to submit information, on the characteristics of patients who have been on HD therapy for twenty years or more.
Results: Seventy-three patients were encountered from a total number of 26000 HD patients to have been on HD therapy; with a range between 20 and 30 years. Males constituted the majority of these patients. Sixty-eight patients were dialyzed through working arteriovenous fistulas (A-V fistulas). The mean urea reduction ratio (URR) of these patients was 0.65±0.095. Acute intradialytic complications afflicted only 20.3% of these patients. More than three-quarters of the patients had a positive serology test for HCV antibodies. None of these patients has diabetes mellitus. On the other hand, complaints related to the skeletal system were present in 47.4% of the patients. There is a statistically significant higher rate of acute complications in the female gender and a statistically significant higher fertility rate after hemodialysis in the male gender.
Conclusion: Long-term dwellers on hemodialysis therapy are not unusual in Egyptian ESRD patients and their characteristics are reasonable.

Keywords: Hemodialysis dwellers; long-term patients; ESRD; Egypt.

1. INTRODUCTION

Hemodialysis is the commonest modality of renal replacement therapy (RRT) in Egypt and many other countries. It is well-known that HD alleviates many of the uremic manifestations and extends the life of ESRD patients, who would have otherwise died. However, in spite of the progress in dialysis techniques and science, the life expectancy of HD patients could vary depending on concomitant medical comorbidities and the treatment plan that the patients follow. The average life expectancy on dialysis is five to ten years; however, many patients have lived well on dialysis for 20 to 30 years [1]. There is much confusion in the public awareness of longevity on HD, with many possible survivals more than 20 years. However, several patients have been observed with survival periods for more than thirty-five years [2].

[1]MOH Nephrology Administration, Mansoura Military Hospital, Department of Nephrology, Mansoura, Ministry of Health, Mansoura, Egypt.
[2]Nephrology and Dialysis Unit (MNDU), Faculty of Medicine, Mansoura University, Mansoura, Egypt.
**Corresponding author: E-mail: dnps2016@gmail.com;*

In long-term dialysis, there are complications as amyloidosis, bone disease, endocrine disturbances, infection, cardiovascular complications, vascular access, and nutrition complication [3]. Many long-term dialysis patients suffer from a multitude of health care problems that disturb their quality of life. Nevertheless, renal physicians and dialysis scientists hope that recent advancements and appropriate care of dialysis practice will close these gaps. The characteristics of long-term patients on HD were not assessed before in Egypt.

1.1 Aim of the Work

The present study aimed at recognizing the specific characteristics of the patients who have survived on hemodialysis for more than 20 years in Egypt.

2. PATIENTS AND METHODS

During the years 2018 and 2019, the twenty- seven governorate health affairs Directories of the Egyptian Ministry of Health, comprising 313 hemodialysis units, were contacted by fax-mails and WhatsApp to participate in data collection. The dialysis physicians in each hemodialysis unit were sent a questionnaire form requesting to submit information, as comprehensive as possible, on the characteristics of patients who have been on hemodialysis therapy for twenty years or more. The data have included their age, gender, marital status and fertility, BMI, vascular access, etiology of CKD, associated comorbidities, acute and chronic HD complications, and available routine investigations. We review the full list of the patients at the end of December 2019. Confidentiality and personal privacy were respected at all levels of the study.

2.1 Statistical Analysis

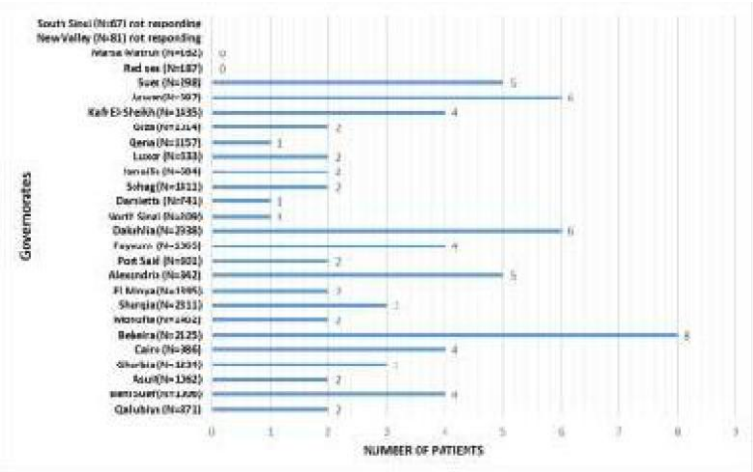
After the collection of data, they were analyzed using the statistical package of social science (SPSS, IBM) software version 24. Categorical data were expressed as numbers and percentages and were analyzed by Chi-square and Fisher-Exact tests. Scale data were expressed as means ± SD or medians (Q1-Q3) as appropriate. Normality was tested using Shapiro Wilkinson or Kolmogorov-Simiranov tests, as appropriate. Parametric data were analyzed using an independent sample T-test, while the Mann-Whitney test was used to analyze non-parametric data. P-value was considered significant if it was < 0.05.

3. RESULTS

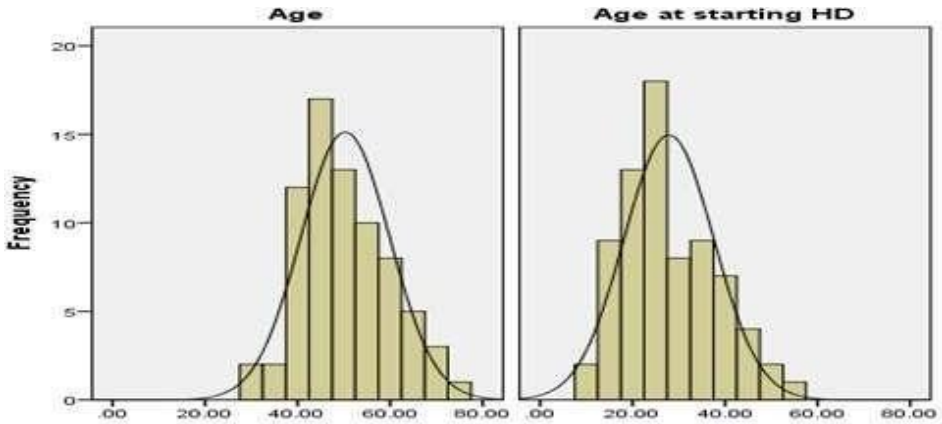
298 units of the approached Health Affairs Directories belonging to 25 Egyptian governorates responded satisfactorily to the questionnaire and participated in data collection. On data analysis of the collected results, Seventy-three patients were encountered from a total number of 26000 HD patients to have been on hemodialysis therapy for 20 years or more; with a range between 20 and 30 years. Males constituted the majority of these patients ischemic heart disease have hypertension. On the and 54.8% other hand, (68.5%). Their mean age was 50±9.63, and they started hemodialysis therapy at a mean age of 27.8 with a range between 10 and 54 years of age. Their mean body mass index was 23.8, with a range between 15.9 and 41.7 kg/m2. (Table 1) Sixty-eight patients were dialyzed through complaints related to the skeletal system were present in as much as 47.4% of the patients, while 19 patients were dependent on walking aids or bound to wheeling chairs (Table 2). Table 3 shows the laboratory data of the studied patients. working A-V fistulas, while five patients have utilized dialysis catheters (Table 1). Two patients Tables 4 a, b, c show gender differences were maintained on two hemodialysis sessions regarding demographic, clinical, and laboratory weekly, while the remaining patients have variables. There are no statistically significant received three sessions weekly; each session differences even comparable results in different lasted for four hours in the majority of patients; although three patients were dialyzed 10 hours weekly (Data were not shown). All sessions have utilized bicarbonate-based dialysate with a dialysate flow rate of 500 ml/min and a blood flow rate of 300 ml/min unless there were compelling problems to do otherwise. Egyptian MOH guidelines were followed for water treatment in variables between both genders. However, there is a statistically significant higher rate of acute complications including

hypotension and muscle cramps in the female gender and a statistically significant higher fertility rate after hemodialysis in the male gender.

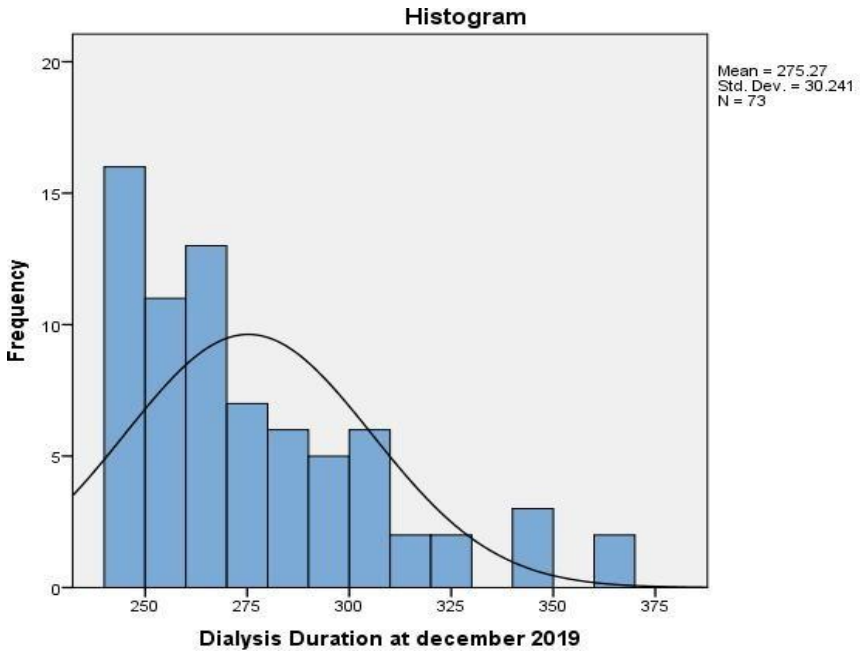
Graph 1: Shows the distribution of long-term All the included HD (https://manshurat.org/node/14544) units (Data were patients in different governorates all over the country. **Graph 2:** Shows histograms of the age not shown). The mean urea reduction ratio of these patients was 0.65±0.095. Acute intradialytic complications afflicted only 20.3% of these patients. Only two patients were smokers; while the majorities (97.3%) were nonsmokers. More than three-quarters of the patients had a positive serology test for HCV antibodies, while only three patients had a positive test for HB distribution of long-term patients at the start of HD and in December 2019, while Graph 3: shows a histogram of dialysis duration distribution in long-term patients by months. The commonest possible etiologies are hypertension (27.4%) followed by urological causes (20.6%), and then unknown etiology (13.7%) are shown in Graph 4. None of these long-term patients has surface antigen. Eight cases of total HCV diabetes mellitus. Graph 5: shows the positive patients have received HCV treatment and showed PCR negative results. None of these patients has diabetes mellitus, while 19.2% have relationship between gender and marital status. Graph 6: shows a histogram of Hemoglobin distribution in the studied group than 20 years on hemodialysis in Egypt and their health-related characteristics.



Graph 1. Total number of patients on HD over twenty years /each governorate considering that the total number of HD patients in participating HD units around 26319 patients



Graph 2. Histograms of the age distribution of long term patients at the start of HD and in December 2019



Graph 3. Histogram of dialysis duration (months) distribution in long-term patients

3. DISCUSSION

Although maintenance dialysis prevents death from uremia, mortality among patients with In the current work, 73 patients had been on HD ESRD remains high. Most of the data concerning the survival of patients treated with maintenance dialysis therapies published in the literature over the years are limited to five to ten-year survival after the commencement of RRT. Long-term survival on HD had been claimed for individual from 20 to 30 years not interrupted by transplant periods, and this is partially in accordance with many international studies. Kirkus et al. have described two patients who had been dialyzed for 35 years, interrupted by short transplant periods [4]. While Heaf et al. stated that patients patients. The aim of the current study is to should be aware that there is no theoretical identify ESRD patients who have spent more upper limit for patient survival on HD [2]

Additionally, Buturovic- Ponikvar (2009) suggested that hemodialysis is neither better nor much worse than kidney transplantation [5].

Long term survival on HD in this survey could be attributed to many factors such as starting dialysis at a young age (mean age 27.8 years old), mostly nonsmokers, and none of them was diabetic, only 27 % having CKD due to HTN and characterized by compliance to local dialysis guidelines. It was observed, during the collection of data, that there was a strong presence of acceptable family support to this group of HD population. This is supported by many international reports that referred to factors associated with long survival on HD including younger ages at the start of HD, norm-tension, absence of diabetes and psychological factors; patient compliance, and willingness to live [6,2].

In the current study, the majority of cases have functioning A-V Fistula. This is similar to a national study organized by ElSharkawy and his colleagues, 2017 [7]. The A-V fistula is considered the best access for HD because of its lower frequency of complications, higher access survival rate, and decreased mortality when compared with either arterio-venous grafts or central venous dialysis catheters. Woods and his associates, 1997, support this finding [8].

The existing survey encountered two patients who persistently insisted to receive only two sessions/week; both of them had low body mass index and low dry body weight (48, 41

kilograms). This finding is reinforced by Weigert et al, 2020 who found that significantly higher treated blood volume per kilogram per session resulting in significantly higher adequacy of HD [9]. However, the presence of low birth weight in these two long-term patients on HD is in divergence with Cohen, 2019 who stated that there is no benefit to having obesity for patients with early stages of CKD, while thin patients on HD have more mortality risks than obese ones [10]. The reason for this survival benefit could be that patients with obesity have a greater caloric reserve making them more resistant to weight loss and causing them to live longer [10].

Table 1. a, b. General and HD characteristics of the studied group

Table 1a. General characteristics of the studied group

Gender n=73	**Female**	**23 (31.5%)**	**Minimum-Maximum**
	Male	50 (68.5%)	
Marital Status n=73	Married after HD	25 (36.2%)	
	Married before HD	19(27.5%)	
	Not married Mean±SD	25 (36.2%)	
Age n=73	Median(Q1-Q3)	50.29±9.63	
		50.00 (43.00-56.50)	31-75
Age of patients at start of dialysis n=73	Mean±SD Median (Q1-Q3)	27.84±9.74	
		26.00 (20.5-33.5)	10-54
DBW n=72	Mean±SD	59.81±12.8	
Height n=72 BMI n=72	Median(Q1-Q3) Mean±SD	60.00 (50.50-65.00)	35.0-94.0
	Median(Q1-Q3) Mean±SD	158.85±13.9	
	Median(Q1-Q3)	160.00 (1.50-1.69)	100-181
		23.81±4.9	
		22.50 (20.25-25.61)	15.92-41.67
Smoking n=73	No-Smoking	71 (97.3%)	
	Smoking	2 (2.7%)	
Serology n=72	Negative	14 (19.4%)	
	Positive HCV*	55 (76.4%)	
	Positive HBV	3 (4.2%)	

Table (1-b). HD characteristics in the studied group

Sessions/week n=73	Mean±SD	2.97±0.164	Minimum-maximum 2-3
	Median (Q1-Q3)	3.00 (3-3)	
Blood flow rate (ml/m) n=73	Mean±SD Median (Q1-Q3)	294.11±22.23	
		300.00 (300-300)	200-350
Vascular Access n=73	AV Fistula	68 (93.2%)	
	Permanent Catheter n (%)	4 (5.4%)	
	Temporary catheter n (%)	1 (1.4%)	
	Free n (%)		
Anticoagulant n=73		1 (1.4%)	
	Heparin n (%)	70 (95.9%)	
Duration of HD (years) n=73	Clexane n (%) Mean±SD	2 (2.7%)	
Dialyzer size n=73	Median (Q1-Q3) Mean±SD	22.45±2.48	
		22 (21-24)	20-30
		1.51±0.17	
UF (Litre /session) n=20	Median(Q1-Q3)	1.40 (1.4-1.6)	1.3-2.2
	Mean±SD Median(Q1-Q3)	2.60±0.69	
		2.50 (2.00-2.38)	1.5-3.5

Table 2. Medical characteristics of the studied group

Hypertension n=73		40	54.8
Ischemic Heart Disease n=73		14	19.2
	No	55	79.7
Acute Complication n=69	Hypotension or cramps	13	18.8
	Resistant Hypertension	1	1.4
	No Bone Disease	37	53.6
Chronic Complication n=69	Bone Disease (Including, Arthritis, Osteoporosis and MBD)	32	47.37
Wheeling chair n=56		19	33.9

***There is no diabetes in the studied group*

Table 3. Laboratory data of the studied group

	N	Mean±SD	Median (Q1-Q3)	Minimum-maximum
Haemoglobin	71	10.45±1.84	10.40 (9-11.5)	6.5-15.7
Albumin	15	3.74±0.57	3.80 (3.5-4)	2.9-4.9
Calcium	29	8.93±0.94	8.8 (8.45 -9.4)	7.2-11.00
Pre-dialytic Bl. Urea	68	119.24±31.81	114.65 (100-144)	40.0 200.0
Post-dialytic Bl. Urea	35	41.25±11.28	40.00 (31-51)	17.0-61.0
Urea Reduction Ratio	36	0.65±0.095	0.65 (0.60-0.72)	0.3-0.8
S. Creatinine	59	7.91±2.71	7.80 (6.30-10.00)	2.40-16.00
Phosphorus	25	5.04±1.78	5.00 (4.00-5.70)	2.4-10.0
S. Potassium	15	5.01±1.54	5.20 (3.7-6.00)	2.50-8.20
S. Ferritin	4	576.25±448.62	450.00 (228.75-1050)	205-1200
PTH	12	613.75±760.89	269.00 (188.75-777)	105-2505

The commonest identifiable potential causes of CKD on HD in this studied group are HTN, urological etiology then-unknown etiology in a chronological arrangement. This is in dissimilarity with the other national studies that were considered the first three potential causes of CKD; HTN, DM, unknown etiology; to be variable in different studies [11-16]. The distribution of possible etiology of CKD in this survey could be a reason for the long-term survival of the studied group; while there is no diabetes mellitus as a possible etiology; many patients have tubule- interstitial diseases with supposed renal reserve for a few years after the start of HD.

One of the characteristics of these long-term patients on HD is the presence of a low frequency of acute complications (<20 % of patients) that could occur during HD sessions. The low frequency of acute complications could be attributed to lower associated comorbidities especially the absence of diabetes and diabetic nephropathy. This finding is in disagreement with a study on Egyptian HD patients performed by El-Sheikh and El-Ghazaly, 2016, showed that 23% of the study population complained of hypotension, 8%complained of Cramps while 19% of the patients reported complaints of dizziness; however their group of patients has diabetic nephropathy in 30 % [17].

The present survey showed some chronic complications and some associated comorbidities. Firstly, 47% of patients have one or more skeletal manifestations around 60 % of them using wheeling chair or walking aid, which might be due to CKD-MBD, and or HD associated amyloidosis. Many studies supported our findings in these aspects; severe spinal cord compression and spondyloarthropathy due to β- M amyloid deposition occurs often after ten years of HD while β-M amyloidosis pathology is not well established and poorly understood. (Habas et al. as well as Otsubo et al, 2007who observed that Hemodialysis-associated amyloidosis was common in long-term survivors [3], [6]. Another study reported that CKD–MBD, and hyperparathyroidism is a common etiology that could be related to skeletal complain in long-term patients on HD [18,19]. Secondly, the frequency of HTN increased from 27 % at the start of HD to near 55 % at the time of the study, and only 19% of them having IHD while none of them

having DM as comorbidity at the time of the study. Despite the high prevalence of comorbidities, there is a long-term follow-up on HD. This may be attributable to the recent advances in hemodialysis technologies similar to a previous publication [20].

Table 4. a, b, and c. Gender difference regarding demographic characters, clinical variables, and laboratory variables

Table 4-a. Gender difference regarding demographic characters

	Male	Female	p
	Mean±SD/ Median (Q1-Q3)		
Age	48.48±9.67	51.12±9.59	0.279#
DBW	59.22±16.63	60.09±10.76	0.789#
BMI	22.86 (20.20-30.11)	22.49 (20.33-25.48)	0.436*
Dialysis hours	12.00 (12.00-12.00)	12.00 (12.00-12.00)	0.684*
Sessions per week	3.00 (3.00-3.00)	3.00 (3.00-3.00)	0.571*
Systolic Blood Pressure	120.00 (107.50-140.00)	120.00 (110.00-130.00)	0.989*
Diastolic Blood Pressure	80.00 (70.00-90.00)	80.00 (70.00-80.00)	0.873*
Age of patients at start of dialysis	25.00 (20.00-36.00)	26.00 (21.00-33.25)	0.699*
Dialyzer size	1.60 (1.40-1.60)	1.40(1.40-1.60)	0.687*
UF(L/session)	2.50 (2.00-3.50)	2.50 (2.00-3.13)	0.877*

Table 4-b. Gender difference regarding clinical variables

Gender		Female		Male		P
		N*	% within Gender	N*	% within Gender	
Bone Disease	No	13	59.1%	23	50.0%	0.482*
	Yes	9	40.9%	23	50.0%	
HTN	No	8	34.8%	25	50.0%	0.225*
	Yes	15	65.2%	25	50.0%	
Smoking	No	23	100.0%	48	96.0%	1*
	Yes	0	0.0%	2	4.0%	
Ischemic Heart	No	18	78.3%	41	82.0%	0.706*
Disease	Yes	5	21.7%	9	18.0%	
Acute	No	14	60.9%	41	89.1%	0.006
Complication	Yes	9	39.1%	5	10.9%	
Wheeling chair	No	13	72.2%	24	63.2%	0.503*
	Yes	5	27.8%	14	36.8%	
Children after	No	20	87.0%	27	54.0%	0.008#
HD	Yes	3	13.0%	23	46.0%	

p value was measured with Chi square

Table 4-c. Gender difference regarding laboratory variables

	Male	Female	p
	Mean±SD/ Median (Q1-Q3)		
Haemoglobin	10.40 (9.00-11.50)	10.30 (9.00-11.55)	0.743*
Albumin	.3.75 (3.05-4.00)	3.80 (3.50-4.30)	0.436*0.743*
Ca	9.00 (8.55-9.60)	18.75 (8.35-9.45)	0.582*
Urea Reduction Ratio	0.64 (0.57-0.71)	0.66 (0.62-0.74)	0.339*
Creatinine	7.65 (6.23-9.00)	7.80 (6.30-10.10)	0.752*
Ph	5.25 (4.48-7.43)	4.50 (3.65-5.35)	0.109*
SK	4.98 (3.83-5.73)	5.20 (3.25-6.35)	0.768*
Ferritin	600 (600-600)	300 (250)	1
PTH	900 (211)	250 (162.5-397)	0.209

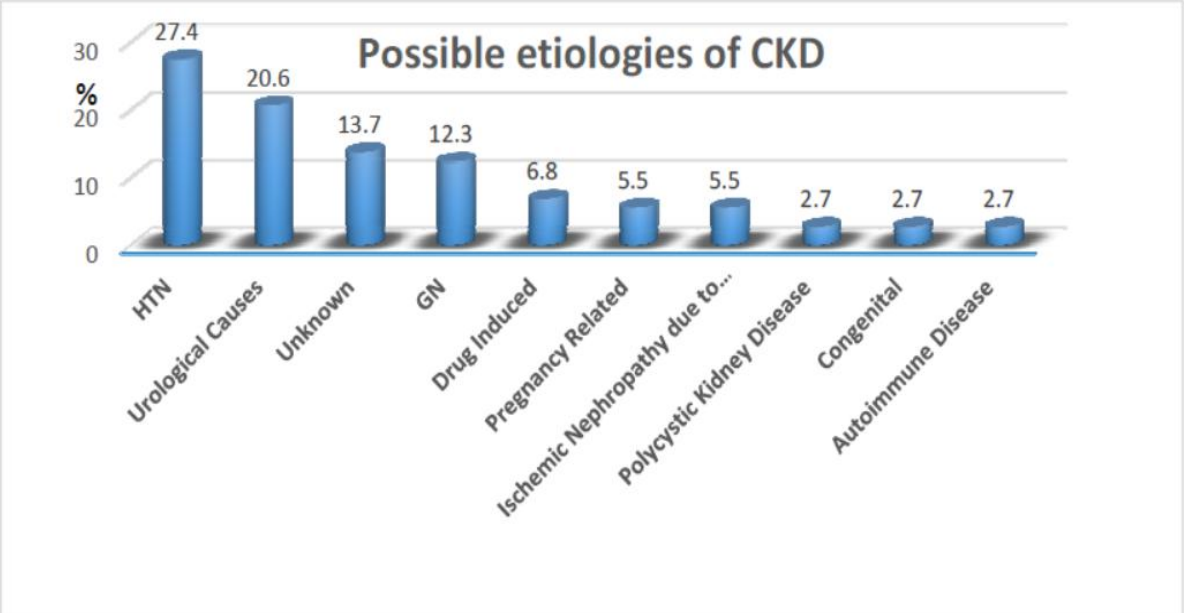
#p value was measured by Fisher-Exact test.N is the number of available data.*p value was measured by Mann-Whitney test #p value was measured by T test*

More than three-quarters of this group of patients had positive serology tests for HCV antibodies and this could be related to the higher frequency of HCV antibodies positive in relation to hemodialysis vintage. This finding is strengthened by many various studies that found higher frequencies of positive HCV antibodies with the increase in hemodialysis duration [21- 22].

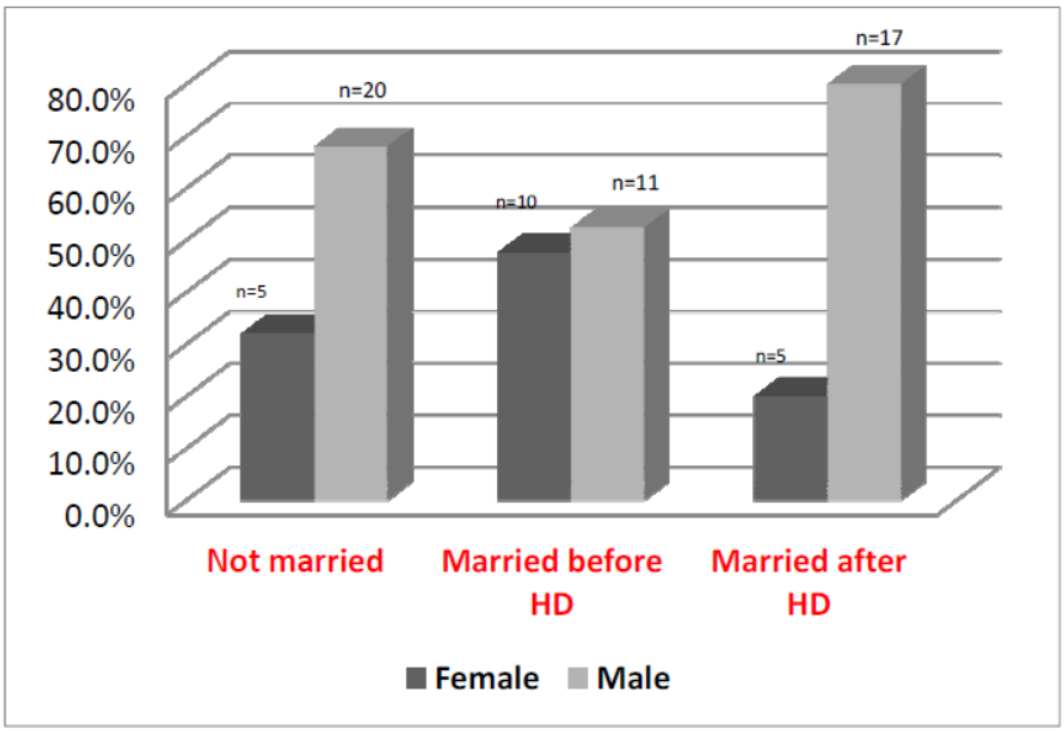
There are comparable results in different variables between both genders of the studied group. However, there is a statistically significant higher rate of acute complications including hypotension and muscle cramps in the female gender. This is in concordance with Bilal et al, 2020 that found the incidence of some dialysis- associated complications is more in females, but they studied CKD secondary to diabetes mellitus [23]. Infertility is markedly more common in women and men with CKD, as compared to the general population. Multiple factors contribute to the reduction in female and male fertility, alongside progressive impairment of the hypothalamic-pituitary-gonadal axes associated with increasing severity of kidney dysfunction. Approaches to improve fertility in CKD focus on the intensification of hemodialysis [24]. The frequency of marital status in the current group is higher in the male gender than in females. Hecking and his colleagues, 2014 who found that men on HD were more frequently married, support this finding [25]. There is statistically significant higher fertility after hemodialysis in the male gender in the current studied group. Early abortion could occur in females on HD and passed unnoticed that possibly will result in lower apparent fertility in females than males.

An idea about good nutrition can be anticipated from reasonable levels of blood hemoglobin, serum creatinine, serum phosphorus and serum albumin. Moreover, near target level of URR gives an idea about accepted range of adequacy of dialysis. These satisfactory laboratory data and reasonable dialysis adequacy are expected to lead to a better health related quality of life in patients with long-term HD.

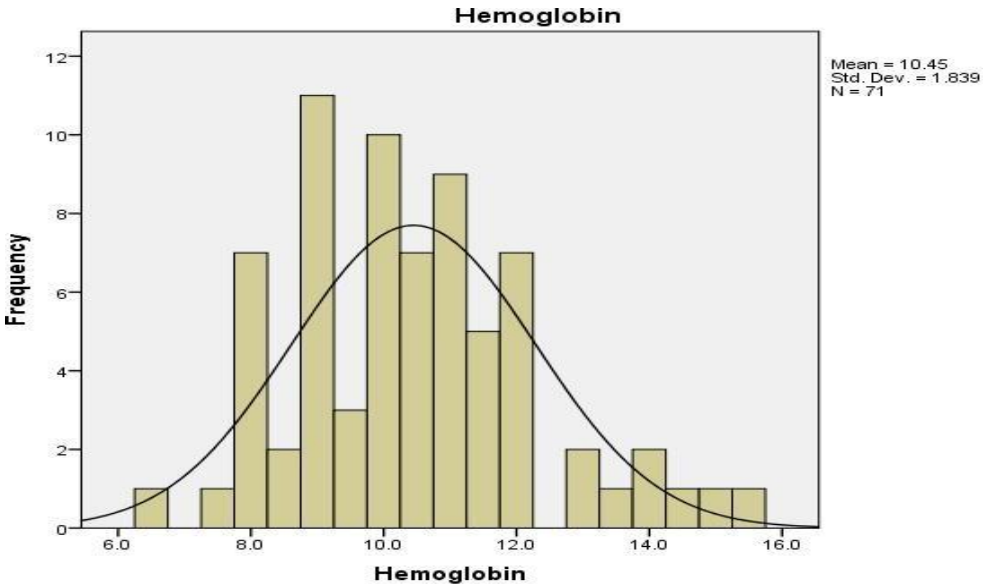
Unfortunately, not all laboratory investigations dictated by the KIDOKI guidelines [26] were fulfilled in all the patient population in the present study; serum ferritin was performed for 5% of patients while parathyroid hormone was performed for 16.4% of patients. These limitations are similar to another recent national report that showed low frequencies of the same laboratory tests [27]. It is suggested that the national nephrology community and different nephrology societies pay more attention to the serial laboratory follow up of HD patients with special concern towards iron studies and parathyroid hormone assay



Graph 4. Possible etiology of CKD in the studied group



Graph 5. Relation between Gender and marital status



Graph 6. Histogram of Hemoglobin distribution in the studied group

4. CONCLUSION

Long-term dwellers on hemodialysis therapy are not uncommon in Egyptian ESRD patients. Patients could live longer on HD, particularly if they were offered good dialysis care. Furthermore, among the special characteristics of these long-term dwellers are younger age at the start of HD with absence of diabetes mellitus and being compliant to dialysis and health care staff instructions and enjoying family support. Compared to females, males had less frequent acute complications on HD, were more frequently married, and had better fertility.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

DECLARATION

The authors declare that there is no conflict of interest. We, hereby declare that this manuscript is an unpublished work which is not under consideration elsewhere and the results contained in this paper have not been published previously in whole or part.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article.

ETHICAL APPROVAL

All procedures were approved by the research ethics committee at the ministry of health, Egypt and carried out under Mansoura University Hospital guidelines.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Canadian National Kidney Foundation. 2015;65(4):PB1-B14.
2. Heaf J, Høj Nielsen A, Post Hansen H. Long-term hemodialysis survival. Clin Kidney J. 2012;5:168-169.
3. Habas E, Rayani A, Khammaj. A Long- term Complications of Hemodialysis; 2012. Available:https://www.researchgate.net/publication/305331602_Long-term_Complications_of_Hemodialysis
4. Kurkus J, Nykvist M, Lindergård B, et al. Thirty-five years of hemodialysis: two case reports as a tribute to Nils Alwall. Am J Kidney Dis. 2007;49:471-476.
5. Buturovic-Ponikvar J. Is Chronic Hemodialysis Really So Inferior to Kidney Transplantation? BANTAO Journal. 2009;7 (1):3-11.
6. Otsubo S, Otsubo K, Sugimoto H, et al. Characteristics of patients on hemodialysis therapy for more than 30 years. Ther Apher Dial. 2007;11:274-279.
7. Elsharkawy M, AbouSeif K, Sarhan I, et al. Current status of hemodialysis access in regular hemodialysis patients in Egypt (abstract); 2017.
8. Woods JD, Turenne MN, Strawderman RL, et al. Vascular access survival among incident hemodialysis patients in the United States. Am J Kidney Dis. 1997;30: 50-57. [PubMed] [Google Scholar]
9. Weigert A, Drozdz M, Silva F, et al. Influence of gender and age on hemodialysis practices: a European multicenter analysis. Clinical Kidney Journal. 2020;13(2):217-224. DOI: 10.1093/ckj/sfz069 Advance
10. Cohen J. Obesity paradox': Patients with ESRD, obesity may have reduced risk for mortality. Nephrology news and issues; 2019.
11. Hamza AM. Epidemiology of end stage renal disease (ESRD) patients on hemodialysis in Dakahlia governorate [dissertation]. Supervised by: Prof Dr. Ali Elsayed Badr, Prof Dr. Nagy Abdel-Hay Sayed-Ahmed, and Prof Dr. Adel Elwehedy Ibrahem. Egypt: Mansoura University; 2015.
12. El-Zorkany KMA. Maintenance hemodialysis in Menoufia governorate, Egypt. Is there any progress? J Egypt SocNephrol Transplant. 2017;17(2):58-63.

13. Ghonemy TA, Farag SE, Soliman SA, et al. Epidemiology and Risk Factors of Chronic Kidney Disease in the El-Sharkia Governorate, Egypt. Saudi J Kidney Dis Transpl. 2016;27(1):111-17.
14. El-Ballat MA, El-Sayed MA, Kamel H, et al. Epidemiology of End Stage Renal Disease Patients on Regular Hemodialysis in El- Beheira Governorate, Egypt. The Egyptian Journal of Hospital Medicine. 2019;76(3): 3618-25.
15. Egyptian Renal Data System (ERDS) 1st Annual Report of End Stage Renal Disease in Egypt; 2018. Available:https://www.esnt-online.com/ images/files/ERDS-2018-final.pdf?fb clid=IwAR1WaNZfjlUZnAMobM0NeMIeAi9 xUwM3NOquesxSFxnTcpsqHFmYZZC0H QM
16. Soliman AR, Fathy A, Roshd D. The Growing Burden of End-Stage Renal Disease in Egypt. Renal Failure. 2012;34(4):425-8.
17. El-Sheikh M and El-Ghazaly G. Assessment of hemodialysis adequacy in patients with chronic kidney disease in the hemodialysis unit at Tanta University Hospital in Egypt. Indian Journal of Nephrology. 2016;26(6):398-404.
18. Passalidou I and Karapavlidou P. Parathyroid hormone levels in hemodialysis patients European Society of Endocrinology 12th European Congress of Endocrinology Prague, Czech Republic; 2010.
19. Megahed AF, El-Said G, Abdelhady MM, Sayed-Ahmed N. Differences between the Incident and Prevalent Hemodialysis Patients in Egypt. Asian Journal of Medicine and Health. 2020 Dec 9:42-54.
20. Piccoli GB, Mezza E, Anania P, et al. Patients on renal replacement therapy for 20 or more years: a clinical profile. Nephrol Dial Transplant. 2002;17:1440-1449.
21. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, et al. Hepatitis C virus and death risk in hemodialysis patients. Journal of the American Society of Nephrology. 2007; 18(5):1584-93.
22. Meyers CM, Seeff LB, Stehman-Breen CO, et al. Hepatitis C and renal disease: An update. Am J Kidney Dis. 2003;42:631- 657.
23. Bilal A, Uz Zaman F, Abrar SM, et al. The effect of age and gender on acute complications of hemodialysis in patients with chronic kidney disease secondary to diabetes mellitus acute Complications of Hemodialysis Pak. Armed Forces Med J. 2020;70 (3):781-86.
24. Dumansk SM and Ahmad SB. Fertility and reproductive care in chronic kidney disease. Journal of Nephrology. 2019;32: 39-50.
25. Hecking M, Bieber BA, Ethier J, et al. Sex-Specific Differences in Hemodialysis Prevalence and Practices and the Male-to- Female Mortality Rate: The Dialysis Outcomes and Practice Patterns Study. 2014;11(10): e1001750.
26. Daugirdas JT, Depner TA, Inrig J, Mehrotra R, Rocco MV, Suri RS, et al. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. American Journal of Kidney Diseases. 2015;884-930:(5)66**.**
27. Egyptian Renal Data System (ERDS) 2nd Annual Report of End Stage Renal Disease in Egypt; 2019.

Biography of author(s)

Dr. Abir Farouk Megahed
MOH Nephrology Administration, Mansoura Military Hospital, Department of Nephrology, Mansoura, Ministry of Health, Mansoura, Egypt.

She was born on 1st September 1966, in Egypt .She is a Visiting Consultant and Head of Nephrology Department in King Salman Specialized Hospital, Hail, Saudi Arabia . She completed MBBCh, Mansoura University, 1989, Master Degree of Internal Medicine, Mansoura University, 1996, and MD in Internal Medicine, Menoufia University, 2009. She has Egyptian Fellowship of Nephrology, 2003. She is a Nephrology consultant in MOH and Visiting consultant in Mansoura military hospital, Coordinator and Supervisor of HD units in MOH , Management of training Nephrology programs for Nephrology doctors and nurses in MOH. She has 21 Published Papers in the national and international journals.

Prof. Nagy Sayed-Ahmed
Nephrology and Dialysis Unit (MNDU), Faculty of Medicine, Mansoura University, Mansoura, Egypt.

He was born in Mansoura Egypt on 19th February, 1959. He is a Professor of internal medicine and nephrology, Mansoura Nephrology and Dialysis Unit (MNDU), Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt. He completed MBBCh, Mansoura University, 1983, Master Degree of Internal Medicine, Mansoura University, 1989, and MD in Internal Medicine, Mansoura, 1994. He is Currently a Member of Nephrology Department of Mansoura university hospital, Currently Chief tutor of Nephrology MD degree in Mansoura University. He supervised many original articles, MD, and MSc thesis in different Nephrology aspects.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Asian Journal of Medicine and Health, 19(8): 37-47, 2021.

Chapter 5
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Rare and Lethal Bleeding Cause of Pulmonary Tuberculosis

Saeed Albogami[1*] and Abdelfattah A. Touman[2,3]

DOI: 10.9734/bpi/rdmmr/v8/2674E

ABSTRACT

Background: Pulmonary aneurysms and pseudoaneurysms are caused by a variety of factors; however, Rasmussen's pseudoaneurysm refers to a focal dilation of a pulmonary artery branch into the adjacent tuberculous cavity. The incidence of such tuberculosis related pulmonary vascular complication is extremely rare, hence, under recognized by many physicians. Pulmonary pseudoaneurysms are challenging to treat because they cause life-threatening hemoptysis. Furthermore, unlike the majority of causes of massive hemoptysis, their bleeding originates in the pulmonary rather than bronchial arteries. Since this is associated with an extremely high death rate, prompt diagnosis and early therapies are required. Case description: We present a case of a young male who presented to our hospital with recurrent episodes of massive hemoptysis and was diagnosed with pulmonary tuberculosis. His hemoptysis persisted despite active treatment. In this case, we discuss the role of various diagnostic modalities as well as the available therapeutic options. Conclusion: Rasmussen's pseudoaneurysm is a rare and potentially fatal tuberculosis pulmonary vascular complication. It should be considered in the differential diagnosis of hemoptysis in patients known or suspected to have pulmonary tuberculosis. Prior to therapeutic interventions, multidetector computed tomography (MDCT) scanning is the investigation of choice to confirm the diagnosis and localise the source of bleeding. There is no head-to-head comparison of interventional radiology procedures and surgery in the treatment of pulmonary pseudoaneurysm, so the choice is dependent on availability and local expertise.

Keywords: Coil embolization; hemoptysis; multidetector computed tomography (MDCT); pseudoaneurysm; rasmussen.

1. INTRODUCTION

Pulmonary tuberculosis (PTB) presents enormous diagnostic and therapeutic challenges because it can manifest as a variety of complications even after complete biological cure [1]. The lung parenchyma, airways, pleura, or pulmonary vessels may be involved in these complications. The mediastinum and chest wall may also be involved. The most common are cavitation, bronchiectasis, and pleural disease. Vascular complications, on the other hand, are a rare sequelae of PTB, but they have a very high mortality rate. Aneurysmal dilatation of the pulmonary artery adjacent to PTB cavity (Rasmussen's pseudoaneurysm) is one of these vascular complications which estimated to occur in 0.25% of PTB patients [2]. It usually presents clinically by massive hemoptysis; thus, carry extremely high mortality rate that exceeds 38% [2]. Massive hemoptysis in the vast majority of PTB cases is from bronchial circulation, however, in Rasmussen's pseudoaneurysm the bleeding is of pulmonary artery origin [3,4]. As a result of its rarity and under recognition by many physicians the diagnosis is usually delayed or missed. Rasmussen's pseudoaneurysm should be considered in the differential diagnosis of hemoptysis in PTB patients along with other causes of hemoptysis such as post PTB bronchiectasis, pulmonary embolism and bleeding from cavitary lesions.

[1]Department of Medicine, King Fahad Hospital, Rabigh Medical College, King Abdul-Aziz University, Jeddah, Saudi Arabia.
[2]King Abdullah Medical City-Makkah, KSA.
[3]1st Respiratory Medicine Department of the National and Kapodistrian University of Athens, Greece.
**Corresponding author: E-mail: dr.s.almarzoqi@hotmail.com;*

In this report we present one such case of Rasmussen's aneurysm and review of the relevant literature.

2. CASE REPORT

We are reporting on 28 years nonsmoker- male, prisoner, who presented to the hospital complaining of coughing up a fresh blood for few weeks. His hemoptysis was associated with fever, loss of appetite and weight. He reported having contact with a prisoner diagnosed to have pulmonary tuberculosis. He had no risk factor of pulmonary embolism or bronchiectasis. He was not on regular medications for any chronic medical illness. On examination, he was fully conscious, alert, oriented and not in acute respiratory distress. However, he looked ill and underbuilt. His chest examination revealed bilateral upper lobes bronchial breathing with diffuse scattered inspiratory and expiratory crepitation. Apart from tachycardia, examination was normal. His chest X-ray revealed bilateral diffuse reticulonodular opacities with some fibrotic changes in both apices (Fig. 1). He was admitted and isolated into the negative pressure room. Sputum acid fast bacilli (AFB) and Nucleic Acid Amplification (NAA) Tests confirm the diagnosis of pulmonary tuberculosis. First line standard medications for PTB were immediately commenced. Despite he had culture proven pansensitive

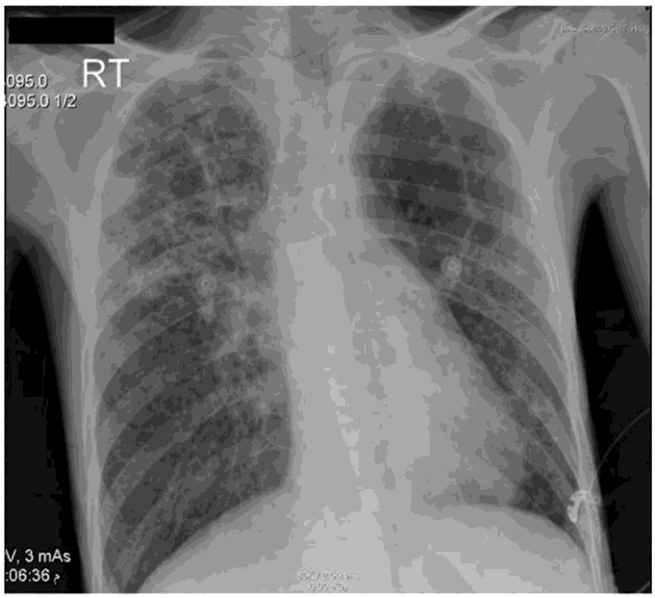


Fig. 1. Chest X-ray showing bilateral reticulonodular opacities with some fibrotic changes in both apices

Mycobacterium he continued to have significant amount of hemoptysis and his AFB remained positive throughout his hospitalization. He received repeated packed red blood cells (PRBCs) transfusion to correct his severe anemia. A total of 3 units of (PRBCs) were required to maintain his Hemoglobin (Hb) around 9 g/dL. Fibreoptic bronchoscopy examination was performed to diagnose the cause of bleeding; inspection showed normal airways, no endobroncheal mass, vascular lesion or other obvious source of bleeding identified. Bronchoalveolar lavage (BAL), brush samples and transbroncheal biopsies were taken during the procedure. Cytology and microbiology results showed abundant polymorph neutrophils and red blood cells consistent with acute inflammation, AFB was present. Histopathology examination showed no abnormal finding other than active chronic inflammatory processes. A computed tomographic (CT) pulmonary angiogram was done, and revealed a thick walled cavitary lung lesion filled with blood, and surrounded by fibrotic and bronchiectatic changes (Fig. 2). A three dimensional reconstruction of the vascular anatomy (MDCT) showed a very large dilatation of pulmonary arterial wall (Rasmussen's pseudoaneurysm) measuring 81 × 65 × 62 mm in the craniocaudal, anteroposterior and transverse diameter respectively. The pseudoaneurysm was originating from a left lower lobe segmental pulmonary artery branch (Fig. 3).

Either pseudoaneurysm embolization or lobectomy was discussed in a multi-disciplinary meeting with thoracic surgeons and interventional radiologists as he continued to have recurrent episodes of major hemoptysis. Psudoaneurysm embolization and subsequent coil insertion were decided and planned. Unfortunately, the patient had hemodynamic collapse during the procedure, and was resuscitated in the angiography suit then shifted to intensive care unit (ICU) where he remained relatively in stable hemodynamic condition. Few days later he had a second sudden cardiovascular collapse and eventually succumbed to his illness.

3. DISCUSSION

A focal dilatation of the pulmonary artery is a rare pathological complication of various pulmonary and systemic diseases. In cases where all three layers of pulmonary artery wall are involved the focal dilatation is termed aneurysm; pseudoaneurysm on the other hand, does not involve all arterial wall's layers [5]. Nevertheless, the term aneurysm and pseudoaneurysm are commonly used interchangeably in the literature [6]. Many etiologies are implicated in pulmonary aneurysms and psudoaneurysm as post-infection as PTB, trauma, congenital, inflammatory (e.g. Behcet disease) and pulmonary hypertension. The term Rasmussen's pseudoaneurysm refers specifically to tuberculous etiology. It results from a PTB cavitary lesion that erodes the adjacent structures in the lung, when a branch of the pulmonary artery come adjacent to or within the cavity, its wall progressively weaken as granulation tissue replaces both the adventitia and the media layer. Thereafter, the artery wall expands until it bursts resulting in pseudoaneurysm formation. These pseudoaneurysms can potentially rupture producing massive hemoptysis [7,8]. Rasmussen's pseudoaneurysm was reported in literature as early as the 19th century [9,10]. It was not well characterized until a detailed pathological description of 11 cases detailed by Dr. Fritz Rasmussen in 1868 and named after him [11].

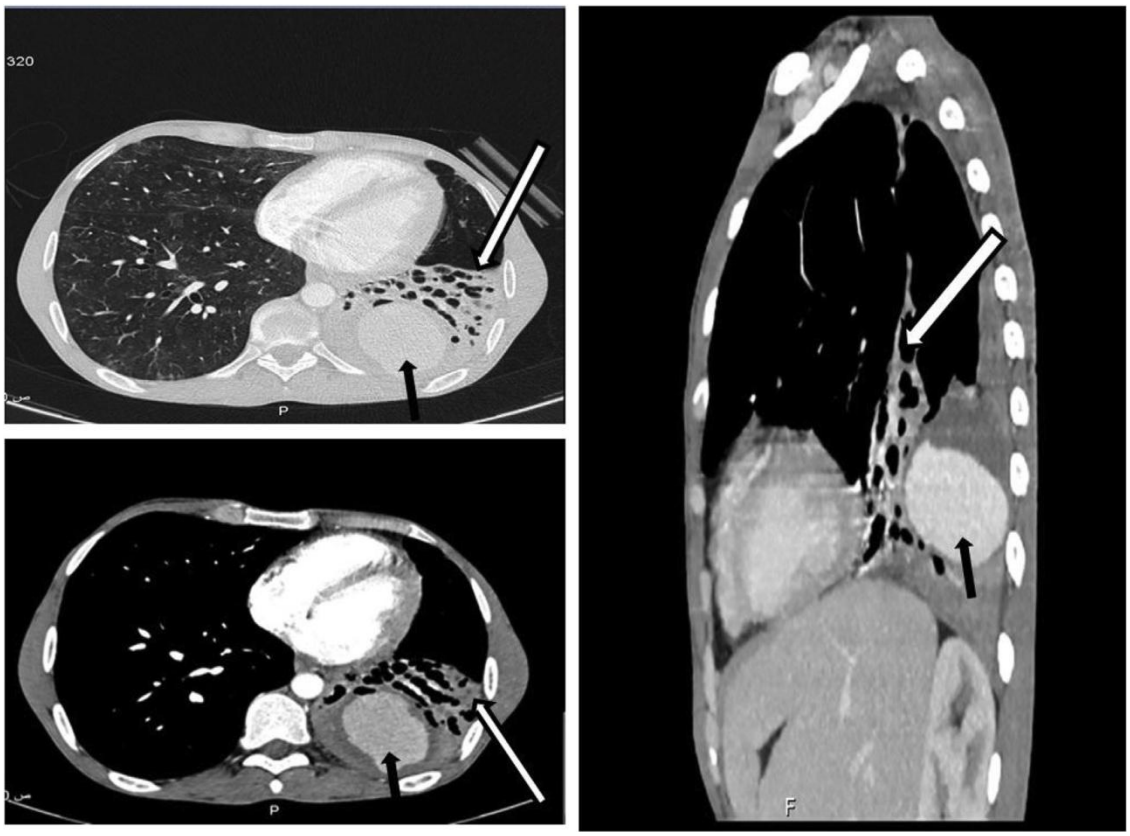


Fig. 2. Chest CT showing blood-filled cavitary lung lesion (black arrows). The cavity is surrounded by fibrotic and bronchiectatic changes (white arrows)

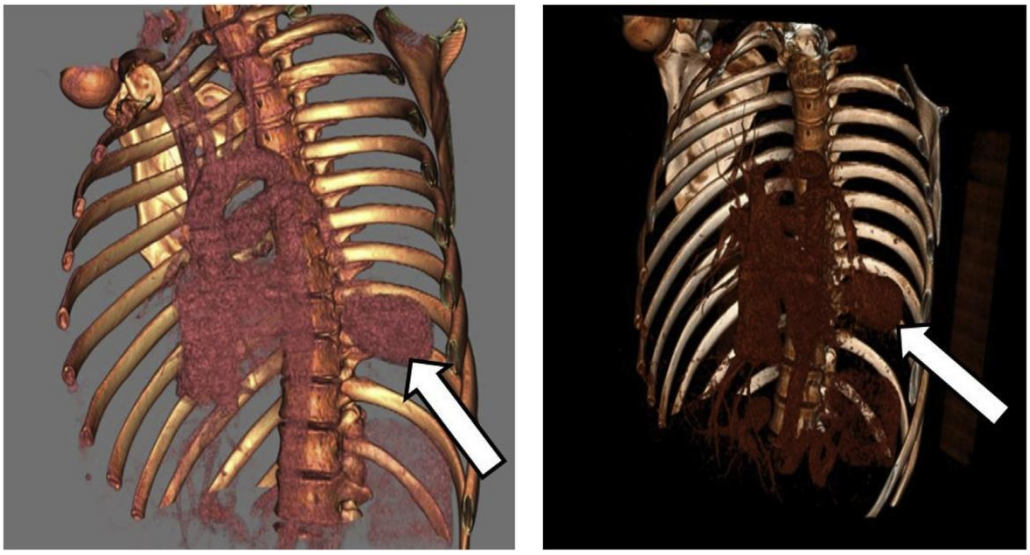


Fig. 3. A three dimensional reconstruction of the vascular anatomy (MDCT) showing details of the lung vascular. A pseudoaneurysm that measures 81 × 65 × 62 mm and originates from a left lower lobe segmental pulmonary artery branch is indicated by a white arrow

In a study were 21.532 patients with confirmed PTB underwent multidetector computed tomography (MDCT) scanning or pulmonary angiography, Rasmussen's pseudoaneurysms were found in only 54 cases (0.25%) [2]. In PTB cases presenting with massive hemoptysis the incidence is higher, as it was shown to be present in 7% in one autopsy series of 80 patients who had PTB and massive hemoptysis [12]. In another serious of 8 patients presented with severe hemoptysis secondary to cavitary PTB and failed arterial embolizations, selective pulmonary angiography diagnosed three patients (38%) to have Rasmussen's pseudoaneurysms [13]. These pulmonary artery pseudoaneurysms are the source of bleeding in this rare tuberculosis related vascular complication; nevertheless, bronchial artery is by far the commonest source of life-threatening hemoptysis even in PTB patients [14,15].

Flexible fibreoptic bronchoscopy is advocated as initial procedure of choice to investigate massive hemoptysis cases as it can be performed at the bedside and has potentially diagnostic as well as therapeutic benefit. It can localize the bleeding site in up to 93% of cases [16]. Moreover, bronchoscopy could localize the bleeding or diagnose its cause when chest x-ray and/or CT fail to do so [16,17]. In the other hand, bronchoscopic examination of the airways does not have specific findings in many important causes of hemoptysis such as bronchiectasis as an example [18]. In our case, bronchoscopic examination was not informative, it merely confirmed the present of AFB in the airways. In centers were urgent fibroptic bronchoscopy is not available, thoracic angio CT scan is being used as alternative diagnostic modality which have high sensitivity to guide the therapeutic intervention [15]. CT scan has been shown in clinical studies to be the most sensitive diagnostic test when employed alone [17]. The Highest diagnostic sensitivity can be achieved by combining a CT scan with a bronchoscopy [17].

The therapeutic roles of the flexible fibreoptic bronchoscopy include localization; ensure hemostasis or isolation of the bleeding segment using different modalities [19]. Such an intervention help prevent asphyxiation and usually used as a bridge for the definite intervention. The superiority of either interventional radiology procedures or surgical treatment of pulmonary aneurysms and pseudoaneurysms has never been established as head-to-head comparisons between these modalities are lacking. Generally, graft placement or aneurysmorrhaphy are performed in aneurysm involving pulmonary trunk [20]. In the other hand, Rasmussen's pseudoaneurysms rise from peripheral branches of pulmonary artery, and thus require lobectomy or even pneumonectomy [21]. Endovascular aneurysm repair (EVAR) a less invasive technique which does not require open surgery has been described in a few case reports as a compassionate release indication [22,23]. Many

centers reserve surgery for cases refractory to angiographic embolization as patients who undergo emergency surgical resection during active massive hemoptysis have a high morbidity and mortality rate [24]. Moreover, as it was the case in this reported patient, many patients presenting with severe hemoptysis are not surgical candidates due to the presence of extensive PTB causing insufficient respiratory reserve [13]. Such cases mandate minimally invasive techniques and thus the interventional radiology procedures are preferred. The success rate of angiographic embolization for massive hemoptysis (of all causes) is reported to exceed 90% [25]. Bronchial artery embolization constitutes the main bulk of the published literature being the commonest source of bleeding in massive hemoptysis cases. Very few cases have been described in literature to have successful interventional angiographic occlusion of the pseudoaneurysms using different techniques [13,14,21,26].

4. CONCLUSIONS

Our case highlights many important points; firstly, the disease rarity hinders its suspicion and hence early investigation and diagnosis. Secondly, it poses diagnostic challenges as despite it causes massive hemoptysis, bronchoscpic examination which is the initial diagnostic tool of choice in cases of massive hemoptysis is usually unrevealing. Furthermore, PTB commonly causes cavitary lung lesions and bronchiectasis; both present with hemoptysis and mimic Rasmussen's pseudoaneurysm on standard chest CT images. Finally, it shows the therapeutic options and highlights the extremely high mortality risk of this illness.

ACKNOWLEDGEMENT

I would like to thank my wife Ms. Hessah Albogami for her assistance and support in preparing & reviewing this chapter. Her efforts were important & greatly appreciated.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Hyae Young Kim, Koun-Sik Song, Jin Mo Goo, Jin Seong Lee, Kyoung Soo Lee, Tae- Hwan Lim, Thoracic sequelae and complications of tuberculosis, Radiographics. 2001;21:839–858. Available:https://doi.org/10.1148/ radiographics.21.4.g01jl06839.
2. Stevan Ivkovic, Tamara Milosavljevic, Aleksandar Ivkovic. MDCT with angiography in Rasmussen aneurysms. Eur. Respir. J. 2014;44(Suppl 58):P2631.
3. Remy J, Remy-Jardin M, Voisin C. Endovascular management of bronchial bleeding, in: J. Butler (Ed.), The Bronchial Circulation, Dekker, New York, NY. 1992;667–723.
4. Sapra R, Sharma G, Minz AK. Rasmussen's aneurysm: A rare and forgotten cause of hemoptysis. Indian Heart Journal. 2015;67:S53-6.
5. Elsie T. Nguyen, C. Isabela Silva, Jean M. Seely, Semin Chong, Kyung Soo Lee, Nestor L. Müller, Pulmonary artery aneurysms and pseudoaneurysms in adults: Findings at CT and radiography, Am. J. Roentgenol. 2007;188:W126–W134. Available:https://doi.org/10.2214/AJR.05.1652.
6. Woong Yoon, Jae Kyu Kim, Yun Hyun Kim, Tae Woong Chung, Heoung Keun Kang. Bronchial and nonbronchial systemic artery embolization for Life-threatening he- moptysis: A comprehensive review, Radiographics. 2002;22(6):1395–1409.
7. Auerbach O. Pathology and pathogenesis of pulmonary arterial aneurysm in tuberculous cavities, Am. Rev. Tubercul. 1939;39:99–115.
8. Santelli ED, Katz DS, Goldschmidt AM, Thomas HA. Embolisation of multiple Rasmussen's aneurysms as a treatment of hemoptysis, Radiology. 1994;193:396–398.
9. Fearn SW. Aneurysm of the pulmonary artery. Lancet. 1840;41(1):679.
10. Kidd P. Unusual cases of pulmonary artery aneurysm, Trans. Pathol. Soc. Lond. 1884;35:98–100.

11. Rasmussen V. On haemoptysis, especially when fatal, in its anatomical and clinical aspects. Edinb. Med. J. 1868;14:385–401.
12. Thompson JR, Mechanisms of fatal pulmonary hemorrhage in tuberculosis. Am. J. Surg. 1955; 89(3):637–644.
13. Sanyika C, Corr P, Royston D, Blyth DF. Pulmonary angiography and embolization for severe hemoptysis due to cavitary pulmonary tuberculosis, Cardiovasc. Intervent. Radiol. 1999;22(6): 457–460.
14. Picard C, Parrot A, Boussaud V, Lavole A, Saidi F, Mayaud C, Carette MF. Massive hemoptysis due to Rasmussen's Aneurysm: Detection with helicoidal CT Angiography and successful steel coil embolisation, Intensive Care Med. 2003;29:1837–1839.
15. Spinu C, Castañer E, Gallardo X, Andreu M, Alguersuari A. Multidetector computed tomography in life-threatening hemoptysis, Radiologia. 2013;55(6):483–498. https://doi.org/10.1016/j.rx.2013.05.006 Epub 2013 Sep. 20.
16. Eric I. Hsiao, Carl M. Kirsch, Richard B. Baxter, et al., Utility of fiberoptic bronchoscopy before bronchial artery embolization for massive hemoptysis, AJR 177 (October 2001).
17. B. Hirshberg, I. Biran, M. Glazer, M.R. Kramer, Hemoptysis: etiology, evaluation, and outcome in a tertiary referral hospital, Chest 112 (2) (1997 Aug) 440–444.
18. Anupam Kumar, Shine Raju, Aparna Das, Atul C. Mehta, Vessels of the central airways a bronchoscopic perspective, Chest 149 (3) (2016) 869–881.
19. S´ebastien Gagnon, Nicholas Quigley, Herv´e Dutau, Antoine Delage,and Marc Fortin. Approach to Hemoptysis in the Modern Era. Canadian Respiratory Journal Volume 2017, Article ID 1565030, 11 pages https://doi.org/10.1155/2017/1565030.
20. Kenji Kuwaki, Kiyofumi Morishita, Hiroki Sato, Raimi Urita, Tomio Abe, Surgical repair of the pulmonary trunk aneurysm, Eur. J. Cardio. Thorac. Surg. 18 (5) (1 November 2000) 535–539 Available:https://doi.org/10.1016/S1010-7940(00)00568-6.
21. Sbano H, Mitchell AW, Ind PW, Jackson JE. Peripheral pulmonary artery pseudoaneurysms and massive hemoptysis, AJR Am. J. Roentgenol. 2005;184:1253–1259.
22. Robert L. Hannan, Kagami Miyaji, Redmond P. Burke, Evan M. Zahn, Endovascular stent graft treatment of a pulmonary artery pseudoaneurysm, Ann. Thorac. Surg. 2001;71:727–729.
23. Park A, Cwikiel W. Endovascular treatment of a pulmonary artery pseudoaneurysm with a stent graft: report of two cases, Acta Radiol. 2007;48(1):45–47.
24. Hakan Kiral, Serdar Evman, Cagatay Tezel, Levent Alpay, Tunc Lacin, Volkan Baysungur, Irfan Yalcinkaya, Pulmonary resection in the treatment of life- threatening hemoptysis, Ann. Thorac. Cardiovasc. Surg. 2015;21:125–131. Available:https://doi.org/10.5761/atcs.oa.14-00164.
25. Woo S, Yoon CJ, Chung JW, Kang SG, Jae HJ, Kim HC, Seong NJ, Kim YJ, Woo YN. Bronchial artery embolization to control hemoptysis: Comparison of N- butyl-2-cyanoacrylate and polyvinyl alcohol particles, Radiology. 2013;269(2):594–602. Epub 2013 Jun 25.
26. Remy J, Lemaitre L, Lafitte JJ, Vilain MO, San Michel J, Steenhouwer F. Massive hemoptysis of pulmonary arterial origin: Diagnosis and treatment, AJR. 1984;143:963–969.

Biography of author(s)

Dr. Saeed Albogami
Department of Medicine, King Fahad Hospital, Rabigh Medical College, King Abdul-Aziz University, Jeddah, Saudi Arabia.

He is a Consultant Pulmonologist & Internist, Head of Pulmonology, Allergy & Immunology Division, Head of Bronchoscopy Unit & PFT Lab, King Fahad Hospital, Jeddah, Saudi Arabia. He has MBBS, SSC, JMC, FRCPC, and FCCP. He is an Assistant Professor, KAAU, Rabigh Medical College, Director of SCFHS Respirology Fellowship Training Program, KFHJ, Member of Saudi Western Region SCFHS Respirology Program Committee & certified SCFHS Saudi Board Examiner and Trainer, Member of several national & international Respirology committees, societies & councils such as ATS, CTS, ACCP, ERS, STS & Elite Doctors Group. He is also an Invited speaker in many national & international Respirology conferences & symposia. He has several published researches & papers in many international journals, books & conferences.

Dr. Abdelfattah A. Touman
King Abdullah Medical City-Makkah KSA and 1st Respiratory Medicine Department of the National and Kapodistrian University of Athens, Greece.

He is a Pulmonology consultant at King Abdullah Medical City-Makkah KSA. He is a Member of ERS and EABIP. He has M.B.B CH, MRCP(UK), SF-PD. He has Interventional pulmonology fellowship from the 1st Respiratory Medicine, Department of the National and Kapodistrian University of Athens, Greece. He has published some research articles in the national and international journals.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Respiratory Medicine Case Reports, 25: 150–153, 2018.

Chapter 6
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Hurdles in Eye Care Services – An Indian Scenario

Gaurav Dubey[1*], Ragni Kumari[2*], Jamshed Ali[3], Vibha Kumari[4], Prasenjit Das[5], Simi Afroz[6], R. K. Manik[7], Nitika Kumari[8], Rajeev Trivedi[9] and Mahesh Chandra[10]

DOI: 10.9734/bpi/rdmmr/v8/10115D

ABSTRACT

Visual impairment affects livings in every aspect of life. Many organizations (W.H.O, IAPB, N.G.O.s, etc.) have initiated a campaign to eradicate preventable blindness under the scheme Vision 2020: The Right to Sight" by 2020. There are three primary considerations, including quality, reliability, and efficiency of eye care facilities, which may reduce vision loss worldwide. Poor practitioner-to-patient ratios, shortage of eye-care staff, insufficient infrastructure, weak state support and lack of medical, specialist or training programs are the hallmarks of obstacles to the usage of eye-care services in India. Significant obstacles to such programs for visually impaired people in rural areas are poor road infrastructure, transit facilities and distances from remote communities that influence surgery and eye care systems. Factors such as age, education, preferences, and psycho-social challenges influence the usage of healthy, affordable, and efficient eye care facilities. To prevent avoidable blindness, the advancement of eye treatment and understanding of appropriate eye care resources must be intense, and the consequences of inadequate eye care must be acknowledged. Rural communities' beliefs and cultural traits must be analyzed to have appropriate education and reduce worldwide vision and blindness. Eye care providers need to start educating people in early life about the role and use of health care resources. In this article we will discuss the current state of eyecare services, as well as the challenges faced by eye doctors in treating and managing eye problems, in this article. There are many hurdles to using eye care services, and administrators and providers must understand them.

Keywords: Visual impairment; obstructions and dissatisfaction in services; eyecare facilities.

1. INTRODUCTION

Visual disability impacts any part of life. Sadly, in many parts of the world, many people have low vision or are blind. It is because of this that the World Health Organization (WHO), the international agency to prevent blinding, non-governmental organizations (NGO), professional associations, and eye care institutions and corporations have developed a global initiative for the elimination of avoidable blindness by the year 2020 [1]. This scheme called "Vision 2020: The Right to Sight," This can be achieved by the utilization of workforce personnel infrastructural development and community-based programs in the rural areas. Worldwide, most cases of blindness are preventable or manageable by surgery and or refractive error corrections [2-7], though; the available resources cannot manage the level of demand for eye care. Eye care services are not readily available in many countries due to the inadequacy of trained personnel or since eye care practitioners are usually

[1]Optometry Faculty, Department of Optometry, Faulty of Paramedical Sciences, UPUMS, Saifai, Etawah, U.P., India.
[2]Amity Institute of Public Health, Amity University, Noida, U.P., India.
[3]Department of Optometry, Allied Health Science IIMT University, Meerut, U.P, India.
[4]Department of Paramedical Sciences, Jamia Hamdard New Delhi, India.
[5]Department of Optometry, School of Nursing Science, ITM University, Gwalior, M.P, India.
[6]Department of Allied Health Science, Sharda University, U.P, India.
[7]Department of Optometry, Subharti University, Meerut, U.P., India.
[8]Department of Paramedical Sciences, Jamia Hamdard, New Delhi, India.
[9]Ansal Medical School, Sushant University, Gurugram, Haryana, India.
[10]Department of Ophthalmology, Dr. Sushila Tewari Hospital & Govt. Medical College, Haldwani, Uttarakhand, India.
**Corresponding author: E-mail: ragnimishraa@gmail.com;*

concentrated in urban areas [7,8]. In this article we will discuss the current state of eyecare services, as well as the challenges faced by eye doctors in treating and managing eye problems, in this article. There are many hurdles to using eye care services, and administrators and providers must understand them.

2. FACTORS AFFECTING THE USE OF VISION CARE

There are three primary factors: availability, affordability, and accessibility of eye care services, which could influence the prevention of visual impairment worldwide. Also, several secondary factors such as demographic, personal, and socio-economic factors may act as barriers to utilizing the available, accessible, and affordable eye care services. All these factors interact to influence the likelihood of an individual's using health care services [9,10]. Factors such as cost, lack of awareness, cultural beliefs, and personal factors have been identified as barriers to eye care utilization [11]. Lack of awareness that causes visual impairment is preventable; non-availability of accessible and affordable services are the leading causes of blindness and visual impairment.

3. EYE CARE SERVICES AVAILABILITY

The availability of eye care services varies globally. The number of eye care providers per million in the richest countries is maybe nine times more than in the poorest countries [12]. Even within a country, the availability of services may vary from region to region, from district to district, even from one community to another. Poor practitioner-to-patient ratios, absence of eye-care personnel, inadequate facilities, insufficient state funding, and lack of educational programs have been considered the hallmarks of impediments in the utilization of eye care services in India. The disproportionate distribution of optometry and ophthalmological services between rural and urban areas in many developing countries may increase the rate of visual impairment in rural areas. Lack of trained personnel and infrastructure has been identified as a barrier to refractive error corrections. Over 43% of the population never had an eye examination [13]. non-availability of low cost, good quality low vision services, and lack of experts or training to support services have hindered the supply of low vision care services in developing countries [14]. In Afghanistan, eye care services are reported to be insufficient both in quantity and quality. The ophthalmologist to population ratio has been estimated as 1:200 000, and the poor distribution compounds this inadequacy among urban (87%) and rural areas (13%) [15]. In Nigeria, the unavailability of low vision devices and lack of awareness in low vision services were significant barriers to inadequate vision care [16]. It should be emphasized that non-availability is not the only barrier to the utilization of eye care services. Lewallen and Courtright [17] reported that cataract surgeries are low in many places due to deficit skilled human resources and supplies, even in areas where services are available. About 33-92% (India, Brazil, and Malawi) of people with the cataract remain blind, even when the services are available [17].

4. CONVENIENCE TO EYE CARE SERVICES

Accessibility to eye care services can be calculated by the time required to reach the nearest eye care, providers. Non-affordability and poor accessibility of the services among rural areas are identified as important indications for the high prevalence of blindness [12]. A proper access to preventive services is essential for asymptomatic detection, disease prevention, and identifying risk factors at an early treatable stage [18]. The underutilized eye care settings in urban areas avert the eye care services necessary for the underserved and unattended rural residents. Significant barriers to these services among visually impaired patients in rural areas are the poor conditions of the roads, transportation facilities, and distance from the rural areas that impact the surgeries, and the eye care services [12, 19, 20, 21, 22, 23] resulting in poor accessibility. Similar evidence was collected from the various studies on the poor accessibility for utilization of eye care services in rural areas [10, 13, 24] Ophthalmic services in Malawi are more likely to be practiced in the areas near district hospitals [25].

5. THE AFFORDABILITY OF EYE CARE

The eye care services are also affected by the monetary impact. Evidence explained the financial issues influencing eye services in developed and developing countries [26]. Poverty can be a significant concern among the rural areas around the globe because people are not able to afford the expense of eye care services and so issues that should have been dealt with at an early stage are not attentive, resulting in low vision and blindness [7, 13]. The reason for not using eye care services could also be personal or socio-economic issues [27]. According to Naidoo and colleagues, the affordability of optometric services should be considered in a wider context against the cost of the spectacle because even a free pair of spectacles could prove inexpensive if the patient has to go back to the clinic many times to collect [28]. The biggest obstacle was due to the indirect costs of the services [29]. Habte and colleagues indicated that the indirect cost of surgery was one of the key obstacles to surgical care for trachomatous trichiasis in northern Ethiopia [30]. Rabiu and Moyet stated that the price was the most common reason not to seek cataract surgeries in parts of Nigeria [31, 32].

Nedgwa and colleagues similarly stated that the lack of money was one of the main obstacles in the eye care services in Kenya [33]. The barrier to cataract surgery was most frequently seen in the Gambia [21]. Chandrashekhar et al. [22] found that the most common reason not to undergo cataract surgery among visual acuity patients less than 6/60 in rural South India was an inability to afford surgery. Similarly, Dhaliwal and Gupta also found that cost and affordability are associated with barriers to surgery in India [23]. Kovai et al. [34] also found that approximately half of rural Andhra Pradesh's populations, South India, cited economic reasons for not seeking care even after observed decreased sight. Nepal alone reported that non-surgical expenses is one-fifth of the rural patient's annual income [35], and finance described by Sapkota et al. as one of the obstacles to cataract surgery in the Gandaki Zone of Nepal [36]. The cost of cataract surgery in Pakistan were described as a significant barrier [37]. Palagyi et al. reported that low utilization of eye care services among rural dwellers in Timor-Leste was the inability to afford transport to eye care service centers. Affordability is, therefore, one of the significant barriers to eye care utilization [19].

6. FACTORS INFLUENCING THE AVAILABILITY, ACCESSIBILITY, AND AFFORDABILITY OF SERVICES

Several factors may influence utilization where accessible and affordable eye care services are available. Given the available eye care services, there has been under-use of available eye care services in the Iranian population [36]. About one-third of the survey participants had never had an eye test, and two-fifths of the visually impaired population had never received an eye care service [38].

In some villages in India where eye camps have taken place, only 7 % of people with eye problems prefer eye care [39]. In India, despite current sustained eye care services, which maxim a doubling of cataract output to 3.5 million in 2000, more than 40% of those with bilateral blindness had never visited an eye doctor [40]. Factors such as demographic profiles, awareness, needs and psycho-social issues impacting the use of safe, effective and reliable eye care services as discussed below.

6.1 Age

In South India, Kovai and colleagues found a substantial correlation between age and vision loss. They indicated this could be due to health preferences for the period in rural areas as age affects follow-up health choices [34]. In a study of glaucoma sufferers in rural South India, Robin and colleagues found that the use of eye care increased dramatically with age. This was due to the very fact that most eye diseases occurred during adulthood [7].

In addition, Schaumberg et al. stated that the probability of using eye care services increased with advancing age due to the higher prevalence of diseases such as diabetes, hypertension, cataract, and associated maculopathy. He also recorded that older American women were more likely to have a frequent eye examination than younger women [41]. Other authors found a correlation between older age and eye care facilities, which was linked to adult health issues [42, 43].

6.2 Gender

Foutouhi and colleagues reported that ladies in Iran were more likely to follow eye care services than men [38]. Other studies reported older African American males with diabetes were less likely to use eye care services than females. Such studies indicate that women are more vigilant about their eye health than men and that gender affects eye care use. Males listed waiting for the cataract to mature more than females, while females (24.9 per cent) recorded "no one to accompany" almost twice as much as males (14.2 per cent) in other studies [12].

6.3 Education Level

Fotouhi and colleagues stated that the probability of eye care in Iran was related to higher education [38]. This relationship was due to increased knowledge and, therefore, to more reasonable behaviour. It was also assumed that because educated people are members of a higher socio-economic class, they could have greater access to eye care services and find them more affordable. Barraza and colleagues reported a positive association between education and eye care use; higher education, the more likely and timely eye examinations are performed. Therefore, the less likely blindness is to occur [44]. Robin et al. [26] found among people with glaucoma in rural South India, the utilization of eye care increased with increasing education. Foran et al. found that people with qualifications after high school were less likely to have an uncorrected visual impairment [45]. Kovai et al. [34] studied in rural Andhra-Pradesh found that most rural populations were illiterate and blind and did not seek eye care services.

6.4 Socioeconomic Status

The socio-economic status has been found to influence the use of eye care services. Zhang et al. found that eye-care facilities were more likely to use people with voluntary insurance and people with higher incomes [46]. Robin and colleague recorded higher the subject's salary, the chances of utilizing eye care dramatically increased. Several other authors also reported a less likely eye examination in individuals with lower socio-economic status [22, 42, 47, 48-52]. Foran and colleagues found a link between the use of eye care, good job and homeownership [45]. However, Laitinen et al. [53] did not find such an association.

6.5 Awareness about Eye Diseases and Eye Care Services

If the eye care services are available, affordable, and accessible, the services will not be used by the target population. In a study conducted in Melbourne, Australia, & India, it was found that low utilization of eye care services was due to a lack of knowledge of available eye care services [13, 23]. In a study on the use and barriers to cataract surgical services in rural South India, Chandrashekar et al. found that the reason for the underuse of eye care services among the agricultural population was lack of awareness of the prevailing free-of-cost services offered by non-governmental organizations and low-cost eye surgical services [22]. Bhagwan et al. found that inadequate knowledge about eye disorders such as cataracts was reported, and respondents were ignorant of the possibility of recovering their sight by surgery [39]. One of the reasons for the under-use of eye care facilities in the rural population of South Africa was a lack of understanding of the services [11]. Lack of information on resources [25] became the most reported hurdle to the initiation of cataract surgery. Better education in the prevention of blindness can help to reduce the prevalence of visual impairment. Research showed that awareness of available eye care resources improved the utilization of eye care services [19, 22,

39, 41, 54]. Muller and colleagues found that, after a public health initiative using metropolitan and regional television, radio and newspaper in Australia, there has been an increase in the use of eye care facilities, particularly for people with diabetes [55]. Health education actions will be expressly tailored to improve understanding of an early diagnosis of symptom-free diseases [56]. The need for unfulfilled refractive error correction among school-aged children has been identified as necessary in China for parental education and an enhanced school-based screening program [57]. Kovai and colleagues suggest that the predominance of personal factors, such as lack of information among respondents, has demonstrated that a greater understanding of the value of pursuing help for visual disability is required to promote the availability of eye care services [34].

6.6 Referral

Lack of awareness on the referral criteria to L.V.C. service among ECPs was the major barrier for referral of patients of low vision, which primarily affected the uptake of L.V.C. services [13].

6.7 Need

There is a consensus that the utilization of eye care services varies with needs. Keeffe and colleagues reported that the likelihood of using eye care services increased significantly with symptoms and overall health status [58]. Schaumberg and colleagues indicated that the risk of eye treatment increased with eye disorders such as cataract, age-related maculopathy, and autoimmune diseases such as diabetes, hypertension, and rheumatoid arthritis [41]. Patients with vision disability with a more significant percentage of co-morbidities are most likely to receive eye care [59]. Palagyi and colleagues found that patients with a gradual loss in vision due to the cataract or refractive error are less likely than those with sudden onset or debilitating problems like eyes accidents to seek medication [19] Laitinen and colleagues found that people with mild visual impairments (VA 0.1 to 0.25 Log-MAR). At the same time, optical low vision aids are more likely to help, have more minor eye therapy, magnifying glasses, or other poor vision devices than individuals with extremely impaired vision (VA < 0.1) [53]. This is because the need was greater among those with poorer eyesight. Fong et al. found higher eye care utilization among older Australians, particularly those with correctable visual impairment [60]. Similarly, Tay et al. found a relatively high need for and high utilization rate of eye care services in the subgroup of older Australians seeking aged care services [61].

6.8 Psycho-social Factors

While blindness is avoidable or curable in most developing countries [57, 62-64], there are many obstacles to overcome, including social and cultural beliefs.[63, 65, 66] Patel et al. [66] reported that the main barriers to eye care services are social attitudes to visual health problems. Dhaliwal and Gupta indicated that the main barriers to the use of eye care have much to do with the habits of the individual, such as the ability to do everyday work given despite poor vision or cataract not matured. The anxiety of surgery and the risk of surgery causing death were other obstacles [23]. Such barriers have been identified more frequently than accessibility and cost [23] one of the most common reasons for not being subjected to cataract surgery has been fear of intervention [21] several studies reported that (70.69%) needed surgery when unable to visualize things. Rabiu et al. [26] said the principal obstacles to cataract surgeries were service expenditure (61%) and improved vision (18%) [9]. Snellingen et al. reported economic (48%) and logistical (44.8%) constraints followed by fear of surgery (33.3%) and lack of time (18.8%) to be the most frequent reason for not accepting surgery [27]. whereas (24%) bilateral blind (33%) unilateral blind wait for the cataract to mature. According to Ashaye et al. [56] many people are still blind because of obstacles, such as beliefs and attitudes, especially in developing regions. The authors found that the beliefs and attitudes of the predominantly rural population are still significant barriers to the utilization of eye care services in Nigeria. This was identified as a major contributor to the lack of use in rural Canadian communities of health services [67]. The most common reason for the non-cataract surgery was fear of surgery and the feeling that such surgery wasn't necessary [22]. Strabismus (tropical or squint) has not been considered treatable

in some areas of India and is not considered a sign of good luck due to vision loss [59]. In most such cultures, children under four years of age still felt it was not appropriate to wear spectacles; others felt the vision of children could not be tested regularly. They felt children's vision had to be checked only if there was a problem for the parents or caregiver or if a child complained [60]. Owsley et al. [68, 69] reports on the importance of preventive strategies and available treatment. Older African Americans do not prioritize eye care as other aspects of health. Elliot et al. found that not having any symptoms and being too busy were a part of the frequently mentioned reasons for not seeking eye care [70]. Oduntan and Raliavhegwa [11] found in South Africa that traditional and personal beliefs regarding Western eye care services include barriers to eye care use in rural communities. Instead of seeking eye care from government hospitals, the authors found that fifty of the research population would consult traditional healers with eye problems even if public eye services were readily available and accessible [12]. The use of remedial shows was deemed particularly unorthodox, and the fear of being mocked was followed by blindness [11]. Peer pressures and parental worries regarding the health of show use have been established in Tanzania as an obstacle to spectacles use by children in high school [31]. Therefore, skepticism of local opticians prescribing procedures and the desire for complementary to conventional vision impairment diagnosis are among the most barriers to the use of eye care services [24].

6.9 Perception

Consumer satisfaction is an essential factor in the sustainable utilization of health care, and it has been reported that dissatisfaction is a barrier to eye care utilization [28]. One reasons for the inefficient use of Indian government health facilities were the fact that general nurses offer care at primary health centers, and these centers are not necessarily fitted with the requisite services [23]. A study reported dissatisfaction with treatment was one of the key barriers to eye care utilization, and satisfaction with treatment from private services was higher than that for government and emigrant service providers [29]. To ensure equal, appropriate and efficient eye treatment, the operation must be increased and efficiency set, along with an improvement in expenses. One mechanism through which this can be achieved is by developing, implementing, and monitoring standards procedures for treatment and clinical guidelines.

6.10 Other Factors

The obstacles to the use of eye care, including low vision care, have been identified as factors such as language barriers and poor systemic health [28, 34, 35, 70]. Social involvements and lack of support may be a barrier to eye care. The main reasons for not having surgery to treat trachomatous trichiasis in Northern Ethiopia included the burden of chores [38], and one of the common reasons for not undergoing cataract surgery among patients with V.A. less than 6/60 in rural South India was the inability to find someone to accompany the patient to surgery [23]. The planning and policies making could improve the utilization of services and surgeries. However, even when surgery is free and transport facilities are available, the rates of cataract acceptance are low, as indicated in the population database of India [58]. In the last few decades, the availability of services has increased significantly in preventing blindness. However, lack of affordability remains an issue and a significant barrier. Recent studies from Andhra Pradesh also reported economic reasons as one of the leading barriers to the uptake of services [58]. Affordability was the leading barrier (41%), like that found in Tamil Nadu (78.2%) and another urban area study of Andhra Pradesh [3, 9, 18, 20]. Tamil Nadu and Karnataka reported more fear of surgery or visual results after surgery. In contrast, Fotouli et al. [38] found a substantial relationship between ocular service consumption and highest educational level, claiming highly educated people are more likely to seek ophthalmic care. Sloan FA et al. [71] found in their study that During the four 15-month follow-up periods, one quarter had only one eye examination total. Patient groups with diagnosed DM had the lowest usage of all three.

7. CONCLUSION

Many factors may serve as obstacles to the use of eye care services. Such aspects must be familiar to healthcare administrators and practitioners. Eye care services must be made available, accessible, and affordable. Factors may then be found and addressed which may act as barriers to their use. Routine planning for rural eye care services must address the eye care barriers perceived by communities to enhance eye care demand and services. Sufficient advertising, good patient performance and efficient overall performance of the eye. To prevent avoidable blindness, the promotion of eye care and awareness of available eye care services must be intensive, and the implications of delayed eye care must be emphasized. Rural communities need to study attitudes and cultural factors and provide adequate education to reduce worldwide vision and blindness. Eye care providers need to start educating people in early life about the role and use of health care resources. Ophthalmic services are not available in rural areas, hence this study indicated grossly poor utilization. The use of nonprescribed eye drops and herbal treatments was forced onto some rural people.

8. RECOMMENDATION

Rural people should be prioritized for public health education and eye care. Many vision-impairing and blinding eye disorders can be avoided with these measures.

ACKNOWLEDGEMENTS

The authors acknowledge the immense help received from the scholars whose articles are cited and included in references to this manuscript. The authors are also grateful to authors/editors/publishers of all those articles, journals, and books from where the literature for this article has been reviewed and discussed."

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. World Health Organization (WHO). Elimination of affordable visual disability due to refractive errors:report of an informal planning meeting (WHO/PBL/00.79) Geneva: World 2000 [Internet] [Last accessed on 3-5 July 2000]
   Available:https://apps.who.int/iris/handle/10665/67800.
2. Lewallen S, Courtright P 2001. Blindness in Africa:present and future needs. Brit J Ophthalmol. 2001;85:897-903.
3. Brilliant GE, Brilliant LB. Using social epidemiology to understand who stays and who gets operated for cataract surgery in a rural setting. Soc Sci Med. 1985;21:553-558.
4. Nwosu SNN. Beliefs and attitude to eye diseases and blindness in Anambra State, Nigeria. Nig J Ophthalmol. 2002;1:16-20.
5. Frick KD. Foster A. The magnitude and cost of global blindness. An increasing problem than can be alleviated. Am J Ophthalmol. 2003;135:471-476.
6. Kluass V, Schaller UC. Tropical Ophthalmological prevention and therapy. Vision 2020:The right to sight. Ophthalmol. 2004;101:764-765.
7. Oduntan AO, Nthangeni, ME, Ramudzuli, MR, Madu, SN. Causes and prevalence of low vision and blindness in black South African adults in the Limpopo province. S Afr Optom. 2003;62:8-15.
8. Onyeluche CE. Constraints to optometric practice in the third world. J Am Optom Assoc. 1993;64:710-715.
9. Andersen R. Revisiting the behavioural model and access to medical care:Does it matter? J Health Soc Behave. 1995:36:1-10.

10. Bradley EH, McGraw SA, Curry L, et al. Expanding the Andersen model: the role of psycho-social factors in long-term care use. Health Serv Res. 2002;37(5):1221-1242.
11. Oduntan AO, Raliavhegwa M. An evaluation of the impact of the eye care services delivered to the rural communities in the Mankweng Health sub-district of the Northern Province. S Afr Optom. 2001;60:71-76.
12. Silva JC, Bateman JB, Contreras F. Eye disease and care in Latin America and the Caribbean. Surv Ophthalmol. 2002;47:267-274.
13. Sarika G, Venugopal D, Sailaja MV, Evangeline S, Krishna Kumar R. Barriers and enablers to low vision care services in a tertiary eye care hospital:A mixed-method study. Indian J Ophthalmol. 2019;67:536-40.
14. Khan SA. Setting up low vision services in the developing world. Comm Eye Health. 2004;17:17-20.
15. Husainzada R. Situation analysis of human resources in eye care in Afghanistan. Community Eye Health. 2007;20(61):12. PMID:17637861;PMCID:PMC1919448.
16. Okoye OI, Aghaji AE, Umeh RE, Nwagbo DFE, Chukwu A. Barriers to the provision of clinical low vision services among ophthalmologists in Nigeria. Vis Imp Res. 2007;9:11-17.
17. Lewallen S, Courtright P. Recognizing and reducing the barrier to cataract surgery. Comm Health. 2000;13:20-21.
18. Di Stefano A. The challenge of leadership for the new millennium. Am J Optom. 2002;73:339-349.
19. Palagyi A, Ramke J, du Toit R, Brian G. Eye care in Timor-Leste:a population–based study of utilization and barriers. Clin Exp Ophthalmol. 2008;36:47-53.
20. Cochrane GM. Access, affordability and appropriate optometric eye care. S Afr Optom. 1995;54:42-43.
21. Johnson JG, Goode SV, Faal H. Barrier to uptake of cataract surgery. Trop Doct. 1998;28:218-220.
22. Chandrashekar TS, Bhat HV, Pai RV, Nair SK. Coverage, utilization and barriers to cataract surgical services in rural South India, Results from a population based study. Pub Health. 2007;121:130-136.
23. Dhaliwal U, Gupta S. Barriers to uptake of cataract surgery in patients presenting to a hospital. Indian J Ophthalmol. 2007;55:133-136.
24. Odedra N, Wedner SH, Shigongo ZS, Nyalali K, Gilbert C. Barriers to spectacle use in Tanzanian Secondary School students. Ophthal Epidemiol. 2008;15:410-417.
25. Courtright P, Kanjaloti S, Lewallen S. Barriers to acceptance of cataract surgery among patients presenting to district hospital in rural Malawi. Trop Geog Med. 1995;47:15-18.
26. Robin A, Nirmalayan P, Ramasamy K, Rengappa R, Katz J, Tielsch J, Ravilla D, Friedman M. The utilization of eye care services by persons with Glaucoma in rural South India. Trans Am Ophthalmol Soc. 2004;102:47-52.
27. Dandona R, Dandona L, Naduvilath TJ, McCarthy CA, Rao GN. Utilization of eye care services in an urban population in Southern India. Pradesh Eye disease study. Brit J Ophthalmol. 2000;84:24-27.
28. Naidoo K, Savage B, Westerfall B. Creating a sustainable spectacle delivery solution. Vision 15 July/ August 2006.
29. Melese M, Alemayehu W, Friedlander E, Courtright P. Indirect cost associated with assessing eye care services as a barrier to service use in Ethiopia. Trop Med Int Health. 2004;9:426-431.
30. Habte D, Gebre T, Zerihun, Assefa Y. Determinants of uptake of surgical treatment for trachomatous trichiasis in North Ethiopia. Ophthal Epidemiol. 2008;15:328-333.
31. Rabiu MM. Cataract blindness and uptake of cataract surgery in a rural community of Northern Nigeria. Brit J Ophthalmol. 2001;85:776-780.
32. Mpyet C, Dineen, BP, Solomon AW. Cataract surgical coverage and barriers to uptake of cataract surgery in leprosy villages of the North Eastern Nigeria. Brit J Ophthalmol. 2005;89:936-938.
33. Nedgwa LK, Karimurio J, Okelo RO, Adala HS. Barriers to utilization of eye care services in Kibera slums of Nairobi. East Afr Med J. 2005;82:506-509.
34. Kovai V, Krishnaiah S, Shamanna BR, Thomas R, Roa GN. Barriers to accessing eye care services among visually impaired population in rural Andhra Pradesh, South india. Indian J Ophthalmol. 2007;55:365-371.

35. Gold D, Zufela B, Hodge WG. Perspectives on low vision in Canada:a pilot study. Can J Ophthalmol. 2006;41:328-354.
36. Sapkota YD, Pokharel GP, Dulal S, Byanju RN, Maharjan IM. Barriers to uptake of cataract surgery in Gandaki Zone, Nepal. Kathmandu Univ Med J 2003;2:103-112.
37. Lewallen S, Courtright P. Recognizing and reducing the barrier to cataract surgery. Comm Health. 2000;13:20-21.
38. Fotouhi A, Hashemi H, Mohammed K. Eye care utilization patterns in Tehran population:A population based cross-sectional study. Brit J Ophthalmol. 2006;6:4-12.
39. Bhagwan J, Rastogi I, Malik J, Dhull C. Knowledge, attitude and practices regarding cataract surgery among severe cataract cases in Hanyana. Indian J Comm Med. 2006;31:66-68.
40. Di Stefano A. The challenge of leadership for the new millennium. Am J Optom. 2002;73:339-349.
41. Schaumberg D, Christen W, Glynn R, Buring J. Demographic predictors of eye care utilization among women. Med Care. 2000;38:638-646.
42. Morales LS, Varma R, Paz SH, Lai MY, Mazhar K, Andersen RM, Azen SP, Los Angeles Latino Eye Study Group. Self-reported use of eye care among Latinos: Los Angeles Latino Eye Study. Ophthalmol. 2010;117:207-215.
43. Kuang TM, Tsai SY, Hsu WM, Cheng CY, Liu JH, Chou P. Correctable visual impairment in an elderly Chinese population in Taiwan: The Shipah Eye Study. Invest Ophthalmol Vis Sci. 2007;48:1032-1037.
44. Barraza J. The role of educational attainment in utilization of eye care services by Medicare recipients with diabetes mellitus. Medicare. 1998;15:253-54.
45. Foran S, Rose K, Wang JJ, Mitchell P. Correctable visual impairment in an older population:the blue mountain study. Am J Ophthalmol. 2002;134:712- 717.
46. Zhang X, Lee PP, Thomson TJ, Sharma S, Bake L, Geiss LS, Imperatore G, Gregg EW, Zhang X, Saaddine JB. Health insurance coverage and use of eye care services. Arch Ophthalmol. 2008;126:1121-1126.
47. Orr P, Barron Y, Schein OD, Rubin GS, West SK. Eye care utilization by older Americans. Ophthalmol. 1999;106:905-909.
48. Baker H, Murdoch IE. Can a public health intervention improve awareness and health seeking behaviour for glaucoma? Brit J Ophthalmol. 2008;92:1671-1675.
49. Baker, R.S, Bazagarn, M, Bazagarn-Hejazi, S, Calderón JL. Access to vision care in an urban low-income multiethnic population. Ophthal Epidermiol. 2005;12:1-12.
50. Liou HL, McCarthy CA, Jin CL, Taylor HR. Prevalence and predictors of under-corrected refractive errors in the Victorian population. Am J Ophthalmol. 1999;118:264-269.
51. Munoz B, West SK, Rodriquez J, Sanchez, R, Broman AT, Snyder R, Klein R. Blindness, visual impairment and problems with uncorrected refractive error in a Mexican-American population: Proyecto VER. Invest Ophthalmol. 2002;43:608-614.
52. Thiagalingam S, Cumming RG, Mitchell P. Factors associated with under-corrected refractive errors in an older population: the Blue Mountains Eye Study. Br J Ophthalmol. 2002;86(9):1041-1045.
53. Latinen A, Koskinene, S, Rudanko S-L, Martelin T, Laatikainen L, Aromaa A. Use of eye care services and need for assistance in the visually impaired. Optom Vis Sci. 2008;85:341-349.
54. Farmer J, Iversen L, Campbell NC, Guest C, Chesson R, Deans G, Macdonald J. Rural /Urban differences in accounts of patients' initial decision to consult primary care. Health and Place. 2006;12:210-221.
55. Muller A, Keeffe JE, Taylor HR. Changes in eye care utilization following an eye health promotion campaign. Clin Exp Ophthalmol. 2007;35:305-309.
56. Ashaye A, Ajuwon A, Adeoti C. Perceptions of blindness and blinding conditions in rural communities. J Nat Med Assoc. 2006;98:887-893.
57. Lewallen S, Courtright P. Blindness in Africa:present and future needs. Brit J Ophthalmol. 2001;85:897-903.
58. Keeffe JE, Weih LM, McCarty CA, Taylor HR. Utilization of eye care services by urban and rural Australia. Brit J Ophthalmol. 2002;86:24-27.
59. Nirmalayan P, Sheeladevi D, Tamilselvi S, Victor A, Vijayalakshmi P, Rahmathulla L. Perception of eye disease and eye care needs of children among parents in rural South India:The Kariapatti Pediatric Eye Evaluation Project (KEEP). Comm Eye Care 2004;2:163-167.

60. Fong CS, Wnag JJ, Rochtchina E, Schneider J, Jakobsen KB, Smith W, Mitchell P. Survey of effect on use of eye care by older persons with correctable visual impairment. Ophthal Epidemiol. 2009;**16:**249-253.
61. Tay T, Rochtchina E, Mitchel P, Lindley R, Wang JJ. Eye care service utilization in older people seeking aged care. Clin Exp Ophthalmol. 2006;34:141-145.
62. Brilliant GE, Brilliant LB. Using social epidemiology to understand who stays and who gets operated for cataract surgery in a rural setting. Soc Sci Med. 1985;21:553-558.
63. Nwosu SNN. Beliefs and attitude to eye diseases and blindness in Anambra State, Nigeria. Nig J Ophthalmol. 2002;1:16-20.
64. Frick KD. Foster A. The magnitude and cost of global blindness. An increasing problem than can be alleviated. Am J Ophthalmol. 2003;135:471-476.
65. Fletcher AE. Low uptake of eye health in rural India. A cultural challenge of blindness prevention. Arch Ophthalmol. 1999;117:1393-1399.
66. Patel D, Baker H, Murdoch I. Barriers to uptake of eye care services in the Indian population living in Ealing, London. Health Educ J. 2006;65:267-276.
67. Pampalon R, Martinez J, Hamel D. Does living in rural areas make a difference for health in Quebec? Health and Place. 2005;12:421-435.
68. Jadoon Z, Shah SP, Bourne R, Dineen B, Khan MA, Gil bert CE, Foster A, Khan MD. Cataract prevalence, cataract surgery coverage and barriers to uptake of cataract surgery service in Pakistan. The Pakistan national blindness and visual impairment survey. Brit J Ophthalmol. 2007;91:1260-1273.
69. Owsley C, McGwin G, Scilley K, Girkin C, Phillips J, Searcey K. Perceived barriers to care and attitudes about vision and eye care:Focus groups with older African Americans and eye care providers. Invest Ophthalmol Vis Sci. 2006;47:2797-2802.
70. Elliot AF, Chou CF, Zhang X, Crews JE, Saaddine JB, Beckles GL, Owens-Gary MD. Eye care utilization among women aged 40 years with eye diseases in 19 states (2006-2008). Morb Mort Weekly Report. 2010;59:588-591.
71. Sloan FA, Yashkin AP, Chen Y. Gaps in receipt of regular eye examinations among medicare beneficiaries diagnosed with diabetes or chronic eye diseases. Ophthalmology. 2014 Dec 1;121(12):2452-60.

Biography of author(s)

Gaurav Dubey
Optometry Faculty, Department of Optometry, Faulty of Paramedical Sciences, UPUMS, Saifai, Etawah, U.P., India.

Author is currently pursuing a PhD in Optometry and having more than 15 years of experience in Optometry. His active contribution to various academic activities like Academic Projects, Research Programs, Eye-Campaign, and National Level Conferences across India meets the higher domain of pedagogy for up-gradation and upliftment of Students, Profession, and University. He earned MOH Oman Optometry License. Seven National Academics Awards formerly felicitated him for promoting the Optometry profession. The Optometry Council of India & Indian Optometry Federation felicitates him for creating Awareness in Optometry. Currently, he is a review board member across several International Journals and has published more than 46 research papers in National and International Journals. The author has published 04 book chapters and two books entitled: Textbook of Clinical Optometry and Handbook of Ocular Terminology. Two of his books entitled 1] "Comprehensive-Ophthalmic lenses, Frames, and Clinical Dispensing" and 2] Professional Ethics is currently in press with a reputed publisher. Besides these achievements author have granted two design patent.

Ragni Kumari
Amity Institute of Public Health, Amity University, Noida, U.P., India.

Author has completed her Master of Clinical Optometry from Amity University, Haryana. She is pursuing a Ph. D. in Public Health from Amity Institute of Public Health, Amity University, Noida, U.P. Author has 15 years of academic and clinical experience. She also has post-graduation in MBA (Hospital Management and Supply Chain Management). She was former and founder of HOD & Assist Professor, Department of Optometry, Era University, Lucknow. She has published more than 30 articles in national and international journals. The author has published 02 book chapters and two books entitled: 1] Indian medicine & Telemedicine and as Co- Author 2] Handbook of Ocular Terminology. She was appointed as a reviewer for many national and international journals; she has been awarded international women researcher awards. She is very keen interested in research, learns, and help others.

Assistant Professor Jamshed Ali
Department of Optometry, Allied Health Science IIMT University, Meerut, U.P, India.

Author is an author of great integrity with a high reputation and confidence. He is working as an Assistant professor and in charge of optometry, collage of Allied Health Sciences, IIMT University Meerut, UP. He completed his Master of Optometry from Amity medical School Amity University Gurugram Haryana. He is a member of the optometry council of india. He has an administrative officer in optometry, IIMT University Meerut, and a mentor and mentee policy committee, member. He is an

experienced optometrist with excellent skills and commended performance in analysing optometric assays and resolving complex clinical and instrumental problems. He has published more than 10 scientific papers in national and international journals of repute. He was awarded Amity Marathon 10 km, winner.

Assistant Professor Vibha Kumari
Department of Paramedical Sciences, Jamia Hamdard New Delhi, India.

Author has more than of 5years of Experience in Optometry. She is actively involved in various academic projects, Research Programs, National and International conferences etc. and presented many papers across India. She has 14 research publications and 02 chapters. Optometry Council of India has felicitated her for spreading awareness in the field of Optometry. She has an active contribution in organising eye camps for the less privileged population of the society.

Assistant Professor Prasenjit Das
Department of Optometry, School of Nursing Science, ITM University, Gwalior, M.P, India.

Research and Academic Experience: 2 Years

Research Area: Binocular vision, public health, Contact lens, Low Vision, Paediatric Optometry, Vision Therapy

Number of Published papers: 1

Special Award: Amity Marathons 10 km winner, Badminton winner in TIPS, Award from Rotary Club, Special appreciation award from Amity University

Assistant Professor Simi Afroz
Department of Allied Health Science, Sharda University, U.P, India.

Research and Academic Experience: 1 Years

Research Area: Public health, Contact lens, Low Vision, Paediatric Optometry, Vision Therapy

Number of Published papers: 1

Assistant Professor R. K. Manik
[7]Department of Optometry, Subharti University, Meerut, U.P., India.

Research and Academic Experience: Two year

Research Area: Optometry

Number of Published papers: Two

Nitika Kumari
Department of Paramedical Sciences, Jamia Hamdard, New Delhi, India.

Research and Academic Experience: 5

Research Area: Myopia progression and low vision

Number of Published papers: 02

Rajeev Trivedi
Ansal Medical School, Sushant University, Gurugram, Haryana, India.

Research and Academic Experience: 2 yrs.

Research Area: Sports Vision

Dr. Mahesh Chandra
Department of Ophthalmology, Dr. Sushila Tewari Hospital & Govt. Medical College, Haldwani, Uttarakhand, India.

Research and Academic Experience: Total 15 Years of experience in clinical including 6 Year in research

Research Area: Clinical Optometry, Community Health

Number of Published papers: 35

Special Award: Emerging Scientist Awards

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
J Ophthalmol Res, 3(2): 45-56, 2020.

Chapter 7
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

A Retrospective Evaluation of Morbidity Pattern and Outcome of Patients Admitted in Paediatric Intensive Care Unit in a Tertiary Care Rural Teaching Hospital

Deepali A. Ambike[1*] and Vijay L. Bhavari[2]

DOI: 10.9734/bpi/rdmmr/v8/13854D

ABSTRACT

Background: The care of severely unwell children continues to be one of the most demanding and difficult elements of paediatrics. The primary goal of the Paediatric Intensive Care Unit is to avoid death by closely monitoring and treating severely ill children who are at high risk of dying. There is a scarcity of data on paediatric critical care in developing countries. The efficacy of treatment can be determined by evaluating the outcomes of medical interventions. This aids in better decision making, improving care quality, and, if necessary, changing management's future direction. This study will also aid in the investigation of the causes of morbidity and mortality among children in our hospital. The study's goals and objectives are to evaluate the morbidity pattern and outcomes of admissions in the PICU of a rural teaching hospital, as well as to take measures to prevent morbidity and mortality by improving critical care facilities.
Methods: This was a retrospective study of cases admitted to our teaching hospital's paediatric ICU in the last two and a half years, taking into account the estimated sample size. Data will be gathered from the PICU and the Medical Records Department. The medical record will be used to study the details, which will then be analysed and interpreted based on the medical record details.
Results: A total of 417 patients were admitted to our PICU over the course of the study's 30 months. Of the total cases studied, Maximum i.e. 180(43.2%) had age below 1 year. The minimum – maximum range of age was between 1 day to 18 years. About 228(54.7%) cases were males and 189(45.3%) were females. LRTI was the most common diagnosis, accounting for 61 (14.7%) of cases. The respiratory system was the most frequently involved system, accounting for 101 (21.8%) of all cases. 357 (85.6 %) of the total cases studied were discharged, 36 (8.6 percent) had DAMA (discharge against medical advice), and 24 (5.8%) expired.
Conclusions: Mortality was low in our PICU. Based on the findings of this study, we conclude that in our rural PICU, with better treatment protocols and skilled expertise/Pediatric Intensivist, we have a better chance of facilitating the care of critically ill patients and achieving a favourable outcome.

Keywords: Critical care; expertise; mortality; morbidity; PICU admission; Survival.

1. INTRODUCTION

The history of intensive care for children holds the key to understanding its current practise. “The past matters more than we realize…we walk on its ground, and if we don’t know the soil we are lost”. The origins of modern paediatric critical care can be traced back to the development of adult intensive care and neonatal intensive care [1]. Intensive care has become critical in the care of critically ill children. The care of critically ill children is still one of the most demanding and difficult aspects of paediatrics. The primary goal of the PICU is to avoid death by closely monitoring and treating

[1]Department of Pediatrics, YCM Hospital, Pimpri, Pune, Maharashtra, India.
[2]Department of Pediatrics, MIMER Medical College, Talegaon Dabhade, Pune, Maharashtra, India.
**Corresponding author: E-mail: ambikedeepa@gmail.com;*

severely sick children who are at high risk of dying. Although patient mortality is affected by a variety of factors such as the population's demographic and clinical characteristics, infrastructural and non-medical factors (administration and organisation), case mix, and admission practises, , it is also affected by ICU performance [2]. *Intensive care has become very important in the management of critically ill children who require advanced airway, respiratory, and hemodynamic supports and are usually admitted into the pediatric intensive care unit with the aim of achieving an outcome better than if the patients were admitted into other parts of the hospital. It becomes important to audit admissions and their outcome, which may help to modify practices if necessary following thorough introspection, leading to better patient outcomes [3].* The neonatal period is a highly vulnerable time for an infant completing many of the physiologic adjustments required for life outside the uterus. As a result, there are high rates of morbidity and mortality. The three major causes of mortality in developing countries include prematurity, infection, and perinatal asphyxia [4].

With the advancement in intensive care facilities, there is a dramatic increase in survival of critically ill children. Previous studies have shown significant positive impact of ICU physicians on the outcome in both children and adults. We, therefore, analyzed the data of our PICU to find out the pattern of diseases and outcome at our center which would help in proper resource allocation and better management of critically ill children [5].

2. METHODS

This is a retrospective study based on the data collected from the Paediatric Intensive Care Unit (PICU) at BSTR hospital and MIMER Medical College Talegaon pune from the January 2016 to July 2018. Study population was the patients admitted in the PICU during this study period.

2.1 Inclusion Criteria

All patients admitted in PICU underage group of 18 yearsduring study period.

2.2 Statistical Methods

The data on categorical variables is shown as n (% of cases). Being an observational non-comparative study, we did not compare the distributions of several categorical variables studied statistically. The entire data was entered and cleaned in MS Excel before its statistical analysis.

All results are shown in tabular as well as graphical format to visualize the frequency distributions of variables studied more clearly. The entire data is statistically analyzed using Statistical Package for Social Sciences (SPSS version 21.0, IBM Corporation, USA) forMS Windows.

The hospital is accredited with five bedded modern PICU which admits pediatric patient's ≤18 years of age. PICU records of all admissions, transfer out, discharges, discharge against medical advice (DAMA) and death were utilized for the purpose of study. Data included Age, sex, diagnosis, duration of stay at PICU; outcome asfar as unit is concerned was taken for study.

All patients in the unit were treated according to the written standard protocol. Relevant investigations including haemoglobin, total and differential leukocyte count, electrolytes, urea, creatinine, blood glucose, blood culture and arterial blood gas were done at admission. Blood tests were repeated subsequently whenever required. Cerebrospinal fluid analysis was done for suspected central nervous system infections. Treatment was started as per the protocol. Antibiotic therapy was modified whenever necessary depending upon the culture and sensitivity pattern. Vasopressors were used for patients in shock or poor perfusion.

3. RESULTS

During a period of 30 months of the study, total of 417 patients were admitted in this PICU at BSTR hospital andMIMER Medical College Talegaon, Pune.

Table 1. Age distribution

Age Group (years)	No. of cases	% of cases
≤1.0 year	180	43.2
1-2 years	58	13.9
2-5 years	59	14.1
>5 years	120	28.8
Total	417	100.0

Table 2. Sex distribution

Sex	No. of cases	% of cases
Male	228	54.7
Female	189	45.3
Total	417	100.0

Of 417 cases studied, 180(43.2%) had age below 1 year, 58(13.9%) had age between 1-2 years, 59(14.1%) had age between 2-5 years and 120(28.8%) had age above 5 years. The minimum-maximum range of age was 1 day to 18 years. Maximum number of patients belonged below 1 year age group, which can be attributed to lesser immunity.

Of 417 cases studied, 228(54.7%) were males and 189 (45.3%) were females. The male to female sex ratio in theentire study group was 1.21:1.0

Of 417 cases studied, the most common diagnosis was LRTI which was observed in 61(14.7%) of cases. This could be related to some epidemiological factors related to our area.

Table 3. Distribution of diagnosis

Diagnosis	No. of cases	% of cases
LRTI	61	14.7
Febrile convulsions	59	14.1
Insect / Snake Bite	34	8.2
Acute Gastroenteritiswith dehydration	39	7.2
Viral fever	28	6.7
URTI	36	8.6
Hyperbilirubinemia	13	3.1
Dengue Fever	18	4.3
Congenital HeartDisease	18	4.3
Pyrexia of unknownorigin	18	4.3
Head injury	16	3.8
Seizure disorders	14	3.4
Sepsis	14	3.4
Poisoning	14	3.4
Type 1 DiabetesMellitus	6	1.4
Meningitis	5	1.2
Anemia	5	1.2
Hepatitis	4	1.0
ABO isoimmunisations	4	1.0
Protein energy malnutrition (PEM)	4	1.0
Meningoencephalitis	3	0.7
Nephrotic Syndrome	2	0.5
Asthma	2	0.5
Total	417	100.0

Of 417 cases studied, 357(85.6%) were discharged, 36 (8.6%) had DAMA(discharge against medical advice) and 24(5.8%) expired. Of 417 cases studied, the most common system involved was respiratory system which was observed in 101(21.8%) cases. This could be related to some typical epidemiology in this area.

Table 4. Distribution of outcome

Outcome	No. of cases	% of cases
Discharge	357	85.6
DAMA	36	8.6
Expired	24	5.8
Total	417	100.0

4. DISCUSSION

The PICU is a special unit primarily concerned with the care of patients with critical illness and demands a broad based knowledge to achieve good outcome. Advances in pediatric sub-specialties including the critical care medicine have improved the survival of sick children. During the 30 months study period, a total of 417 children were admitted to the 5 bedded PICU. Majority of the patients were males (54.7%) a finding similar to a study by Sahoo et al, and the Nigerian Study [6,2]. Of the 417 cases studied, 180(43.2%) had age below 1 year, 58(13.9%) had age between 1-2 years, 59(14.1%) had age between 2-5 years and 120(28.8%) had age above 5 years. The minimum-maximum range of age was 1 day to 18 years. Maximum number of patients belonged below 1 year age group which was same as in Sahoo et al, Nigeria and Nepal study [6,5]. This study revealed that the most common system involved was respiratory system which was observed in 101(24.2%) cases., followed by Septicaemia/ Infectious diseases in 21.5% cases and Neurological system in 17.7% cases followed by Gastrointestinal in 14.3% cases. Our finding was similar to Sahoo et al, [6] and Nepal study [5] but in Nigerian study, cardiovascular cause was leading [2].

Table 5. Distribution of systemic involvement

System involved	No. of cases	% of cases
Respiratory	101	24.2
Multi-organ/ Sepsis	90	21.5
Neurological	74	17.7
Gastrointestinal	60	14.3
Poisoning	27	6.5
Surgical	18	4.3
Cardiovascular	18	4.3
Haematological	9	2.1
Endocrinological	8	1.9
Genitourinary	4	1.0
Nephrology	3	0.7
Autoimmune	2	0.5
Dermatology	1	0.2
Metabolic	1	0.2
Psychological	1	0.2
Total	417	100.0

Our most common diagnosis was LRTI (14.7%) of all cases, followed by febrile convulsions (14.1%) cases. Similar findings were seen in Nepal and Brazilian study but contradictory to the AIIMS Delhi study and others [4,7,8,9]. where Septicaemia was the commonest diagnosis. This shows that paediatric intensive care admissions vary in different countries and one should be aware of the prevalent conditions to develop the facilities and prepare treatment protocols accordingly.

Of the cases studied, 357(85.6%) were discharged, 36(8.6%) had DAMA (discharge against medical advice) and 24(5.8%) expired. Overall mortality in the study was 5.8% which was similar to Sahoo et al, (4.1 % but higher than Nigerian Study, 2.1 % and lower than Nepal study, 12.6% [2,5]. Our set up was a resource limited setting with lack of manpower both doctors and Nurses, lack of technical expertise/ Intensivist, less Nurses per patient and lack of specialised equipments. However as compared to other studies with good set-up, our mortality rate was acceptable [10-14].

The present study had a number of limitations. First it was based on secondary data, extracted retrospectively. This database did not contain information on the length of PICU Stay of each patient and also prior stay in the paediatric ward. Secondly, there is no mention of co- morbidities in this data and not reflecting on the study. Hence adequate analysis of the effect of each of these sources may have had on the length of the stay andmortality could not be done.

5. CONCLUSION

We conclude based on the present study that in this rural set up PICU , Mortality was low .We conclude based on the present study that in this rural set up PICU, with better treatment protocols, skilled expertise/ Paediatric Intensivist we have chances to facilitate the care of critically ill patients giving desirable outcome.

ETHICAL APPROVAL

The study was approved by theInstitutional Ethics Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Fuhrman BP, Zimmerman JJ. Pediatric Critical CareE-Book. Elsevier Health Sciences; 2016.
2. Abhulimhen-Iyoha BI, Pooboni SK, Vuppali NK. Morbidity pattern and outcome of patients admitted into paediatric ICU in India. Ind J Clin Med. 2014;51-5.
3. Mridha D, Saha S, Ganguly S, Bose K. A Retrospective Evaluation of Morbidity Pattern and Outcome of Patients Admitted into a Pediatric Intensive Care Unit in India. J Med Sci Clin Res. 2017;5(11):30586-90.
4. Demisse AG, Alemu F, Gizaw MA, Tigabu Z. Patterns of admission and factors associated with neonatal mortality among neonates admitted to the neonatal intensive care unit of University of Gondar Hospital, Northwest Ethiopia. Pediatric health, medicine and therapeutics. 2017;8:57.
5. Shah GS, Shah BK, Thapa A, Shah L, OP M. Admission patterns and outcome in a paediatric intensive care unit in Nepal. Br J Med Res. 2014;4(30):4939-45.
6. Sahoo B, Patnaik S, Mishra R, Jain MK. Morbidity pattern and outcome of children admitted to a paediatric intensive care unit of Eastern India. Int J Contemp Pediatr. 2017 Mar;4:486-9.
7. Kapil D, Bagga A. The profile and outcome of patients admitted to a pediatric intensive care unit. Ind J Pediatr. 1993;60(1):5-10.
8. El Halal MG, Barbieri E, Mombelli Filho R, de Andrade Trotta E, Carvalho PR. Admission source and mortality in a pediatric intensive care unit. Ind J Crit Care Med. 2012;16(2):81-86.
9. Khilnani P, Sarma D, Singh R, Uttam R, Rajdev S, Makkar A, Kaur J. Dempgraphic profile and outcome analysis of tertiary level paediatric intensive care unit. Indian J Paediatrics. 2004; 1(2):161-6.
10. Haque et al. Clinical profile and outcome in a paediatric intensive care unit in Pakistan. J Coll Physicians Surg Pak. 2009;19(8):534-35.
11. Tilford JM, Roberson PK, Lensing S, Fiser DH. Differences in pediatric ICU mortality risk over time. Crit Care Med. 1998;26(10):1737-43.
12. Earle M, Natera OM, Zaslavsky A, Quinones E, Carrillo H, Gonzalez EG, Torres A, Marquez MP, Garcia-Montes J, Zavala I, Garcia-Davila R. Outcome of pediatric intensive care at six

centers in Mexico and Ecuador. Crit Care Med. 1997;25(9):1462-7.
13. Pollack MM, Katz RW, Ruttimann UE, Getson PR. Improving the outcome and efficiency of intensive care: the impact of an intensivist. Crit Care Med. 1988;16(1):11-7.
14. Goh AY, Lum LC, Chan PW. Brief report. Paediatric intensive care in Kuala Lumpur, Malaysia: a developing subspecialty. J Trop Pediatr. 1999;45(6):362-4.

Biography of author(s)

Deepali A. Ambike
Department of Pediatrics, YCM Hospital, Pimpri, Pune, Maharashtra, India.

Research and Academic Experience: Total 20 Research Publications, Both National & International Publications. Total Academic & ResearchExperience 23 years in various private medical colleges and presently in Maharashtra Govt PG Institute at Pimpri, Pune.

Research Area: Neonatology, Critical care

Number of Published papers: 20

Special Award (If any): Distinction in UG, Gold Medal in DCH. Best teacher award by DR D.Y Patil Medical college, Pimpri, Pune in 2002

Vijay L. Bhavari
Department of Pediatrics, MIMER Medical College, Talegaon Dabhade, Pune, Maharashtra, India.

Research and Academic Experience: 13 Years

Research Area: Pediatrics Intensive Care

Number of Published papers: 06

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
International Journal of Contemporary Pediatrics, 6(5): 2064-2067, 2019.

Chapter 8
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Determination of Isolated Lesion of the Lateral Pectoral Nerve due to Repeated Trauma

Faik Budak[1], Buket Özkara[1*] and Emre Aydın[1]

DOI: 10.9734/bpi/rdmmr/v8/5066F

ABSTRACT

We present two cases of progressive isolated damage to the lateral branch of the pectoral nerve with marked atrophy of the clavicular portion of the major pectoral muscle. In our patients, the mechanism of isolated lesions of lateral pectoral nerves have been attributed to repetitive external microtraumas and pressure on the nerve trajectory between the chest and shoulder during sports or occupational activities. With this case report, we aimed to consider that repetitive microtraumas can cause isolated nerve damage.

Keywords: Pectoral nerve; pectoralis major muscle; nerve compression

ABBREVIATIONS

LPN : Lateral Pectoral Nerve
NCS : Nerve Conduction Studies
EMG : Electromyography
MRI : Magnetic Resonance Imaging

1. INTRODUCTION

The lateral pectoral nerve (LPN) sub serves the proximal two thirds of the pectoralis major muscle. It does not contain cutaneous sensory fibers. Clinical findings of lateral pectoral nerve injury include asymmetry of chest wall associated with atrophy and weakness of the pectoralis major muscle. Mononeuropathy of the lateral pectoral nerve occurs less frequently [1-4]. In this report we present two cases of progressive atrophy and weakness of the clavicular part of pectoralis major muscle innervated by lateral pectoral nerve.

2. CASE 1

A twenty-six years old man, who had progressive atrophy of the right clavicular portion of pectoralis major muscle accompanied by pain on the right chest and shoulder for three months, was referred to our neurology outpatient clinic. He was a worker of an automotive plant. He had been working in a leaning position at a narrow place with his right arm stretched out. At this position he had to lean up and forward and pounding tools were causing an intermittent but chronic load on the right side of his chest and his right shoulder. On a follow- up physical examination, asymmetry of the lateral pectoral region was noted due to moderate atrophy of the pars clavicularis of the right pectoralis major muscle (Figs 1 and 2). There was no tenderness on the chest or shoulder. Motor strength, deep tendon reflexes and sensation of the upper extremites were normal. Nerve conduction studies (NCS) demonstrated prolonged motor latency and decreased amplitude of the right lateral pectoral nerve. (Right 3.3 msec and 2,4 mV; Left 2.1 ms and 6.3 mV) (Table 1). Needle electromyography (EMG) of the right clavicular portion of pectoralis major muscle revealed a few denervation potentials, increased number of polyphasic motor units with decreased recruitment and suggestive of an axonal

[1]Kocaeli University, School of Medicine, Department of Neurology, Umuttepe Campus, 41380 Kocaeli-Turkey.
**Corresponding author: E-mail:buketozkara4188@hotmail.com*

injury. EMGs of the other muscles were within normal limits, as were NCS of the upper extremities. Magnetic Resonance Imaging (MRI) of the cervical spinal cord and brachial plexus were normal. Following a period of physiotherapy including soft tissue mobilization in combination with exercise program and changes in labor circumstances, the patient progressively recovered normal muscle bulk in approximately six months.

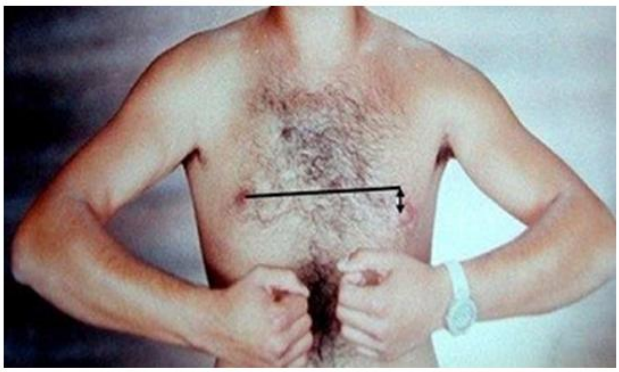


Fig. 1. Pronounced areolar asymmetry due to atrophy of right pectoral muscle in case 1

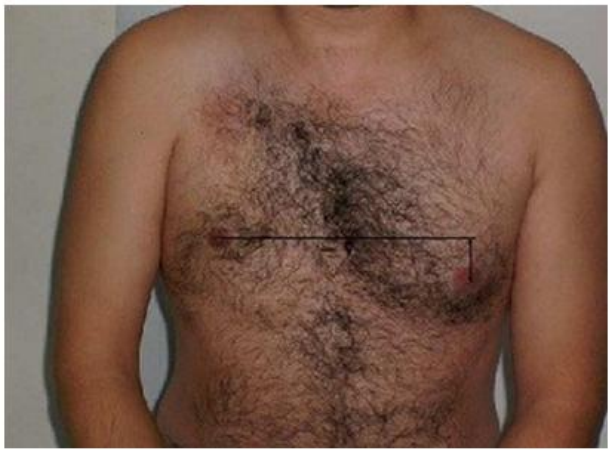


Fig. 2. Pronounced areolar asymmetry due to atrophy of right pectoral muscle in case 2

Table 1. Nerve conduction studies (NCS) demonstration

	Distal Latency (m/s)	Amplitude (m/V)	Velocity (m/s)
Lat. Pectoral, R	3.3	2.4	32.8
Lat. Pectoral, L	2.1	6.3	54.2

3. CASE 2

A twenty-two years old man noticed progressive wasting and weakness of his right chest muscle. Six months earlier, the patient had undertaken a rigorous, intensive program of supervised, kick-boxing training, involving repeated fists to the region between the chest and the shoulder. Examination showed moderate atrophy with visible contraction of the pars clavicularis of the right pectoralis major muscle. (Figs 3 and 4). Motor strength, deep tendon reflexes and sensation of the upper extremites were normal. NCS demonstrated prolonged motor latency and decreased amplitude of the right lateral pectoral nerve (Right 3.5 ms, 2.1 mV; Left 2.2 ms, 5.9 mV) (Table 2). EMG of pars clavicularis of the right pectoralis major muscle revealed dense denervation activity decreased voluntary motor unit potentials (MUAPs) which were of polyphasic. EMG and NCS of the other muscles and nerves of

the upper extremities were normal. MRI of the cervical spinal cord and brachial plexus were normal. The patient received physiotherapy and rested the affected regions; there was mild atrophy of the right pectoralis major muscle at his sixth month follow- up.

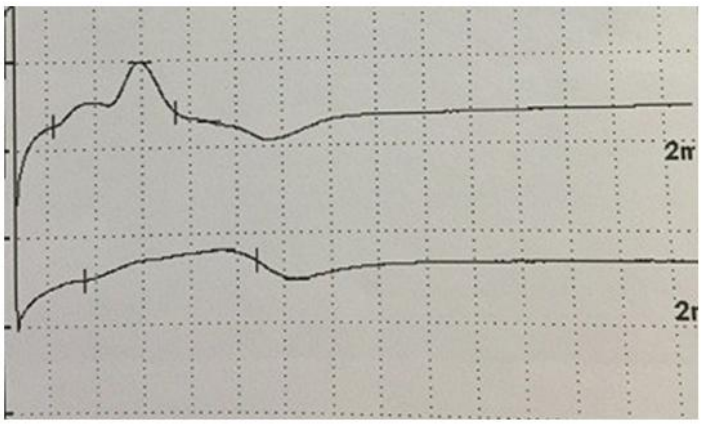


Fig. 3. Lateral pectoral nerve conduction in a normal control subjects. (A) Needle (upper trace) and surface (lower trace) recording in the pectoralis major muscle by Erb stimulation. (B) Needle (upper trace) and surface (lower trace) recording in the pectoralis major muscle by axilla stimulation

Table 2. Nerve conduction studies (NCS) demonstration

	Distal latency (m/s)	Amplitude (m/V)	Velocity (m/s)
Lat. Pectoral, R	3.5	2.1	38.3
Lat. Pectoral, L	2.2	5.9	55.1

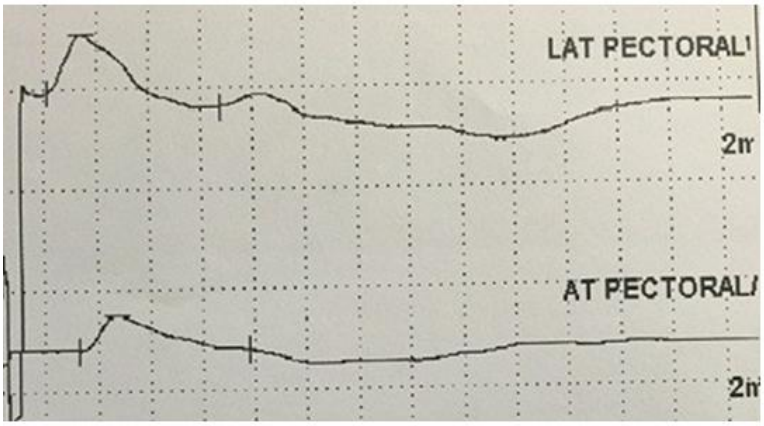


Fig. 4. Lateral pectoral nerve conduction in a patient with unilateral brachial plexopathy by Erb stimulation. Note the prolonged motor conduction time at the pathological side

4. DISCUSSION

Isolated injury of lateral pectoral nerve is unusual. In the literature there are cases described and attributed to nerve damage as a result of traction injuries, seat belt trauma and as a complication of mastectomy [1-3]. Two cases of non-acute damage to the lateral pectoral nerve were recently described by Gardetto in whom there were gradual development of focal pectoralis atrophy and weakness for two years following initiation of a high intensity weight training program [4].

Our cases were exposed to external forces on the nerve between chest and shoulder while using a

tool, or repetitive fists in a certain manner for a long period. The lateral pectoral nerve (LPN-lateral anterior thoracic) arises from the lateral cord of the brachial plexus, and through it from the fifth, sixth, and seventh cervical nerves. It passes across the axillary artery and vein, pierces the coracoclavicular fascia, and is distributed to the deep surface of the pectoralis major muscle. In our cases the sternocostal part of the muscle innervated by the medial pectoral nerve was spared.

5. CONCLUSION

Anatomical studies of this region showed that the nerve branches of the lateral pectoral nerve, having to pierce through a connective tissue septum that is thicker here by a few millimetres, may be subjected to a risk of compression [5]. In both of the cases there was no contraction of the clavicular part of pectoralis major muscle which is innervated by the lateral pectoral nerve. Based on the anatomy of the lateral pectoral nerves and medical history in the cases, the possible pathogenic mechanism causing traumatization of the lateral pectoral nerve is an external local mechanical compression due to sports or occupational activities [6,7]. These forceful repetitive traumas can heavily stretch or compress the lateral pectoral nerve while it passes through the thick clavipectoral fascia of the pectoralis major muscle. These traumatizations are also believed to cause intraneuronal ischemia and edema resulting nerve dysfunction [8]. Physiotherapy including exercise program to strengthen, resting the affected part, changes in the design of workstation or sport activities may also prevent further damage and permit recovery

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Birds SJ, Brown MJ. Acute focal neuropathy in male weight lifters. Muscle Nerve. 1996;19:897-899.
2. Marrero JL, Goldfine LJ. Isolated lateral pectoral nerve injury: trauma from a seat belt. Arch Phys Med Rehabil. 1989;70:239-240.
3. Giannini F, Cioni R, Paradiso C, Rossi S, D' Aniello C, et al. Neurophysiological evaluation of pectoralis major muscle after mastectomy. Int Rev Neurobiol. 1992;38:407-412.
4. Gardetto A, Thaler C, Kiechl S, Maurer H, Piza-Katzer H. Isolated Compression of pectoral nerve resulting in atrophy of the major pectoral muscle. Muscle Nerve. 2003;28:760-763.
5. Standring S, Ellis H, Healy JC, Johnson D, Williams A. Gray's Anatomy. (39th Edn). Edinburgh: Churchill Livingstone. 2005;835:836, 847.
6. Ryvedik B, Lundborg G, Bagge U. Effect of graded compression on intraneural blood flow. J Hand Surg Am. 1981;6:3-12.
7. Larionov A, Yotovski P, Link K, Filgueira L. Innervation of the clavicular part of the deltoid muscle by the lateral pectoral nerve. Clinical Anatomy. 2020;33(8):1152-8.
8. Tessema CB. Abrant origion and distribution of pectoral nerves with prominent ansa pectoralis and absent lateral pectoral nerve. Int J Anat Var. 2020;13(2):1.

Biography of author(s)

Buket Özkara
Kocaeli University, School of Medicine, Department of Neurology, Umuttepe Campus, 41380 Kocaeli-Turkey.

Research and Academic Experience:
1-F.Budak, B.Ozkara, Benign Episodic Mydriasis, J Neurol Epidemiol,2016, 2309-6179
2-F.Budak, B.Ozkara, A.Kockaya, E.Aydın, İsolated VerticalOphtalmoplegia and Mydriasis due to Bilateral Midbrain İnfarction,J Neuro Epidemiol 2016; 2309-6179,
3-F.Budak, H.Kaya, B.Ozkara, Neurobehçet's Disease Presented with One and a Half Syndrome; J Neurol Epidemiol, 2016; 2309-6179
4-F.Budak, B.Ozkara, E.Aydın, İsolated Lesion of the Lateral Pectoral Nerve due to Repeated Trauma; J Neurol Neurophysiol, 2017: 8:1
5-B.Ozkara, F.Budak, İsolated Horizontal Gaze Palsies As Presenting Symptoms İn Multipl Sclerosis, EJMI; 2018.91885
6-B.Ozkara, F.Budak, Bilateral Facial Paralysis,EJMI; 2017: 1(3):00-00DOI: 10.14744/ejmi.2017.97752
7-B.Ozkara, M.Ozcan, F.Budak; Fahr Syndrome with Fluctuation in Consciousness and Temporary Vision Loss; Archives in Neurology and Neuroscience; 2019; ISSN: 2641-1911
8-Buket Özkara, Yiğit Can Güldiken, Faik Budak, Özge Demirkol, Sedat Gül; Evaluation of 52 patients with Guillain Barré syndrome between 2015 and 2019 in Kocaeli, Turkey – An epidemiological study; Ref: Ro
J Neurol. 2020;19(4) DOI: 10.37897/RJN.2020.4.10 9-Buket Özkara, Faik Budak, İntracranial Superficial Siderosis, Turk J Neurol, 2015; 21: 168-170
10-Buket Özkara, Faik Budak, Spinal Muscular Atrophy With Myoclonic Epilepsy, Epilepsi, 2016.08860/DOI:10.44744
11-Buket Özkara, Faik Budak, Optic Neuritis After İnfluenza Vaccination, Turkiye Klinikleri J Neur, 2016; 11(3):73-75

Research Area: Neurology

Number of Published papers: 11

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Journal of Neurology & Neurophysiology, 8(1): 2017.

Chapter 9
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Evidence of Woven Bone Formation in Carotid Artery Plaques: A Recent Study

Mirzaie Masoud[1*], Zaur Guliyev[1], Michael Schultz[2], Peter Schwartz[2], Johann Philipp Addicks[3] and Sheila Fatehpur[1]

DOI: 10.9734/bpi/rdmmr/v8/1978C

ABSTRACT

Objective: Plaque morphology plays an important prognostic role in the occurrence of cerebrovascular events. Echolucent and heterogeneous plaques, in particular, carry an increased risk of subsequent stroke. Depending on the quality of the plaque echogenicity based on B-mode ultrasound examination, carotid plaques divide into a soft lipid-rich plaque and a hard plaque with calcification. During onset of thrombembolic events in arteresclerosis, vulnerable plaques play an important role. The aim of this study was to investigate structural changes in the basement membrane of different carotid artery plaque types.
Patients and Methods: Biopsies were taken from 10 male patients (average age; 75 + 1 years) and 7 females (68 + 3 years). The study population included patients suffering from a filiform stenosis of the carotid artery, 8 patients with acute cerebrovascular events and 9 with asymptomatic stenosis. Scanning electron and polarised light microscopic investigations were carried out on explanted plaques to determine the morphology of calcified areas in vascular lesions.
Results: By means of scanning electron microscopy, multiple foci of local calcification were identified. The endothelial layer was partially desquamated from the basement membrane and showed island-like formations. Polarised light microscopy allows us to distinguish between soft plaques with transparent structure and hard plaques with woven bone formation.
Conclusion: The major finding of our study is the presence of woven bone tissue in hard plaques of carotid arteries, which may result from pathological strains or mechanical overloading of the collagen fibers. These data suggest a certain parallel with sclerosis of human aortic valves due to their similar morphological characteristics. The detection of woven bony tissue suggests that inadequate strain favours the mineralization of carotid plaques.

Keywords: Woven bone; carotis artery plaques.

1. INTRODUCTION

In addition to the degree of stenosis, analysis of the internal morphological structure of the plaques is becoming an increasingly important, contributory factor in stroke risk. Compared with calcium-containing “hard plaques”, plaques with a high lipid content are associated with an increased risk of ipsilateral cerebral ischemia [1,2]. Most of the trials emphasizing the relationship between plaque echo structure and stroke risk are based on high-resolution ultrasound (US) using a visual method of classification [3,4]. To date, the plaques of carotid arteries are divided into friable, fibroatheromatous and atheromatous forms [5]. In a previous study on explanted human aortic valves, calcified areas showed characteristic morphological features of woven bone formation [6]. In this report, we describe the morphology of plaques of carotid arteries using polarised light microscopy in addition to conventional electron microscopical techniques. Especially, we were interested in the identification of bony structures mimicking valve calcification.

[1]Department of Vascular Surgery, Lippe-Lemgo Hospital, University clinics OWL, Germany.
[2]Institute for Anatomy, University of Göttingen, Göttingen, Germany.
[3]Institute of Neuroradiology, Lippe-Lemgo Hospital, University Clinics OWL, Germany.
**Corresponding author: E-mail: masoud.mirzaie@klinikum-lippe.de;*

2. MATERIALS AND METHODS

2.1 Tissue Biopsies

Tissue samples from the carotid artery were taken from patients undergoing routine endarteriectomy of the carotid artery in operations at the Department of Thoracic, Heart and Vascular Surgery. 17 biopsies were taken from 10 male patients (average age; 75 + 1 years) and 7 females (68 + 3 years). The study population included patients suffering from filiform stenosis of the carotid artery. In 9 cases, stenosis of the carotid artery occurred without any symptoms, in 8 patients signs of circulatory disturbance of the vertebrobasila system or the carotid artery were observed. Table 1 summarizes the basic data of the study patients.

Table 1. Baseline characteristics of the study population

Male(n=10, age: 75 + 1 years)		Female (n=7, age: 68 + 3 years
Symptoms		
	Vertigo	4 (23.5%)
	Acoustic Aphasia	3 (17.6%)
	Paresis	
Previous surgeries	TEA of carotid artrey	1 (5.8%)
Concomitant Diseases		
	CHD	3 (17.6%)
	HLP	5 (29.4%)
	Smoking	9 (52.9%)
	Arterial Hypertension	10 (58.8%)
Statins		7 (41.1%)

Continous variables are presented as mean + standard deviation. Categorical variablesare presented as an absolute percentage.
Abbreviations: HLP: Hyperlipoproteinaemia, CHD: Coronary Heart Disease, TEA: Thrombendartriektomy

2.2 CT-Angiography

All patients underwent preoperative CT angiography in a 64-row CT scan. For this purpose, the bolus-triggered examination technique was used with a bolus of 80 - 100 ml KM at flow rates of 3-5 ml/s with scan velocities up to almost 10 cm/s after reaching an enhancement of 100 HU with a delay of 6-12 s. The source recordings were then reconstructed in 3-D technique.

2.3 Scanning Electron Microscopy

In order to reveal the surface morphology of the explanted valves, scanning electron microscopy was performed. Specimens from valve leaflets were fixed for 6h in a solution containing 2.5% glutaraldehyde and 0.2 M cacodylate. Afterwards, samples were dehydrated in a series of increasing concentrations of alcohol. After critical point drying, all samples were sputtered with gold-palladium. Samples were visualized using the digital scanning microscope Zeiss DSM 960.

2.4 Polarised Light Microscopy

To evaluate the presence of woven bone tissue in calcified areas of pathologically altered aortic and mitral valves, polarized light microscopy was performed. To prepare thin ground sections from non-decalcified materials for polarized light microscopy, a special technique was established based upon the method of plastination developed by Hagens, et al. and modified for histological purposes by Schultz and Drommer [7,8]. Samples were dehydrated using ascending concentration steps of alcohol, washed in methyl chloride as an intermediate solution for the exchange of substances and embedded in epoxy resin Biodur®. Unstained thin ground sections (30, 50 and 70 µm) were prepared

and viewed in (the) transmitted plane and in polarised light using a hilfsobject red 1st order (quartz), equipped with photo documentation [9,10].

2.5 Ethics

The Ethics Committee of the University of Göttingen has approved the investigations on expanted carotid artery plaques on patients to determine of woven bone formation in carotid artery (reference: 25/6/2010).

3. RESULTS

3.1 CT-Angiography Findings

The CT-angiography of a patient with soft plaque shows bilateral high-grade internal carotid stenosis due to artheromatous plaque. Compared to the vascular environment, hypodense concentric plaque is shown intraluminally. The lumen itself contrasts hyperdensely calcified plaque is not detectable (Fig. 1a).

The CT angiography of a patient with hard plaque also shows high-grade internal carotid stenosis due to calcifying plaques. There is hardly any evidence of hypodense internal plaques. A small hyperdensely contrasted lumen with extensive, bizarre, fissured calcifications, sometimes with adjacent hardening artefacts, is shown (Fig. 1b).

3.2 Scanning Electron Microscopical Findings

Fig. 2a demonstrates a conserved endothelium, whereas the surface of the observed plaques was uneven and partially broken open. Endothelial cells appeared to be hypertrophied (Fig. 2a). The endothelial layer was divided by small islands. At higher magnification, multiple initial tearings were observed and the matrix was uncovered. In these areas, incorporation of erythrocytes into the extracellular matrix was observed. Some large plaques were covered with a thin layer of endothelial cells (Fig. 2b, c).

3.3 Polarised Light Microscopical Findings

Recent techniques employing polarised light microscopy as described by Bloebaum, et al. are potentially useful to evaluate the presence of woven bone tissue [10]. Tissue samples from normal artery walls revealed no pathological alterations.

Polarised light microscopy enabled a distinction between two different types of plaques. In transmitted plane light, the collagenous fibers as well as intravascular deposits were transparent. Using a hilfsobject red 1st order, deposits looked lucent (Fig. 3a, b). When unstained thin ground sections of pathologically altered samples of the second group were viewed in transmitted plane light, the intravalvular localized inhomogeneous inclusions appeared as a secondary substance of yellowish or blue color (Fig. 3c). In regular light, the character of this substance could be described as fibrous resembling natural woven bone. At high magnification (620 x), bundles of collagen fibers were detected (Fig. 3d).

We detemine paque group 1 with evidence of woven bone formation in 4 patients with symptoms and 4 asymptomatic patients. The palque group without evidence of woven bone formations was found predominantly in symptomatic patients (5 symptomatic versus 3 asymptomatic patients). Nevertheless, a clinical correlation between plaque form and symptomatology cannot be deduced.

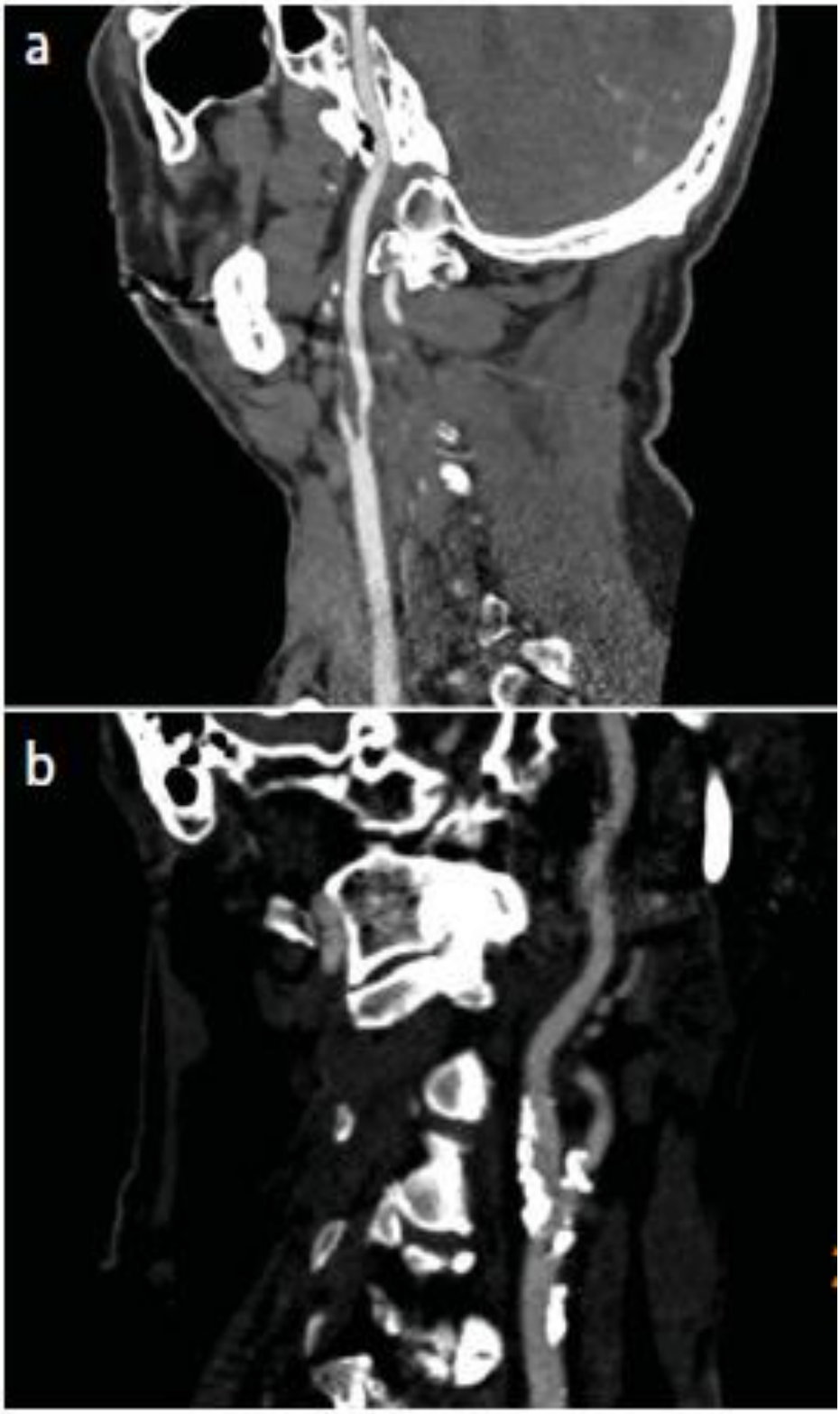


Fig. 1. a: CT-Angiographie finding from a patient with soft plaque: intraluminally hypodensic concentric plaque without calcified areas. b: CT-Angiographie finding from a patient with hard plaque: high-grade internal carotid stenosis with extensive, bizarrely fissured calcifications

Fig. 2. a: Scanning electron microscopical findings of internal carotid plaque (50 x magnification): the surface of the observed plaques was uneven and partially broken. b: Scanning electron microscopical findings of internal carotid plaque (200 x magnification): multiple initial tearings and the uncovered extracellular matrix. c: Scanning electron microscopical findings of internal carotid plaque (1000 x magnification): incorporation of erythrocytes into the extracellular matrix with partially thin layer of endothelial cells

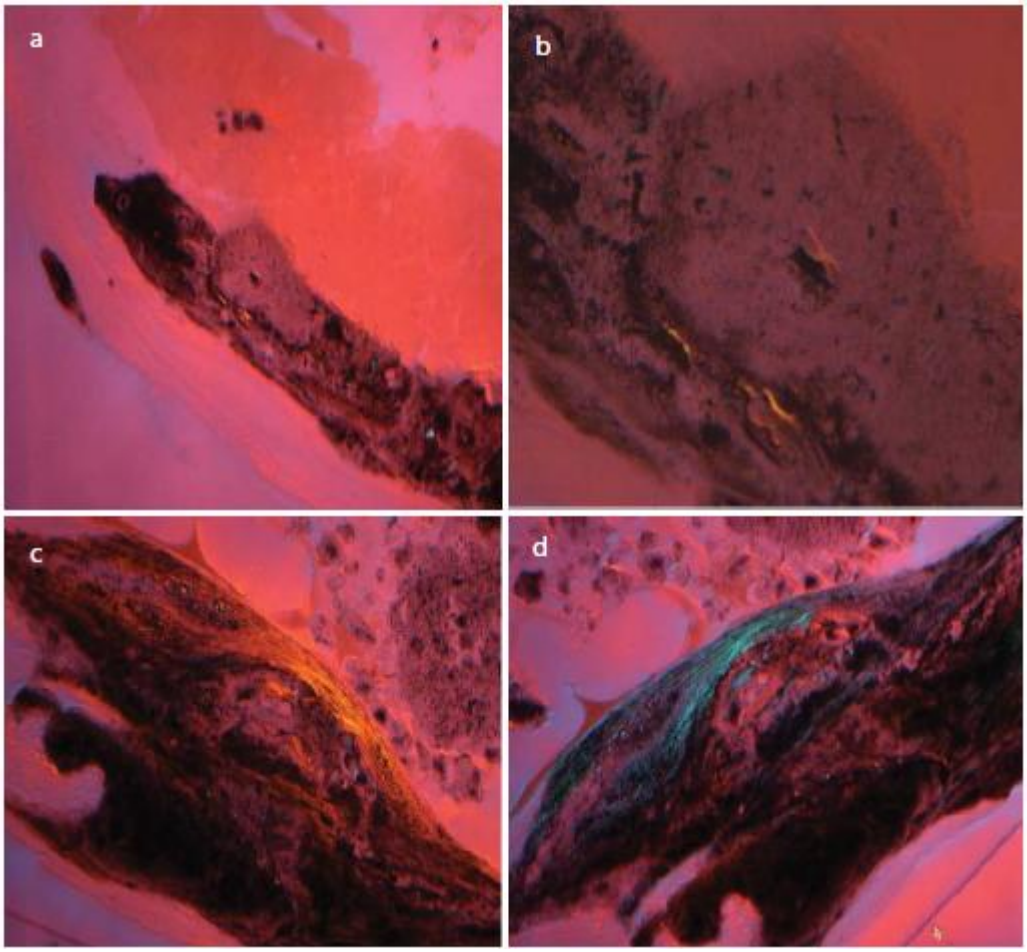


Fig. 3. a: Polarised light microscopical findings of internal carotid plaque: impressed hyaline, collagenous fibers and intravascular deposites apear in transmitted plane light transparent.
b: Polarised light microscopical findings of internal carotid plaque: lucent deposits using a hilfsobject red 1st order.
c: Polarised light microscopical findings of internal carotid plaque: the intravalvular localized inhomogeneous inclusions of calcified plaques represented as a secondary substance of yellowish or blue color.
d: Polarised light microscopical findings of internal carotid plaque: at high magnification (620 x) bundles of collagen fibers and blue color structures resembling natural woven bone

4. DISCUSSION

Thromboembolism from extra-cranial atherosclerosis accounts for the neurological deficit in approximately half of the patients with ischaemic stroke [9]. Selection for eradicating interventions is conventionally determined by measuring luminal stenosis that results from in situ atheromatous plaques [7-9]. Apart from the degree of stenosis, plaque morphology has emerged in recent years as an important contributory factor in stroke risk [3]. During onset of thrombembolic events in arteresclerosis, vulnerable plaques play an important role [10]. Histological studies of coronary atherosclerosis suggest that plaques can be identified by thin fibrous caps that overlie large, often necrotic lipid cores [11,12]. A multimodal assessment of plaque vulnerability involving the combination of systemic markers, new imaging methods, for example, ultrasonic investigation, ct-imaging and MRI that target inflammatory and thrombotic components, and the potential of emerging therapies may lead to a new stratification system for atherothrombotic risk and to a better prevention of atherothrombotic stroke [3-5,13-16]. Mechanisms of plaque rupture have been extensively studied

and several parameters have been found to interact: extracellular matrix, inflammatory cells, gelatinases, stromelysins, matrilysin and MMp expression induced by oxidised lipids etc. [17-22].

In a previous study on degenerative explanted human aortic valves, calcified areas were detected with characteristic morphological features of woven bone formation. Pathologically altered heart valves appear to exhibit distinct stages of desmal osteogenesis [6]. Formation of woven bone formation indicates an inappropriate biomechanical stress of collagenous fibers, potentially due to malsynthesis [23,24].

In this paper we report on our systematic SEM and polarized light microscopical investigations on explanted human carotid plaques. In all the samples, we detected uniform changes in the endothelium and the basement membrane. The endothelial cells often showed hyperplasia with loose binding to each other. Rarely, an endothelial layer was complete. The loss of endothelial cells may expose the extracellular matrix, which obviously sets various pathological processes in motion [25-28]. The increased activation of matrix metalloproteinases in pathologically altered human cardiac valves emphasizes the crucial role of the extracellular matrix in the development of this disease [28]. Similar mechanisms are held responsible for rupture of atherosclerotic plaques [21].

Polarised light microscopy identified two different types of plaques, a soft one with a transparent structure and without the presence of bone tissue, called soft plaques, and hard plaques with woven bone structures. These findings are probably identical with echolucent (predominant lipid core) und echo-opaque plaques (predominantly fibrous tissue/ calcium) as identified by sonography and magnetic resonance tomography [29-33]. The major finding of our study is the presence of woven bone tissue in hard carotid plaques. Dystrophic calcification first described by Mönckeberg is the most common pathological finding in surgically explanted valves [34]. Virchow recognized already that the mineralization of the walls of arteries in atherosclerosis is a process of ossification and not only a process of calcification [35]. Several case reports and clinical studies have identified bone proteins in ossified areas. The studies on the pathophysiology of heterotopic enchondral ossification in atherosclerotic plaque of arterial walls showed that osteoprogenitor cells resemble microvascular pericytes [36,37]. Myofibroblast-like cells, situated throughout the fibroid layer of cardiac valves and cultured in vitro, are capable of phenotypic differentiation into osteoblast-like cells [38,39]. Many authors, therefore, suggest the existence of a population of ossifying cells in both aorta and cardiac valves [36-40]. Atherosclerosis is a multifactorial, multistep disease that involves chronic inflammation as well as oxidation [36]. Detection of woven bone structure in pathologically altered human aortic valves and in carotid plaques indicates an additional pathogenic factor in the onset of atherosclerosis. In accordance with findings on human aortic valves, malsynthesis of collagenous fibers might contribute to pathogenesis of atherosclerosis of carotid arteries. Dystrophic calcification is a passive process in degenerating connective tissue, whereas heterotrophic ossification is an active process of abnormal tisssue repair. During the process of desmal ossification, collagen is produced which can easily be diagnosed by light microscopic examination using polarized light. The newly formed primitive woven bone separates intravalvular inclusions from surrounding collagen fibers [6].

The detection of woven bony tissue suggests that inadequate strain favours the mineralization of carotid plaques. The altered mechanical environment and the associated abnormal hemodynamic flow conditions may induce proliferative stimuli for the endothelium resulting in a combination of degenerative and hyperplasic responses. Pathological strains on the aortic walls finally result in the development of primary bundle bone-like tissue. The findings of the present and prior studies document the complex nature of atherosclerosis. Further studies employing biochemical and biophysical techniques may reveal the pathological basis of the underlying bony development and will help to understand the contribution of calcification in the context of atherosclerosis.

5. CONCLUSION

The submitted study demonstrated 2 fundamentally different carotid plaques. Whereas the first group shows a distinct of woven bone tissue, the second group completely lacks this tissue. In the past, we could demonstrate the woven bone tissue in degenerated aortic and mitral valves. We assume that, in

addition to flow physiocomechanical changes in blood flow, collagen metabolism disorders play a central role in the pathogenesis of carotid stenosis.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Moroni F, Ammirati E, Norata GD, Magnoni M, Camici PG. The role of monocytes and macrophages in human atherosclerosis, plaque neoangiogenesis, and atherothrombosis. Mediators Inflamm. 2019;7434376.
   PubMed:https://pubmed.ncbi.nlm.nih.gov/31089324/
2. Zhu G, Hom J, Li Y, Jiang B, Rodriguez F, et al. Carotid plaque imaging and the risk of atherosclerotic cardiovascular disease. Cardiovasc Diagn Ther. 2020;10:1048–1067.
   PubMed:https://pubmed.ncbi.nlm.nih.gov/32968660/
3. Johri AM, Nambi V, Naqvi TZ, Feinstein SB, Kim ESH, et al. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk. JASE. 2020;33:917-933.
   PubMed:https://pubmed.ncbi.nlm.nih.gov/32600741/
4. Momjian S, Lalive P, Sztajzel R. Carotid plaque: comparison between visual and grey-scale median analysis. Ultrasound Med Biol. 2003;29:961-966.
   PubMed:https://pubmed.ncbi.nlm.nih.gov/12878241/
5. Mughal MM, Khan MK, DeMarco JK. Symptomatic and asymptomatic carotid artery plaque, Expert Rev Cardiovasc Ther. 2011;9:1315–1330.
   PubMed:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243497/
6. Mirzaie M, Schultz M, Schwartz P. Evidence of woven bone formation in heart valve disease. Ann Thorac Cardiovasc Surg. 2003;9:163-169.
   PubMed:https://pubmed.ncbi.nlm.nih.gov/12875637/
7. Von Hagens G. Impregnation of soft biological specimens with thermostetting resins and elastomers. Anat Rec. 1979;94:247–255.
   PubMed:https://pubmed.ncbi.nlm.nih.gov/464325/
8. Schultz M, Drommer R. Possibilities of preparation production from the craniofacial area for macroscopic and microscopic examination using new plastics techniques. Exp Mund-KieferGesichts Chir. 1983;28:95–97.
9. Meershoek A, van Dijk RA, Verhage S. Hamming JF, van den Bogaerdt AJ, et al. Histological evaluation disqualifies IMT and calcification scores as surrogates for grading coronary and aortic atherosclerosis. Int J Cardiol. 2016;224:328-334.
   PubMed:https://pubmed.ncbi.nlm.nih.gov/27668706/
10. Nambi V, Chambless L, Folsom AR. He M, Hu Y, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: The ARIC (Atherosclerosis risk in communities) study. J Am Coll Cardiol. 2010;55:1600-1607.
    PubMed:https://pubmed.ncbi.nlm.nih.gov/20378078/
11. Toutouzas K, Karanasos A, Tousoulis D. Optical coherence tomography for the detection of the vulnerable plaque. Eur Cardiol. 2016;11:90–95.
    PubMed:https://pubmed.ncbi.nlm.nih.gov/30310454/
12. Hua Y. Chinese guidance on vascular ultrasound examination in stroke. Chin J Med Ultrasound. 2015;8:599-610.
13. Pelisek J, Wendorff H, Wendorff C. Age-associated changes in human carotid atherosclerotic plaques. Ann Med. 2016;48:541-551.
    PubMed:https://pubmed.ncbi.nlm.nih.gov/27595161/
14. Jinnouchi H, Sato Y, Sakamoto A, Cornelissen A, Mori M, et al. Calcium deposition within coronary atherosclerotic lesion: Implications for plaque stability. Finn Atherosclerosis. 2020; 306:85-95.
    PubMed:https://pubmed.ncbi.nlm.nih.gov/32654790/

15. Antipova D, Eadie L, Makin S. The use of transcranial ultrasound and clinical assessment to diagnose ischaemic stroke due to large vessel occlusion in remote and rural areas, PLoS One. 2020; 15: e0239653.
PubMed:https://pubmed.ncbi.nlm.nih.gov/33007053/
16. Ahluwalia N, Genoux A, Ferrieres J, Perret B, Carayol M, et al. Iron status is associated with carotid atherosclerotic plaques in middleaged adults. J Nutr. 2010;140:812–816.
PubMed:https://pubmed.ncbi.nlm.nih.gov/20181783/
17. Sun B, Zhao H, Liu X, Lu Q, Zhao X, et al. Elevated hemoglobin A1c is associated with carotid plaque vulnerability: Novel findings from magnetic resonance imaging study in hypertensive stroke patients. Sci Rep. 2016;6:33246.
PubMed:https://pubmed.ncbi.nlm.nih.gov/27629481/
18. Brophy ML, Dong Y, Wu H, Rahman HNA, Song K, et al. Eating the dead to keep atherosclerosis at bay. Front Cardiovasc Med. 2017;4:2.
PubMed:https://pubmed.ncbi.nlm.nih.gov/28194400/
19. Vaidya K, Martínez G, Patel S. The role of colchicine in acute coronary syndromes. Clin Ther. 2019;41:11-20.
PubMed:https://pubmed.ncbi.nlm.nih.gov/30185392/
20. Ruddy JM, Ikonomidis JS, Jones JA. Multidimensional contribution of matrix metalloproteinases to atherosclerotic plaque vulnerability: Multiple mechanisms of inhibition to promote stability. J Vasc Res.2016;53:1-16.
PubMed:https://pubmed.ncbi.nlm.nih.gov/27327039/
21. Alhendi AMN, Patrikakis M, Daub CO, Kawaji H, Itoh M, et al. Promoter usage and dynamics in vascular smooth muscle cells Exposed to fibroblast growth factor-2 or interleukin-1β. Sci Rep. 2018;8:13164.
PubMed:https://pubmed.ncbi.nlm.nih.gov/30177712/
22. Veseli BE, Perrotta P, De Meyer GRA, Roth L, der Donckt CV, et al. Animal models of atherosclerosis. Eur J Pharmacol. 2017;816:3-13.
PubMed:https://pubmed.ncbi.nlm.nih.gov/28483459/
23. Macdonald DS, Zhang L, Gu Y. Calcification of the external carotid arteries and their branches. Dentomaxillofacial Radiology. 2012;41(7):615-618.
24. Ohbayashi Y, Miyake M, Nagahata S. A long-term study of implanted artificial hydroxyapatite particles surrounding the carotid artery in adult dogs. Biomaterials. 2000;21(5):501-509.
25. Nikkari ST, O'Brien KD, Ferguson M, Hatsukami T, Welgus HG, et al. Interstitial collagenase (MMP-1) expression in human carotid atherosclerosis. Circulation. 1995;92:1393-1398.
PubMed:https://pubmed.ncbi.nlm.nih.gov/7664418/
26. Chen X, Cao X, Jiang H, Che X, Xu X, et al. SIKVAV-modified chitosan hydrogel as a skin substitutes for wound closure in mice. Molecules. 2018;23:2611.
PubMed:https://pubmed.ncbi.nlm.nih.gov/30314388/
27. Cheng S, Wang D, Jin Ke J, Ma L, Zhou J, et al. Improved in vitro angiogenic behavior of human umbilical vein endothelial cells with oxidized polydopamine coating. Colloid Surface B. 2020;194:111176.
PubMed:https://pubmed.ncbi.nlm.nih.gov/32540767/
28. Chia JS, Du JL, Hsu WB, Sun A, Chiang CP, et al. Inhibition of metastasis, angiogenesis, and tumor growth by Chinese herbal cocktail Tien-Hsien Liquid. BMC Cancer. 2010;10:175.
PubMed:https://pubmed.ncbi.nlm.nih.gov/20429953/
29. Latha S, Samiappan D, Kumar R. Carotid artery ultrasound image analysis: A review of the literature. Proc Inst Mech Eng H. 2020;234:417-443.
PubMed:https://pubmed.ncbi.nlm.nih.gov/31960771/
30. Saxena A, Kwee Ng EY, Teik S. Imaging modalities to diagnose carotid artery stenosis: progress and prospect, Bio Med Eng. 2019;18:66.
PubMed:https://pubmed.ncbi.nlm.nih.gov/31138235/
31. Banaei A. The comparison between digital subtraction angiography, CT angiography, and doppler ultrasonography in evaluation and assessment of carotid artery stenosis. Ann Mil Health Sci Res. 2017;15:e61661.
32. Correia M, Maresca D, Goudot G, Villemain O, Bizé A, et al. Quantitative imaging of coronary fl ows using 3D ultrafast Doppler coronary angiography. Phys Med Biol. 2020;65:105013.
PubMed:https://pubmed.ncbi.nlm.nih.gov/32340010/

33. Morbiducci U, Kok AM, Kwak BR. Atherosclerosis at arterial bifurcations: Evidence for the role of haemodynamics and geometry. Thrombosis and Haemostasis. 2016;115:484492.
PubMed:https://pubmed.ncbi.nlm.nih.gov/26740210/
34. Monckeberg JG. Normal histological construction and sclerosis of aortic valves. Virchows Archiv Pathol Anat Physiol. 1904;176:472-514.
35. Virchow R. Cellular pathology: as based upon physiological and pathological histology. Nutr Rev. 1989;47:23-25.
PubMed:https://pubmed.ncbi.nlm.nih.gov/2649802/
36. Yang P, Troncone L, Augur ZM, Kim SSJ, McNeil ME, et al. The role of bone morphogenetic protein signaling in vascular calcifi cation. Bone. 2020;115542.
PubMed:https://pubmed.ncbi.nlm.nih.gov/32736145/
37. Sun M, Chang Q, Xin M. Endogenous bone morphogenetic protein 2 plays a role in vascular smooth muscle cell calcifi cation induced by interleukin 6 in vitro. Int J Immunopathol Pharmacol. 2017;30:227–237.
PubMed:https://pubmed.ncbi.nlm.nih.gov/28134597/
38. Nagy E, Eriksson P, Yousry M, Caidahl K, Ingelsson E, et al. Valvular osteoclasts in calcifi cation and aortic valve stenosis severity. Int J Cardiol. 2013;168:2264-2271.
PubMed:https://pubmed.ncbi.nlm.nih.gov/23452891/
39. Low EL, Baker AH, Bradshaw AC. TGFβ, smooth muscle cells and coronary artery disease: a review. Cell Signal. 2019;53:90-101.
PubMed:https://pubmed.ncbi.nlm.nih.gov/30227237/
40. Shioi A, Ikari Y. Plaque calcifi cation during atherosclerosis progression and regression. J Atheroscler Thromb. 2018;25:294–303.
PubMed:https://pubmed.ncbi.nlm.nih.gov/29238011/

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
J Cardiol Cardiovasc Med., 6: 001-006, 2021.

Chapter 10
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

A Case Report on Delayed Diagnosis of Turner Syndrome in a Short Statured Adolescent

I. O. Oluwayemi[1*], A. O. Odeyemi[2] and T. O. Ayeni[2]

DOI: 10.9734/bpi/rdmmr/v8/5198F

ABSTRACT

Turner syndrome has an incidence of 1/ 2500 female live births. Clinical signs such as lymphoedema in childhood, as well as short stature and delayed puberty, are common reasons for screening for Turner syndrome. Almost all affected females experience ovarian failure. We present a 15-year-old female with short stature and delayed puberty. Her mother remembered noticing swelling in both hands and feet as a child but made no sense of it. The patient's weight and height were both below the third percentile, and she exhibited no secondary sexual characteristics. The diagnosis was confirmed by the patient's karyotype (45, XO).Her serum estradiol level was low, her uterus was small, and her ovaries were atretic. Primarin was used to stimulate puberty for two years, during which she gained 3kg of weight, 4cm of height, and breast development from Tanner stage 1 to 4. Clinicians must be on the lookout for common clinical signs of Turner syndrome in order to make an early diagnosis, refer, and manage affected children for optimal growth and development.

Keywords: Turner syndrome; adolescent; delayed diagnosis; short stature.

1. INTRODUCTION

Turner syndrome, a chromosomal anomaly characterised by the loss of all or part of one sex chromosome, affects one in every 2500 female live births [1]. The most common reason for screening for Turner syndrome during infancy is lymphoedema of the hands and feet, while short stature is the most common presentation during childhood and adolescence [2]. In late adolescence and early adulthood, they frequently present with delayed puberty [1] and primary amenorrhoea. Growth failure, the most common abnormality in Turner syndrome, begins prenatally, and poor growth is often clinically evident within the first three years of life, with untreated adults being approximately 20 cm shorter than the average normal population [3-5]. In Turner syndrome ovarian failure begins by 18th week of gestational age and rapidly progresses to fibrous degeneration of the ovarian follicles [6]. Serum FSH and LH which show a rise during infancy and early childhood gradually decline until 6 years of age and then rise again at the normal age of puberty [7]. Almost all of them eventually show sign of ovarian failure with only few able to achieve spontaneous puberty/ menarche and spontaneous pregnancies occur in 2-5% of Turner syndrome especially those with mosaic karyotypes [8-10].

2. CASE REPORT

We present OC, a 15 year old girl who presented with short stature and delayed puberty. She was a product of term gestation. Mother noticed swelling of both hands and feet soon after delivery but made no meaning of it and no medical intervention sought since her growth appeared apparently normal during infancy and early childhood. Her mother however became bothered about absence of secondary sexual characteristics and short stature compared to her peers hence the presentation in the Paediatric endocrinology clinic. Essential findings on examination revealed small for age female

[1]Department of Paediatrics, Faculty of Clinical Sciences, College of Medicine, Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria.
[2]Department of Paediatrics, LAUTECH Teaching Hospital, Osogbo, Osun State, Nigeria.
**Corresponding author: E-mail: dareoluwayemi@gmail.com;*

adolescent, not acutely ill looking, had a small for age weight of 40kg (< 3rd percentile), and height of 1.38m (<3rd percentile). Mother's height was 1.60m while estimated father's height was 1.90m; the mid parental height was 1.69m and the target centile range was 1.61-1.77m. She had wide carrying angle, widely spaced prepubertal nipples. She had normal volume pulses, synchronous, no radio-femoral delay, blood pressure of 90/60mmHg, heart rate of 120/minute, only the first and second heart sounds were heard with no murmur.

An assessment of Turner syndrome with delayed puberty was made. She had a reduced bone age compatible with 8 years of age. Pelvic ultrasound showed small for age uterus but the ovaries were not visualized presumably due to hypoplasia or atresia. Karyotype 45 XO confirmed the diagnosis of Turner syndrome (Fig. 1). Serum hormonal assay showed low estradiol 22.2pg/ml (30-350pg/ml), high FSH 70.4mmol/L (3-22mmol/L) and high LH 23.4ng/ml (0.9-1.05ng/ml). She was commenced on hormone replacement therapy using Primarine 0.15mg alternate days for one year, then increased to 0.3mg daily the second year and 0.625 daily the 3rd year when she was referred to the gynaecologists for continued management having exceeded the age limit for Paediatrics. She attained steady growth and development of breasts and pubic hairs from Tanner stage 1 to stage 4; her height and weight also increased from 1.38m to 1.42m and 40.0kg to 43.0kg respectively during the two years period of hormone replacement therapy with remarkable improvement in her mood and general outlook.

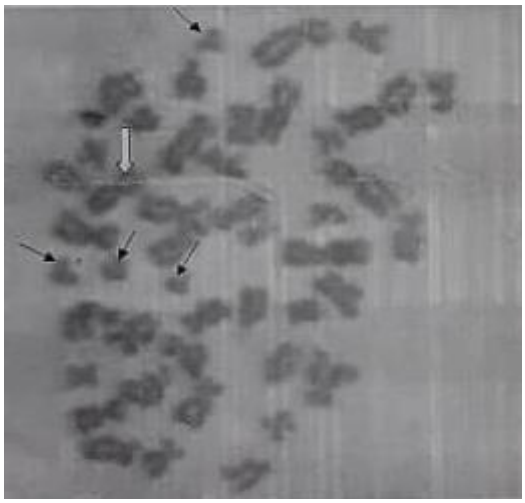


Fig. 1. Karyotype: 45,XO
Chromosomes were examined from the whole blood cells cultured full term. The Chromosomal Sex of the patient is Female as the arrows indicate the 4Gs. The block arrow indicates the X chromosome

3. DISCUSSION

Turner syndrome, if diagnosed early can benefit from growth hormone therapy which could help optimize their growth potential before induction of puberty in the majority of affected children who failed to enter puberty spontaneously. Clinicians in developing countries with limited diagnostic facilities can reliably make diagnosis of Turner syndrome using clinical signs that are very common in Turner syndrome patients from fetal life in utero to adolescence. Ultrasound finding of increased nuchal translucency or cystic hygroma in a fetus can predict Turner syndrome in 30-70% cases [11]. Lymphaedema of the hands and feet is the most common (97% of cases) presentation in infancy while short stature is more common (82% of cases) during childhood and adolescence [12]. Clinicians need be aware of these early clinical signs and use them for prompt referral of suspected cases for definitive diagnosis and multidisciplinary specialist management. The index patient presented with clinical features suggestive of Turner syndrome in infancy but neglected until she was 15 years of age after suffering needless emotional and psychological trauma. Major depressive disorder has been reported in adolescent with Turner syndrome [13]; this can be prevented by early diagnosis and holistic management of all Turner syndrome patients as early as possible [13,14]. She achieved

remarkable progress in development of secondary sexual characteristics within two years of hormone replacement therapy and appreciable linear growth with commensurate psychological and emotional boost. She continued to make progress looking and feeling more like a female adolescent as she continued her management with the Gynaecologists.

4. CONCLUSION

Turner syndrome has notable clinical signs that can help clinicians suspect the syndrome in-utero (by ultrasonography), during infancy, childhood and adolescent. These should be used to aid early diagnosis and referral for specialist management and optimal growth of affected children.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab. 2006;91:3897–3902.
2. Gravholt CH. Clinical practice in Turner syndrome. Nat Clin Pract Endocrinol Metab. 2005;1:41–52.
3. Davenport ML, Punyasavatsut N, Gunther D, Savendahl L, Stewart PW. Turner syndrome: a pattern of early growth failure. Acta Paediatr. 1999;Suppl 88:118–121.
4. Ranke MB, Pflu¨ ger H, Rosendahl W, Stubbe P, Enders H, Bierich JR, Majewski F Turner syndrome: Spontaneous growth in 150 cases and review of the literature. Eur J Pediatr 1983;141:81–88.
5. Davenport ML, Punyasavatsut N, Stewart PW, Gunther DF, Sa¨vendahl L, Sybert VP Growth failure in early life: An important manifestation of Turner syndrome. Horm Res. 2002;57:157–164
6. Pinsker JE. Turner syndrome: Updating the paradigm of clinical care. J Clin Endocrinol Metab. 2012;97(6):E994–E1003.
7. Fechner PY, Davenport ML, Qualy RL, Ross JL, Gunther DF, Eugster EA, Huseman C, Zagar AJ, Quigley CA. Differences in follicle-stimulating hormone secretion between 45,Xmonosomy Turner syndrome and 45,X/46,XX mosaicism are evident at an early age. J Clin Endocrinol Metab. 2006;91:4896–4902.
8. Bannink EM, van Sassen C, van Buuren S, de Jong FH, Lequin M, Mulder PG, de Muinck Keizer-Schrama SM. Puberty induction in Turner syndrome: Results of oestrogen treatment on development of secondary sexual characteristics, uterine dimensions and serum hormone levels. Clin Endocrinol (Oxf). 2009;70:265–273.
9. Pasquino AM, Passeri F, Pucarelli I, Segni M, Municchi G. Spontaneous pubertal development in Turner's syndrome. Italian Study Group for Turner's Syndrome. J Clin Endocrinol Metab. 1997;82:1810–1813.
10. Mortensen KH, Rohde MD, Uldbjerg N, Gravholt CH. Repeated spontaneous pregnancies in 45,X Turner syndrome. Obstet Gynecol. 2010;115:446–449.
11. Alpman A, Cogulu O, Akgul M, Arikan EA, Durmaz B, Karaca E, Saðol S, Ozkinay C, Ozkinay F Prenatally diagnosed Turner syndrome and cystic hygroma: incidence and reasons for referrals. Fetal Diagn Ther. 2009;25:58–61.
12. Gravholt CH. Clinical practice in Turner syndrome. Nat Clin Pract Endocrinol Metab. 2005;1:41–52.
13. Mao S, Sun L, Li R, Zhao Z, Yang R. Major depressive disorder in an adolescent with Turner syndrome: a case report. Gynecological Endocrinology. 2016;32(5):354-6.
14. Kavoussi SK, Christman GM, Smith YR. Healthcare for adolescents with Turner syndrome. Journal of pediatric and adolescent gynecology. 2006;19(4):257-65.

Biography of author(s)

I. O. Oluwayemi
Department of Paediatrics, Faculty of Clinical Sciences, College of medicine, Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria.

Research and Academic Experience: Associate Professor of Paediatrics

Research Area: Paediatric Endocrinology

Number of Published papers: 73

Special Award: Best Graduating Fellow, 2014, Paediatric Endocrinology Training Centre for West Africa.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Innovative Journal of Medical and Health Science, 9(4), 413–415, 2019.

Chapter 11
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Septic Cavernous Sinus Thrombosis Associated With Bilateral Orbital Cellulitis: A Case Study of A 10 Year Old Rural Girl from Sub-Saharan Region

R. Mohammed-Nafi'u[1*], A. S. Alhassan[2], E. J. Okon[3], V. Aliche[4], J. Asemoh[5] and E. T. Nnadi[6]

DOI: 10.9734/bpi/rdmmr/v8/5047F

ABSTRACT

Septic Cavernous Sinus Thrombosis (CST) is a rare infective condition affecting the cavernous sinus in the brain associated with high morbidity and mortality, especially when appropriate and prompt intervention is delayed. Although there is limited data on CST globally, the low prevalence in developing countries may not be unconnected with factors such as poor health seeking behaviour of the people, inadequate healthcare facilities and the dearth of radio-imaging diagnostic techniques, as well as low level suspicion for CST amongst physicians. Here is a case report on a 10 year old indigent nomadic (Fulani) girl diagnosed to have septic cavernous sinus thrombosis and bilateral orbital cellulitis confirmed by enhanced computed tomography (CT) scan of the brain. The case would have been missed, were it not for the intervention of a "Good Samaritan" who facilitated her access to the right medical facility for timely intervention.
Objective-To highlight the clinical presentation, management as well as create awareness on the need for a high index of suspicion and early diagnosis of children with CST in order to reduce morbidity and mortality in a resource constraint settings.

Keywords: Cavernous sinus thrombosis (CST); orbital cellulitis; high index of suspicion.

1. INTRODUCTION

Cavernous sinus thrombosis (CST) is the formation of septic or aseptic blood clots within the cavernous sinus. Septic CST usually results from sepsis or spread of infections from surrounding facial or other intracranial structures while aseptic CST can arise from trauma or pro-thrombotic aetiology [1]. Because of the complex neurovascular anatomy of the cavernous sinus and its intimate relationship with other intracranial structure, septic thrombosis involving the sinus is usually taken with very serious concern. Propagation of septic emboli from infected foci on the face and other intracranial structures through valveless veins constitute major source of infections [2,3]. Other risk factors for CST include trauma, immunosuppressive states, obesity, thrombophilia, chemotherapy and dehydration [4].

It is a rare disease which can end with a fulminant outcome. However, the introduction of antibiotics has significantly reduced the morbidity and mortality. Despite that, early diagnosis and prompt treatment is key to favourable outcomes in the management [3,5]. Septic causes are mostly caused by bacterial organisms, but other micro-organism such as viruses, parasitic and fungal are also seldom implicated. Staphylococcus aureus is the commonest organism accounting for about 70% of

[1]*Department of Paediatrics, State Service Hospital, Abuja, Nigeria.*
[2]*Department of Public Health, State Service Hospital, Abuja, Nigeria.*
[3]*Departments of Paediatrics, National Hospital, Abuja, Nigeria.*
[4]*Departments of Optometry, State Service Hospital, Abuja, Nigeria.*
[5]*Departments of Medicine, State Service Hospital, Abuja, Nigeria.*
[6]*General out Patient Department, State Service Hospital, Abuja, Nigeria.*
**Corresponding author: E-mail: rabbashiya2008@yahoo.com;*

septic causes; others include streptococcal species, pneumococcal, gram negative species, Bacteriodes and Fusobacterium. Other rarely implicated organisms such as the human immunodeficiency virus (HIV), cytomegalovirus, measles and aspergillus have been reported [6].

There is dearth of data on the incidence of CST [7]. It account for up to 1-4% of cerebral and sinus thrombosis. Frank et al. [8] estimated an annual incidence of 0.2- 1.6/1000,000 per year, [8] while Maliha et al. [9] reported an incidence of 7/1000,000 in India, they attributed the increasing incidence to the emergence of newer and more advance diagnostic imaging technology in the evaluation of suspected cases. There is conflicting reports in sex prevalence, Weerasinghe et al. [10] documented a male predominance with a ratio of 2:1.

The clinical presentation of CST depends on the structures affected. Most often the symptoms and signs are as a results of venous obstruction and damage to cranial nerves [11]. The classical symptoms include headache, fever, photophobia, chemosis, visual impairment, vomiting, convulsion or altered level of consciousness [12,13]. Complications such as cranial nerve palsy, visual impairment, thrombosis in the lateral and superior sagittal sinus, infarct or ischaemia around related structures could occur [12].

Radio imaging, especially enhanced contrast Computed Tomography and Magnetic Resonance Imaging (MRI) are the most preferred diagnostic modalities. However, diagnosis could be challenging and easily missed in resource constraint settings where there is dearth of modern diagnostic facilities, unless where physicians maintain high index of suspicion and follow it up, accordingly [11,14]. Other investigations are targeted at suspected causes [3].

Prompt and early use of broad spectrum intravenous antibiotics is the main stay of treatment. This practice takes into consideration, the commonest causative agents or based on culture and sensitivity pattern. Anticoagulant has also been found to be useful, other modalities of treatment depend on identified causes [15].

We report a case of an indigent 10 year old nomadic Fulani girl, from a rural setting in North-west, Nigeria, who was brought into our facility on the 21st September, 2019. She presented with three day history of high grade fever, generalized throbbing headache, generalized body rashes, bilateral purulent eye discharge, red eyes with swelling and inability to see. There was also history of joint and bone pain associated with inability to walk, no associated convulsion or irrational talk, neither was there history of any insect or snake bite. No history of boil on the face or nasal discharge. All the above symptoms were noticed about three hours after she came back from the bush where she went to fetch firewood. Parents gave about 10mls of herbal concoction diluted with water twice and applied an unknown eye drop obtained from a local patent medicine shop twice to both eyes before presentation.

Significant examination findings at presentation, were that of an acutely ill-looking child, in obvious painful distress, irritable, febrile 38.6°C (axillary temperature), fully conscious, in obvious painful distress, generalized maculopapular rashes of varying sizes with few intersperse hyper pigmented patches, pale, bilateral purulent eye discharge, redness and swelling of the eyes, marked photophobia, proptosis, conjunctival chemosis, inability to open both eyes and tenderness over the eye balls. She had tenderness in all the limbs but no swelling, no cranial nerve palsy, no significant lymphadenopathy, no scratch or sting mark, acyanosed, anicteric, bilateral pitting pedal oedema up to the mid-thigh, no nuchal rigidity, kerning and brudzinski signs not elicited because of severe pain across the joints. Vital signs were; PR-92b/m, regular with good volume and BP-100/60mmhg, HS-SIS2 only, RR-24c/m. Other systems were essentially normal.

Initial diagnosis was that of sepsis (meningitis and bilateral orbital cellulitis) with cavernous sinus thrombosis, other differentials considered were Sickle Cell Disease (SCD), Leukaemia, Rheumatic fever and Lyme disease. She was commenced on high dose intravenous ceftriaxone, crystalline penicillin, dexamethasone, pentazocine, and dexamethasone eye ointment and gutt ciprofloxacin.

Forty eight hours after admission, fever and headache had resolved, other symptoms were still present. Patient was jointly reviewed by an Ophthalmologist and an Optometrist with examinations findings of copious purulent eye discharge, conjunctival and orbital chemosis, generalized bilateral blepharitis, peri-ocular and corneal oedema with associated proptosis, photophobia, significant loss of light perception and widely fixed and dilated pupils with extraocular muscle limitations. Slit lamp biomicroscope showed anteriorly displaced granulomatous uveal tissues in the right eye while the left eye shows iris bombe and anterior chamber cells. Raised intraocular pressure in the right eye (35mmHg) while that of the left eye (30mmHg).

Normal saline irrigation was commenced before all the eye medications are applied. Subconjunctival dexamethasone, gutt timolol, tab Diamox, Maxitrol ointment and later gutt diclofenac (replaced Maxitrol). Gutt Pilocarpine was also added to the treatment but was not available. Five days after admission, she was able to open her eyes unaided.

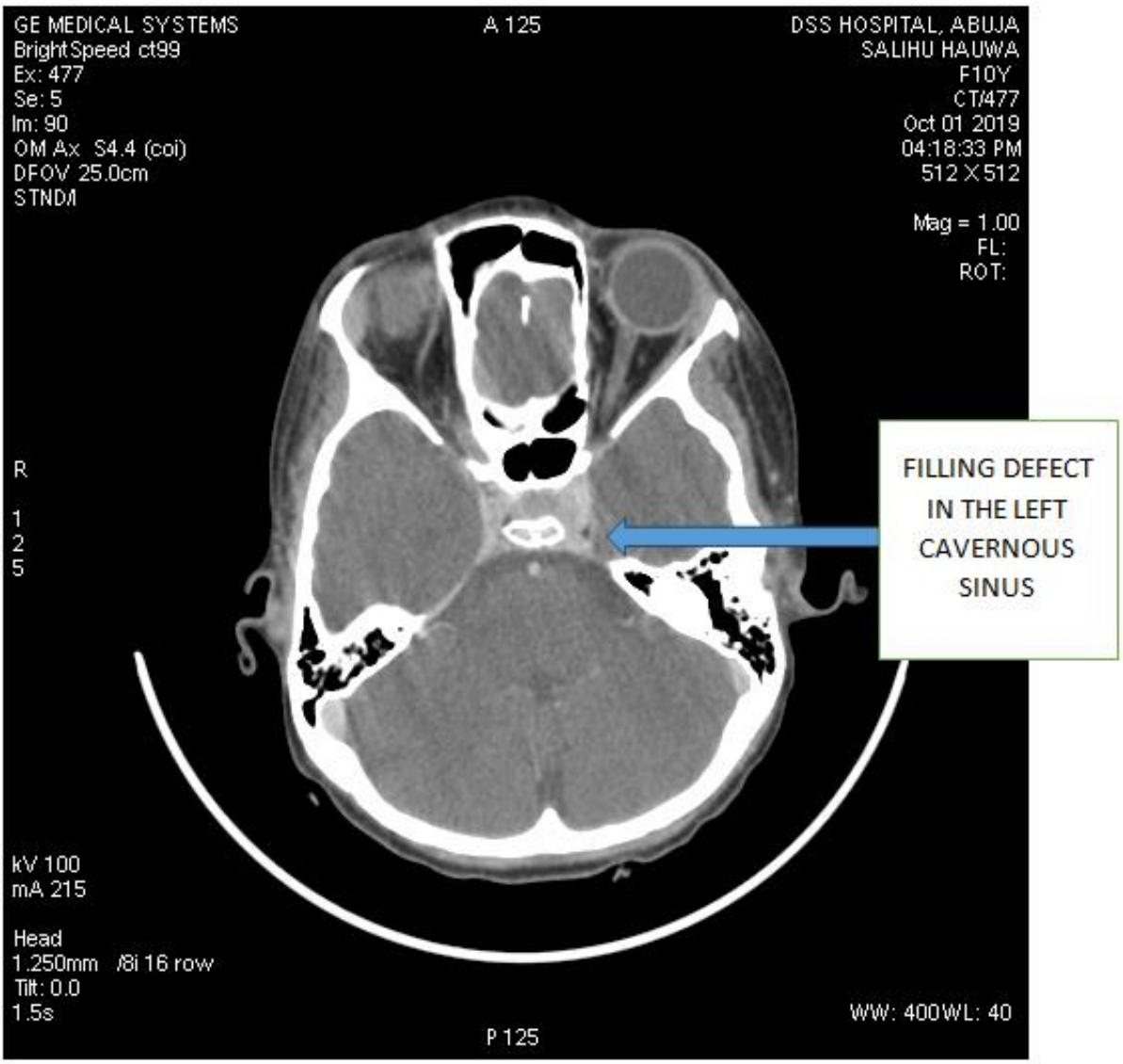


Fig. 1. Contrast enhanced Computer tomography showing filling defect in the left cavernous sinus as shown by the arrow in blue on day 8th of Admission

On day eight, enhanced Computed Tomography (CT) was done which revealed a left Cavernous sinus thrombosis with the following findings (There is a small filling defect in the left cavernous sinus which measures HU 40 in post-contrast studies, where the surrounding cavernous sinus measures HU 142 (7 days post-presentation). This finding was highly suggestive of cavernous sinus thrombus. The ophthalmic veins and the dura sinuses were normal in appearances. The internal jugular veins were also normal. The optic nerves and the optic chiasma were normal with uniform enhancements present. There were no intracranial lesions within the orbits. The globes were not flattened posteriorly. The cerebral hemispheres were normal in CT densities with no intracranial collection present in the intra-axial or extra-axial regions. There were no areas of meningeal enhancements, which exclude meningitis. There were no solid lesions present, and midline structures maintained their positions. The pituitary gland was found to be normal. The circle of Willis was normal. The lateral, 3rd and 4th ventricles were normal in size with no effacements and no features of raised intracranial pressure.). Fig. 1 based on the above findings a definitive diagnosis of left cavernous sinus thrombosis complicating bilateral orbital cellulitis and sepsis was established.

She was also reviewed by the Dermatologist who documented post inflammatory hypo and hyper pigmented rashes in keeping with meningococcaemia.

By the tenth day on admission, pain had resolved and rashes were healing. Although she developed limitations of movement on both elbow and left leg, urgent x-ray of affected limbs showed no abnormality.

Ophthalmic review showed a reduction in the intraocular pressure to 25mmhg. However, there was corneal haziness on the right eye with formation of occlusio pupillae. The left eye however, was found to have a mid-dilated pupil with photophobia and pupillary membrane, as well as lens opacity and posterior synaechia. Patient could only follow hand movement in both eyes. Gutt timolol was continued with gutt Xalatan, while gutt diclofenac was replaced with dextracin for the left eye and gutt Ivyflur for the right eye.

Having completed 21 days of intravenous antibiotics, patient showed significant clinical improvement. The rashes have healed appreciably, and she could move all limbs, and was able to open both eyes, although visual impairment persisted. There were no neurological deficits. She was eventually discharged and scheduled for a follow up. She was seen 15days later with sustained improvement except for the visual impairment. She was followed up for further evaluation and management by the Ophthalmologist. All the investigations done and the results are as shown on Tables 1 & 2.

2. DISCUSSION

Cavernous sinus thrombosis is a rare disease entity, especially in children. However, when it occurs, it is usually associated with high morbidity and mortality [1,16,17]. There is paucity of published data especially in an era of abundant antibiotic therapeutic options. Sweis and co-author [1] were only able to report 12 cases in thirteen years (2000-2013) at Philadelphia children hospital in United States (USA) while a retrospective study by Press et al. [12] reported 10 cases in a retrospective study over a period of ten years among children aged 3-17 years, in university of Colorado, also from USA. In Nigeria, a study done over a ten year period, Adeoti et al. [18] in Osogbo, South-Western region only reported 2 cases with CST among subjects aged 2-85 years. It is difficult to attribute the apparent low incidence of the reporting of CST in developing countries, this might be as a result of missed diagnosis or death of those affected at home because of poor health seeking behaviour, distance of health facility, mystification of disease condition or poverty unlike in developing countries which might be related to early and prompt use of appropriate antibiotics. Our patient, a 10 year old nomadic Fulani girl from a rural setting in North-West, Nigeria had already resorted to alternative treatment with herbal concoctions until help came her way through unexpected means.

Our patient presented with bilateral purulent eye discharge, redness of the eyes, swelling and inability to open the eyes. She also had fever and typical skin rashes suggestive of meningococcaemia, along with laboratory evidence of sepsis such as leukocytosis with absolute neutrophilia and elevated erythrocyte sedimentation rate. Suspicion was more to bilateral orbital cellulitis and general sepsis as risk factors that predisposed the young girl to CST.

Table 1. Investigations results

Investigations	Date	Date	Date	Date	Date	Date	Date	Normal Range	Comment
Full Blood Count (FBC)	21/9/19	23/9/19	30/9/19	3/10/19	4/10/19	9/10/19	10/10/19		
White Cell Count (WBC)	30.6 x 10^9		15.6 x10^9	14.8 x10^9		7.5x10^9			Leucocytosis with NeNeutrophilia
Packed Cell Volume (PCV)	27%		32%	30%		29%			
Haemoglobin(Hb)	10.2g/dl,		11.3g/dL	10.8g/dL		10.4g/dL			
Platelets(PLT)	158		736	545		430			
Neutrophils	92%		78%	56%		56%			
Lymphocytes	4%		16%	26%		27%			
Erythrocytes Sedimentation Rate (ESR)	116mm/hr						75mm/hr	(male= 0-7mmhr) (female= 0 – 20mmhr)	Elevated
Malaria Parasite(MP)	Negative								
Electrolytes									
Sodium (Na)	131.3				131	139.3			Hyponatreamia
Potassium(K)	3.2				3.4	3.6			Hypokalaemia
Chlorine (CL)	94.8				102.8	109			Low
Creatinine (Cr)	19.4				16.8	18.4			
Urea (Ur)	5.6				2.3	2.3			
Blood film	Essentials normal								
Blood Group	O Rhesus negative								
Urinalysis									
Protein		negative							
Blood		negative							
Bilirubin		negative							
Specific gravity (SG)		1.010							
PH		8.0							
Total Protein		6.3g/dl						(6.6 – 8.8mg/dl)	
Albumin		4.1g/dl						(3.5 – 5.2) g/dl	
Widal		Non-Significant Titres							
Skin Snip			No microfilaria						
Uric Acid					1.5mg/dl			(2.6 – 6mg/dl)	
Wound swab Microscopy anand sensitivity			No growth						
Blood Culture					negative				

Table 2. Further investigation results

	30/9/19	4/10/19	10/10/19	Normal RangeComment
Clotting Profile				
Prothrombin Time (PT)			18.4sec	(6.5-13.1)sec
Partial Activated Prothrombin Time (PTTK)			32.1sec	(26-41)sec
International Normalised Ratio (INR)			1.98	(0.6-1.2)
Serological Tests				
HIV		Negative		
HBsAg		Negative		
HCAB		Negative		
Hb Phenotypes(HPLC)				
HbF	0.4%			
HbC	35%			
HbA	60.2%			
HbA_2	4.4%			
Rheumatoid Factors(Quantitative	17.9IU/ml		(0 - 14IU/ml)	
Anti DNA B	76.8 U/L		(0- 170U/L)	
Lyme Disease (Borrela B)	Negative			
Antistreptolysis Titre (ASO)	150.6IU/ml		(0 -200IU/ML)	
Antinuclear Antibodies (ANA)	Negative			

Cavernous sinus thrombosis has a variable clinical presentation, [3,14,18] the clinical features usually reflect the various causes or risk factors [1]. Headache, fever, redness of the eyes, swelling and inability to open the eyes were the commonest presenting symptoms in our patient. While the major clinical signs included redness, swelling and inability to see, photophobia, conjunctival chemosis and proptosis indicating that the eyes were the main source of the infection. Headache is related to the involvement of the ophthalmic and maxillary branches of the fifth cranial nerves [12]. while the ophthalmic signs and visual disturbances were related to the involvement of oculomotor, abducent nerves and posterior spread of the infections due to their relationship to the cavernous sinus [12,2] Where affectation of the eyes is the main cause of CST, orbital manifestation become the most predominant clinical presentation. This has been documented in many literatures [3,12,13,1].

No organism was isolated from both tissue and blood cultures. The inability to culture any organism may not be unconnected with the fact that there was delay in carrying out relevant investigations including blood and cerebrospinal fluid (CSF) culture due to financial constraints. This would have affected the culture results. This findings is consistent with reports in other literatures including that of weerasinghe et al. [10,11,19,20]. Similarly lumbar puncture was not done in this patient at presentation and few days after because of the unstable clinical conditions and suspected raised intracranial pressure. Serological tests for HIV, Hepatitis B and C were all negative, although other viral causes cannot be completely ruled out since facility for viral culture was not available. The haemoglobin phenotype was HbAC.

Central nervous system manifestation such as irritability, confusion, convulsion, mental status changes and coma are not uncommon in septic CST [19]. Our patient presented with irritability and confusion but she was conscious.

Various radio imaging techniques are available for the diagnosis of CST, however, enhanced CT and MRI are the diagnostic investigations of choice [8]. Definitive diagnosis of CST in our patient was made using enhanced CT with a finding consistent of left CST.

Early diagnosis and use of broad spectrum antibiotics, anticoagulant and surgical drainage are the modality of treatment [16,21]. Prompt use of antibiotics have been found to be associated with good outcome and has significantly reduced both morbidity and mortality in CST [1,16,17]. Consistent with other reports in the literatures, [1,16,17,20] our patient responded very well to intravenous antibiotics.

Patient received ceftriaxone and crystalline penicillin for 21 days. She also had intravenous dexamethasone, clexane and oral warfarin upon resolution of clinical and laboratory finding, although visual disturbances persisted.

Neurological deficits especially cranial nerve palsy and visual impairment are usually the commonly reported complications in CST [13]. Our patient suffered visual impairment with ophthalmic findings of panuveatis, lenticular opacities, ocular synchiae and reduced corneal reflex, dilated and fixed pupil. This was the only complication which is consistent with findings reported in other studies [8,12,22,23]. It is pertinent to note that the extent of retinal involvement was not ascertained due to media opacity resulting from complications of panuveitis and lenticular opacities. Patient would have benefitted from B-scan but, she was unable to access it due to financial constraint.

The management of this case was not without challenges. The patient was indigent and could barely afford the cost of treatment except for the philanthropic gesture of the managing team and the hospital Management. This resulted in delay in carrying out most of the laboratory and imaging tests. The parents initially resorted to the use of herbal concoction.

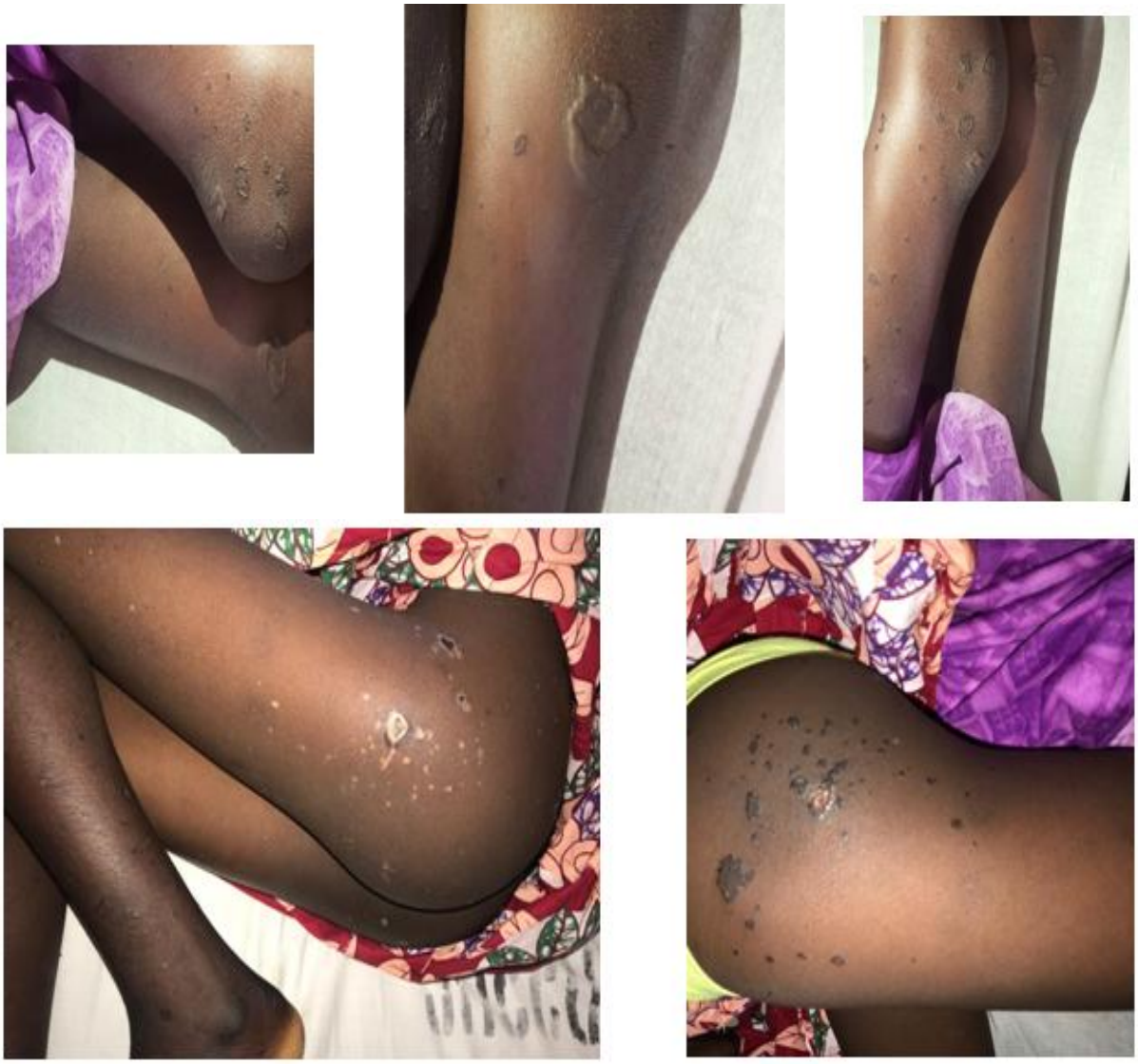


Fig. 2. Photograph of patient on day 5 of admission

Fig. 3. Photograph of patients on day 5 of admission

Fig. 4. photograph of patient on day 8 of admission showing healing process

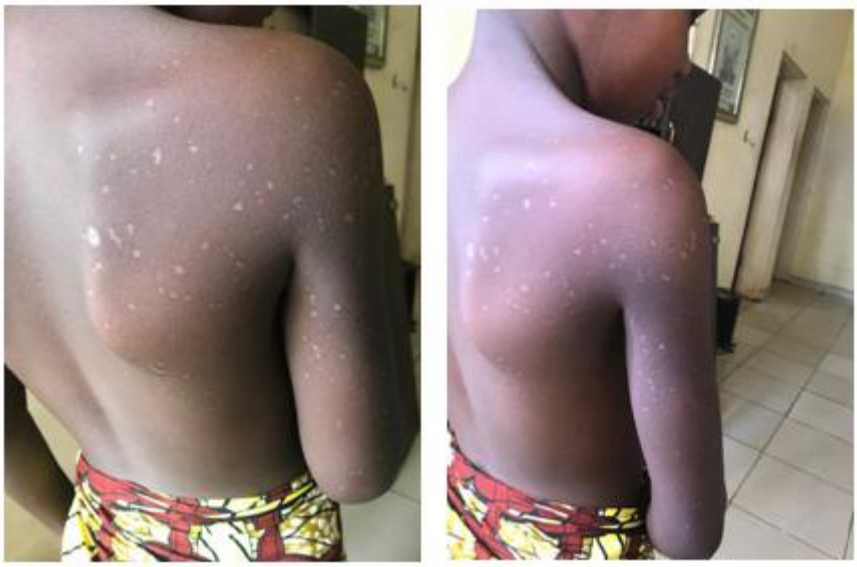


Fig. 5. Photograph of patient at follow up, 15 days after discharged

3. CONCLUSION

We present this case to highlight that with high index of suspicion and prompt use of antibiotics, morbidity and mortality in highly fatal disease condition like CST can be drastically reduced even in resource constraint countries such as Nigeria.

ETHICAL AND CONSENT

Ethical Consent was obtained from parents and assent from the child to enable us publish this case and provide information for research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sweis Rochelle, Jose Biller. Pediatric Neurology Briefs. Pediatr Neurol Briefs. 2016;30:1–4.
2. Lee H, Kim H, Park J, et al. Septic cavernous sinus thrombosis with infectious arteritis of the internal carotid artery; 2015.
3. Mallick A, Pathak S, Shankar S, et al. Early cavernous sinus thrombosis following unilateral pansinusitis in a child. BMJ Case Rep. 2015;1:1–4.
4. Torretta S, Guastella C, Marchisio P, et al. Sinonasal -related orbital infections in children: A clinical and therapeutic overview. J Clin Med. 2019;8:PMC6351922.
5. Jessica Sop D, Tager A. Pediatric Cavernous Sinus Thrombosis. Ann Clin Case Rep. 2019;4: 1706.
6. Dinkin M, Patsalides A, Ertel M. Diagnosis and Management of Cerebral Venous Diseases inNeuro-Opthalmology; Ongoing controversies. Asia Pac J Opthalmol(Phila). 2019;8:73–85.
7. Ranjith KM, Lokesh S, Jaya SK, et al. A Combination of Moyamoya Pattern and Cerebral Venous Sinus Thrombosis: A Case of Tubercular Vasculopathy. J Trop Pediatr. 2015;61:393–396.
8. Frank G, Smith G, Davies B, et al. Opthalmic manifestations and outcomes after cavernous sinus thrombosis in children. In: 45th Annual Fall American Society Of Opthalmic Plastic and Reconstructive Surgery(ASOPRS), Scientific Symposium, Chicago. 2014;16–17.

9. Maliha S, Akheel M, Singh S. Cavernous sinus thrombosis-Asuccinct outlook. J Head Neck. 2014;2:67–72.
10. Weerasinghe D, Lueck CJ. Septic cavernous sinus thrombosis: Case report and review of the literature. Neuroophthalmology. 2016;40:263–276.
11. Smith D, Vossoung A, Vorona G, et al. Pediatric cavernous sinus thrombosis. Neurology. 2015; 85:763–769.
12. Press CA, Lindsay A, Stence NV, et al. Cavernous sinus thrombosis in children: imaging characteristics and clinical outcomes. Stroke. 2015;46:2657–60.
13. Ebright JR, Pace MT, Niazi AF. Septic thrombosis of the cavernous sinuses. Arch of Intern Med 2001;161:2671–2676.
14. Okunola PO, Ofovwe GE, Abiodun MT, et al. Superior Sagittal Sinus Thrombosis Complicating Typhoid Fever in a Teenager; 2012.
15. Mathew T, Hussein A. Atypical cavernous sinus thrombosis: A diagnosis Challenge and Dilemma. Cureus 2018;10:e3685.
16. Dlamini N, Billinghurst L, Kirkham F. Cerebral Venous Sinus (Sinovenous) Thrombosis in Children. Neurosurg Clin N Am. 2010;21:511–527.
17. Mokgacha K, Maruza M, Sesay S, et al. Cavernous Sinus thrombosis. Turk J Pediatr. 2017;59: 719–723.
18. Adeoti C, Adejumo O, Isawumi M, et al. Orbital Cellulitis in a Tertiary Institution in Nigeria: Improving Outcomes. Niger J Ophthalmol. 2017;25:141–5.
19. Taylor P. Cavernous sinus thrombophlebitis. Br J Opthalmol. 1957;41228–237.
20. Kojan S, Al-Jumah M. Infection related cerebral venous thrombosis. J Pak Med Assoc. 2006;56: 494–497.
21. DiNubile MJ. Septic thrombosis of the cavernous sinuses. Arch Neurol. 1988;45:567–72.
22. Visudtibhan A, Visudhiphan P, Chiemchanya S. Cavernous sinus thrombophlebitis in children. Pediatr Neurol. 2001;24:123–12.
23. Varshney S, Malhotra M, Gupta P, et al. Cavernous sinus thrombosis of nasal origin in children. Indian J Otolaryngol Head Neck Surg. 2015;67:100–105.

Biography of author(s)

R. Mohammed-Nafi'u
Department of Paediatrics, State Service Hospital, Abuja, Nigeria.

Research and Academic Experience: Participated In Over 8 Academic Researches Since Residency Training Till Date.

Research Area: In all subspecialties of paediatrics but now interested in paediatric infectious disease.

Number of Published papers: 8 In Local and International Journals

Special Award: College Prize for the Best Graduating Student in Part 2 Fellowship Exam.

Any other remarkable point(s): Consultant Paediatrician Interested In Infectious Disease.

Effiong J. Okon
Departments of Paediatrics, National Hospital, Abuja, Nigeria.

Research and Academic Experience: Participated in 10 published articles

Research Area: Paedіatric endocrine and diabetes. Paediatric haemato-oncology.

Number of Published papers: 10

V. Aliche
Departments of Optometry, State Service Hospital, Abuja, Nigeria.

Research and Academic Experience:
SOME OF HIS UNPUBLISHED RESEARCH PAPERS INCLUDE;
-COMPARATIVE STUDY OF AMPLITUDE OF ACCOMMODATION (AA) BETWEEN MYOPES AND MYOPIC ASTIGMATS
- CONDOM USE: PREJUDICE AND ATTITUDE OF UNDERGRADUATE YOUTHS IN UNIVERSITY OF ABUJA, NIGERIA

Research Area: OCULAR PATHOLOGY

Number of Published papers: 2

Special Award: COMMENDATION AWARD BY NATIONAL YOUTH SERVICE CORP

Any other remarkable point(s): PATIONATE ABOUT THE NEEDY

J. Asemoh
Departments of Medicine, State Service Hospital, Abuja, Nigeria.

Research and Academic Experience: Participated in 3 Academic Researches

Research Area: Familial Chronic Kidney Disease

Number of Published papers: 1

Number of Published papers: Consultant Nephrologist with a Wealth of Experience

E. T. Nnadi
General out Patient Department, State Service Hospital, Abuja, Nigeria.

Research and Academic Experience: Participated in 2 Academic Researches

Research Area: General Practice

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
International Journal of Scientific and Research Publications, 10(3), 2020.

Chapter 12
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Rehabilitation of Patients with Vascular Diseases

Castor Leonardo Maduro-Maytín[1*] and Marina Maduro-Maytín[2]

DOI: 10.9734/bpi/rdmmr/v8/4891F

ABSTRACT

A supervised Vascular Rehabilitation program has demonstrated the improvement of the absolute walking distance and the elimination of pain at rest of peripheral obstructive arterial origin, the adequate treatment of chronic venous insufficiency, the healing of arterial and venous vascular ulcers even in patients previously amputees or disabled to walk and reverse the chances of further amputations, allowing patients to be more functionally independent. In patients with lymphedema, it stops and reverses the pathology.

Our work plan is a scientific and evidence-based medical evaluation to determine the degree of vascular health of the legs and to organize a personalized therapeutic plan. The high prevalence and incidence of these pathologies, their high cost of treatment, studies and research, the loss of working hours and all the importance in the quality of life of the people who suffer from them, make this issue of great importance in the present.

Keywords: Vascular Rehabilitation; Veno-Arterial-Lymphatic Rehabilitation.

1. INTRODUCTION

Vascular diseases have a high prevalence and incidence with an important socio-economic impact in the Western world, due to their high costs in their investigation, treatment and loss of working days [1,2,3,4].

The objective of therapy in patients with vascular disease is to improve their functional status, and any program that is designed begins with a systematic assessment of the candidate's exercise tolerance and relative measures of venous hypertension that will support an individual exercise program.

2. MATERIALS AND METHODS

At the Vascular Laboratory, appropriate studies are carried out to objectively determine the severity of these diseases' functional impairment. A high degree of linear relationship was found in our practice [5] as well as other studies [6,7] for PPG-LRR-VRT and Refilling time measured by means of Ambulatory Venous Pressure, which became the hemodynamic gold standard used in the development of noninvasive methods for screening of patients with Chronic Venous Insufficiency (CVI) [8]. Fig.1.

The first study to be performed on the patient will be a sitting position Photoplethysmography (PPG) type Light Reflection Rheography (LRR) with the complete diagnostic algorithm. If the Venous Refilling Time (VRT) is normal, the study is concluded; if it is abnormally short (<25 seconds), the test will be repeated after a 2.5 centimeter wide cuff tourniquet is positioned above the knee, below the knee, above the ankle or any place where the technician requires to occlude the superficial vein return of the blood. Normalization of the VRT after occlusion of the superficial veins suggests that reflux is confined to the superficial venous system.

[1]University of Carabobo. MD, MSc, PhD. Director of the Vascular Laboratory and Vascular Rehabilitation Service CMGM Retired, Venezuela.
[2]PT, DPT, WCC, CLT-LANA MLD/CDT. Academy of Lymphatic Studies. Director of curriculum, Venezuela.
**Corresponding author: E-mail: clmadurom@gmail.com;*

If the PPG-LRR study is abnormal, an Eco-Doppler scanning will be used for evaluation of obstruction, reflux or both and their anatomic extent just for diagnostic purposes.

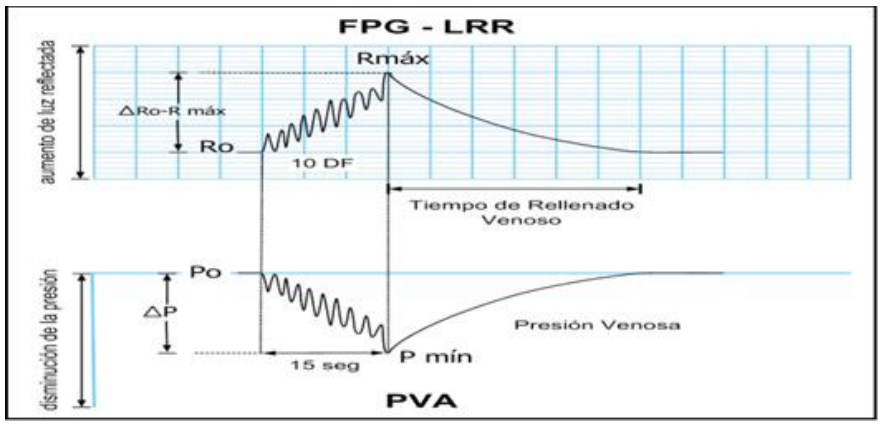


Fig. 1. High degree of linear relationship for PPG-LRR-VRT and Refilling time measured by means of Ambulatory Venous Pressure. Reproduced from Maduro-Maytin, CL [5]

Simultaneously a supine and standing position venous pressure at rest will be measured by Doppler. Values larger than 20 mmHg, and between 20 mmHg and 50mmHg, have been determined at our Vascular Laboratory as normal values and normal range values for those measurements, respectively. At this moment, a non-weight bearing goniometric measurement of the active Range of Motion (ROM) of the ankle joint is obtained. During measurement, the foot is held by a plantar platform as a goniometric mobile arm to control the entire forefoot and prevent any unacceptable position. There is a variety of instruments [9].

It is useful to get a hard copy of the data obtained. Such printed data obtained by goniometry is important to: Establish a diagnosis, determine and quantify a dysfunction, develop therapeutic objectives and goals, look at the effectiveness of specific therapeutic techniques, establish and modify protocols for treatment, give information to the patient as it can encourage them to continue protocols, prove treatment effectiveness and objective measurements of improvement for insurance purposes.

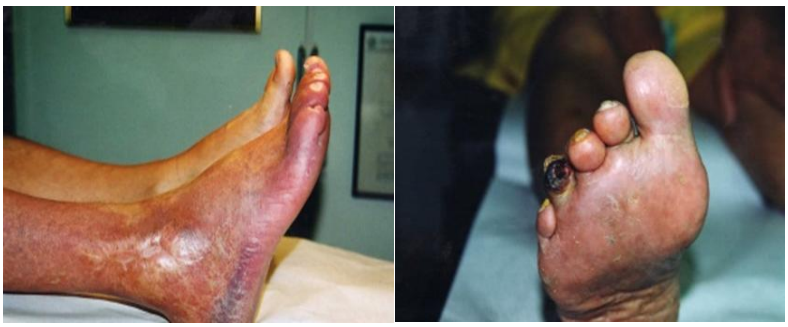
Following the venous study, the Ankle-Brachial Index (ABI) is obtained by dividing the posterior tibial systolic pressure found at rest with a pocket Doppler, by the brachial systolic blood pressure. It will include segmental pressures obtained at the high thigh, eight centimeters above the knee, eight centimeters below the knee and above the ankle joint. The normal range for ABI is 0.9 to 1.2. Most patients with intermittent claudication will have an ABI of 0.4 to 0.8 and an ABI less than 0.3 will indicate critical lower limb ischemia [10].

After that, a classic standardized treadmill test **(**Constant-Load Exercise Testing) will be done allowing the patient to walk on the treadmill band with a speed of 2 miles/hr during five minutes and 10% of inclination. The technician will obtain the distance of the beginning of the pain, intensity and character of the pain and its evolution until the final distance. The test ends if the patient reaches a maximum level of claudication pain (absolute claudication distance).

3. RESULTS

3.1 Rehabilitation of Patients with Arterial Disease

With supervised exercise programs, we have achieved an increment of a total walking distance, abolishing pain at rest, healing vascular ulcers, and preventing amputation of affected limbs and second amputation in residual limbs in all our patients including some of them unable to walk. Fig. 2.



Symptomatic patient **Finger necrosis**

Fig. 2.

The treatment is done in four phases and the main exercise program consists of a walking program that the patient does on the treadmill band with a gradual increase of the speed, inclination of the band and time exposure. Many protocols have been used by different groups .We use a protocol consisting of a nine stage program [11]. Table 1.

Table 1. Nine stage program protocol [10] Mph: miles per hour; min: minutes; m: meters

Stage	Speed (Mph)	Grade of Inc. (%)	Time (min)	Distance (m)
I	1.0	0	2	48
II	1.5	0	3	120
III	2.0	0	4	208
IV	2.0	10	7	368
V	2.0	10	10	528
VI	2.0	10	13	688
VII	2.0	10	16	848
VIII	2.0	10	19	1008
IX	2.0	12	22	1168

The patient is stationary at the beginning of the program and the speed is then adjusted in 1/10 mph increments until the maximum planned speed is reached. The grade of inclination and time programmed for each session is given as shown in the stage progress.

During each session, the Vascular Rehabilitation staff (physical therapist, nurse and physician) will monitor the heart rate and blood pressure during the exercise session and will encourage the patient for the best performance.

After each stage is done, a five minute rest, or whatever time is needed to eliminate the pain, is given to the patient and the exercise re-starts at the next stage. The complete time for each session will be of forty five minutes to one hour each day.

An amputee or walking disabled patient follows the same resisted strengthening exercise program to increase calf muscle strength as do CVI patients. In patients unable to ambulate, the results equivalent to Vascular Stress Test were obtained by referring the patient to exercises on the worktable following the protocol of resistance exercises until fatigue. Vascular Stress Test performed on our service, not published

3.2 Rehabilitation of Patients with Venous Disease

The normal functioning of the venous pump of the calf is the ability to keep the venous outflow from the lower leg equal to the arterial inflow during exercise, without undue dilatation of the vein of the lower leg with low pressure in the input area, mainly in the ankle region. During the walking cycle,

Flexion (F) of the ankle produces a significant increase of pressure in the Anterior Compartment of the leg (AC); meanwhile, Extension (E) causes an increase in pressure of the Posterior Compartment (PC). During each movement, a highly significant boost in pressure occurs in a single compartment. [12]

The Calf Muscle Venous Pump (CMVP) expels the blood coming from the arterial inflow, acting with a diastolic period and a systolic period for the contraction of the muscles. This begins with the inside AC compression and the peak F torque occurs in the late terminal stance as the E torque is reduced to zero. As the ankle joint moves in a single plane, all the controlling muscles function either as flexors or extensors.

Torque, by definition, is a twisting effort applied to an object that tends to make a turnabout its axis of rotation. The magnitude of torque is equal to the magnitude of the applied force multiplied by the distance between the object's axis of rotation and the point where the force is applied. In many ways, torque is the rotational analogue to force [13].

The hemodynamic of the lower leg's venous return depends then on several factors:

Efficacy = AC torque + Foot squeeze + PC torque + Sequential Mode + Healthy valves

The efficacy is equivalent to the management of the load (Venous Volume) by the torque (Strength of the muscle and maximal range motion of the ankle joint) in sequential mode (including prime of the pump) with healthy valves. Hence, improving one or all of the factors, will improve the efficacy of the pump.

It has been demonstrated that the severity of the reflux, obstruction or both in venous disease is not enough to produce CVI [14], and it has been demonstrated as well that the ROM decreases significantly with increasing C class [CEAP classification for CVI patients [10]. The more symptomatic the CVI patient is, the smaller the ROM of the ankle joint is [15,16]. Fig. 3. Similarly, increasing the ROM as a result of an exercise program increases the performance of the CMVP [17,18,19]. Hence, the key for the rehabilitation of such kinds of patients will be the evaluation and rehabilitation of the ROM of the ankle joint.

Ankle joint movement is limited by means of "soft-parts" and "hard-parts", a radiological study of the foot in front and lateral views has to be considered to look for bony factors, and it can also be considered if the pain, as well as the edema, limits the motion of a joint.

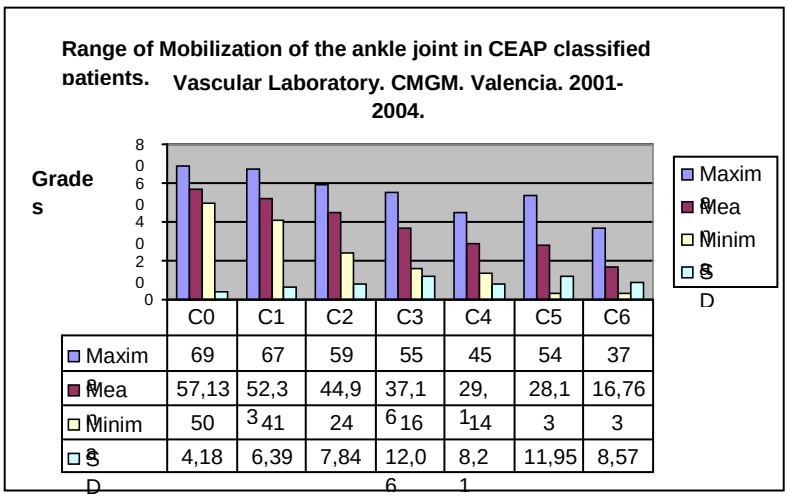


Fig. 3. Decreasing of ROM in the clinical stages (CEAP) of CVI. Source: Maduro-Maytín, C. [20,21]

3.3 Range of Motion Exercises

Andersen has demonstrated that a change of 1.5 cm in the axis of rotation of the ankle results in a change of the peak torque by 8.3% for an extension movement [22]. Hence, any small change in one factor of the ankle movement could cause a bigger hemodynamic effect.

1. Exercises to increase ankle's ROM.

a. The passive and active - non weight bearing motion of the foot.

The motion of the foot can be done by a Physical Therapist (PT), instrumentally, or by the patient. Any of these modalities will have a goal, a program based on a ROM assessment, to avoid pain.

All exercises will be performed on the worktable with the leg fully extended and the knee straight, the same way as the ROM data achieved by goniometry was obtained.

The **Flexion-Extension** is done as follows:

I. The foot is pulled back or pushed forward by the PT, the machine, or the patient. The motion will continue back or forward until the discomfort is felt.
II. This position is maintained for15 seconds.
III. Return to the neutral - rest position.
IV. Repeat steps 1 to 3 ten times

2. Exercises to increase ankle's muscles strength.

a. Isometric Strengthening Exercises.

The foot will be pushing outward (Extensors muscles) or pulling inward (flexors muscles) a fixed object. It will cause a contraction of the muscles and the object will not be moved.

b. Resisted Strengthening Exercises.

Each exercise will be performed with an elastic band or a pulley with weight providing resistance to the movement. Special machines can be used for this purpose. (Pedal stretcher) Fig. 4. A and B.

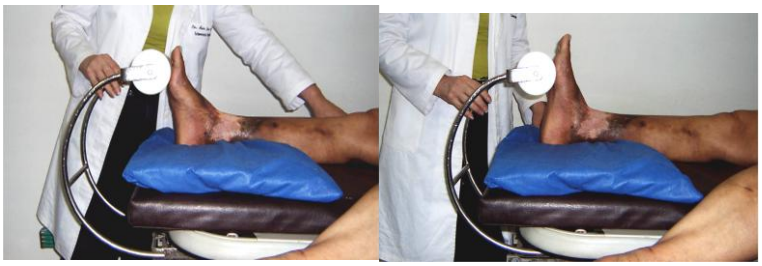


Fig. 4 A. Extension. **Fig. 4. B. Flexion.**

The **Flexion-Extension** exercises are done as follows:

I. The patient pulls his/her foot back or pushes his/her foot forward against the resistance by moving the ankle joint while keeping the knees straight.
II. Return to initial neutral - rest position.
III. The exercise is repeated until the patient gets tired and then he/she gets one minute rest.
IV. Repeat steps 1 to 3 ten times.

V. If the patient is able to lift or push a weight 10 times, the weight is increased for the next session.

3.4 Rehabilitation of Patients with Lymphedema

The lymphedema rehabilitation unit would be designed to educate, assist, rehabilitee and support patients suffering from lymphedema, even though these patients will be less in number compared to the rest of the vascular patients.

The unit will implement the latest approach of rehabilitation to help patients improve their quality of life and ability to manage their lymphedema condition following the advice of the Lymphedema treatment program of the Academy of Lymphatic Studies. Fl. USA.

3.5 Complex Decongestive Physical Therapy (CDPT)

The CDPT components are the Manual Lymph Drainage (MLD), exercises, bandages and skincare, and there are two phases for it:

1. First phase (intensive): The primary goal is to decongest the limb completely. The MLD is performed daily, ideally in the clinic, until the goal is achieved. After the MLD is done, short-stretch bandages are applied.

2. Second phase (improvement and/or maintenance): The MLD is performed as needed. The main goal is to prevent the re-accumulation of evacuated lymph and the lymphatic channels are kept open and active; this way the fibrosis will be treated, ROM increased, and the compression treatment will continue. The patient has to wear a compression garment every day, 24 hours a day and supplementary exercises must be performed. Skin hygiene and medical monitoring are also needed.

Manual Lymph Drainage (MLD) technique: The MLD is a gentle manual treatment technique that improves the activity of the lymph vessels with mild mechanical stimuli to re-route the lymph flow around blocked areas into more centrally located lymph vessels, in order to drain into the venous system. The MLD main goal is to relieve the swelling by increasing the lymphangion intrinsic movements, relieve the pain, increase the parasympathetic neural system effects, create a relaxing effect, and increase lymphatic loads transportation.

Therapeutic Exercises for lymphedema patients will be basically the same as those exercises performed by the patient with CVI. The patient will be wearing the garment to improve the lymph kinetic effects of the joint muscle pumps. Contraction of the muscles is an important part of the treatment as it stimulates the lymphatic system, which greatly assists the lymph drainage and thus helps to reduce the swelling in the limbs. The patient will always be encouraged to walk with a normal gait.

Compression Bandages: When bandaging, a short stretch bandage is used.

Skincare: Patients will be assisted to take care of their skin and nails to avoid infection and the therapy will not proceed until all infections, either bacterial or fungal are under control.

3.6 Other Physical Therapies Modalities

Many are the modalities that have been used in physical therapy. At the beginning of the Service, some of these methods were used and then all were abandoned. They were used to interest and encourage the patient in the execution of the programmed exercises.

4. CONCLUSION

A supervised Vascular Rehabilitation program has demonstrated the improvement of the absolute walking distance and the elimination of pain at rest of peripheral obstructive arterial origin, the

adequate treatment of chronic venous insufficiency, the healing of arterial and venous vascular ulcers even in patients previously amputees or disabled to walk and reverse the chances of further amputations, allowing patients to be more functionally independent. In patients with lymphedema, it stops and reverses the pathology.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Widmer LK. Peripheral Venous Disorders: Prevalence and Socio-Medical importance: Observations in 4529 Apparently Healthy Persons: Basle III Study. Bern, Switzerland: Hans Huber. 1978:1-90.
2. Da Silva A, Widmer LK, Martin H, et al. Varicose veins and chronic venous insufficiency: prevalence and risk factors in 4376 subjects in the Basle Study II. Vasa. 1974;3:118-125.
3. Widmer LK. Incidence and course of occlusive peripheral artery disease in geriatric patients. Possibilities and limits of prevention. International Angiology. 1985;4(3):289-94.
4. Widmer, L K. The importance of peripheral- arterial occlusive diseases in medical practice. Conclusions from the Basel study. Schweiz Medicine Wochenschr. 1983;113(49):1824-7.
5. Maduro-Maytin, CL; et al. A Fotopletismografia no Estudo da Insuficiencia Venosa Cronica. Capítulo 13.p.141. Thomaz & Belczak. "Tratado de Flebología e Linfologia". Editora Rubio Ltda. Rio de Janeiro; 2006.
ISBN 85-87600-64-8.
6. Abramowitz HB, et al. The use of Photoplethysmography in the assessment of venous insufficiency: A comparison to venous pressure measurements. Surgery. 1979;86:434-441.
7. Nicolaides AN, Miles C. Photoplethysmography in the assessmentof venous insufficiency. Journal Vascular Surgery. 1987;5:405-412.
8. Nicolaides AN, et al. Investigation of Chronic Venous Insufficiency. A Consensus Statement. Circulation. 2000;102-126.
9. Maduro-Maytin CL, Maduro-Maytin M. Theoretical bases. Types of goniometers. 67-69. Vascular Rehabilitation. Venous-Arterial-Lymphatic.2021. Lambert Academic Publishing.
ISBN: 978-620-3-85603-3
10. Sanfelippo PM. The evolution of the management of claudication due to peripheral arterial disease. Journal of the American College of Angiology. 2003;1(2):221-223.
11. Hiatt WR, Nawaz D, Regensteiner JG, Hossack KF. The evaluation of exercise performance in patients with peripheral vascular disease. Journal of Cardiopulmonary Rehabilitation. 1988;12: 525-532.
12. Alami YS, et al. Venous pump of the calf: A study of venous and muscular pressure. Journal of Vascular Surgery. 1994;20(5):728-35.
13. Araki CT, et al. The significance of calf muscle pump function in venous ulceration. Journal of Vascular Surgery 1994;20:872-9.
14. Christopoulos DG, Nicolaides AN, et al. Pathogenesis of venous ulceration in relation to the calf muscle pump function. Surgery. 1989;106:829-35.
15. Back TL, Padberg FT, et al. Limited range of motion is a significant factor in venous ulceration. Journal of Vascular Surgery. 1995;22(5):519-23.
16. Dix FP, et al. Venous disease is associated with an impaired range of ankle movement. European Journal of Vascular and Endovascular Surgery. 2003;25(6):556-61.
17. Yang, D; et al. Effect of exercise on calf muscle pump in patients with chronic venous disease. British Journal of Surgery, 1999;86(3):338-41.
18. Kan YM, Delis KT. Hemodynamic effects of supervised calf muscle exercise in patient with venous leg ulceration: a prospective controlled study. Arch Surgery. 2001;136(12):1364-9.
19. Belczak CEQ. Reabilitacao cinesioterapica da bomba muscular da pantorrilha na Insuficiencia Venosa Cronica. En: Godoy MFG. Reabilitacao linfovenosa. Rio de Janeiro: DiLivros. 2005;187-201.
20. Maduro-Maytin CL. Inclusion of the Range of Motion (ROM) of the ankle joint as part of the evaluation of patients with Chronic Venous Insufficiency. PhD Thesis; 2007.

21. Maduro-Maytín CL, Evi Kalodiki et al. The range of motion of the ankle joint as part of the evaluation of patients with chronic venous insufficiency. Chapter 29. Tips and tricks in Angiology. 2016. Minerva Ed.
22. Andersen H. Reliability of isokinetic measurements of ankle dorsal and plantar flexors in normal subjects and in patients with peripheral neuropathy. Arch Physical Medicine Rehabilitation. 1996;77(3):265-8.

Biography of author(s)

Prof. Castor Leonardo Maduro-Maytín
University of Carabobo. MD, MSc, PhD. Director of the Vascular Laboratory and Vascular Rehabilitation Service CMGM Retired, Venezuela.

He obtained MD degree, University of Carabobo, (UC) Valencia, Venezuela in 1973, And PhD. UC 2007. He is a Professor of Surgery, UC, 1980-2009, a Magister Scientiarum Surgery, Central University of Venezuela, Caracas, Venezuela. He has Training at Minnesota University Hospital and Saint Paul Ramsey Medical Center. USA, Sociedad de Beneficiencia Portugesa (Hospital Infante Henrique) -Instituto de Molestias Cardiovasculares, Sao José do Rio Preto. Sao Paulo, Brasil . He was a Member of the Venezuelan Society of Surgery, Director of the Phlebology and Lymphology Committee 2003-2011, Director of the Thoracic and Cardiovascular Surgery Section, 1991-1992, Venezuelan Society of Phlebology and Lymphology. Founder 1992, President 1995-1998 , Society of Vascular Technology. USA, He published “The Range of Motion of the ankle joint as part of the evaluation of patients with chronic venous insufficiency”. Chapter 29. “Tips and Tricks in Angiology”. Allegra. Edizioni Minerva Medica. Torino. 2016 ISBN: 978-88-7711-868-4. And “A Fotopletismografia no etudo daInsuficiencia Venosa Cronica”. Capítulo 13. “Tratado de Flebología e Linfología”. Joao Batista Thomas / Cleusa Ema Quilici Belczak. Editora Rubio. www.rubio.com.br, Brasil 2006 ISBN 85-87600-64-8.

Ms. Marina Maduro-Maytín
PT, DPT, WCC, CLT-LANA MLD/CDT. Academy of Lymphatic Studies. Director of curriculum, Venezuela.

She is a Faculty, Medical Advisor Academy of Lymphatic Studies, Director of Curriculum, Academy of Lymphatic Studies. Florida. USA. She received her doctoral degree in 2011 from Shenandoah University in Virginia, and her BA in Physical Therapy in 1988 from Washington University in St. Louis, MO. She is licensed as a DPT; she was certified as a wound specialist by the National Alliance of Wound Care (NAWC) in 2004 and as a Lymphatic therapist by the Lymphology Association of North America (LANA) in October of 2008. She received her certification as an MLD/CDT therapist from the Academy of Lymphatic Studies in 1996 and has dedicated her career to lymphedema, wound care, and vascular rehabilitation ever since. Since 1994, she has lectured about lymphedema, wound care and vascular rehabilitation in North America, South America and Western Asia countries at different courses and classes as well as at different congresses and symposiums of Phlebology and Lymphology. She joined the Academy of Lymphatic Studies as an instructor in 2007 and was promoted to Curriculum Director in 2012.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Journal of Phlebology and Lymphology, 2: 1-7, 2009.

Chapter 13
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Determination of Precise Iris Positioning in Ocular Prosthesis Using an Eyewear

M. P. Manjita[1*], A. A. Meena[1], C. Vidya[1] and R. Praveen[1]

DOI: 10.9734/bpi/rdmmr/v8/4966F

ABSTRACT

Positioning the iris to the ideal symmetrical position is a critical step in the fabrication of an ocular prosthesis. Any asymmetry in this position leads to a squinted eye look which leaves a psychological impact on the patient. A correctly placed iris lends a natural and aesthetic appearance to the ocular prosthesis. This case report illustrates the use of transparent graphic grid held in position using a spectacle frame which is easier to use without the need of any assistance.

Keywords: Ocular prosthesis; iris positioning; graph grid; eyewear method.

1. INTRODUCTION

The loss or absence of an eye may be the result of congenital defects, irreparable trauma, tumor, sympathetic opthalmia, etc. Surgical intervention for these ocular lesions often includes the following approaches: evisceration, enucleation or exenteration [1]. The disfigurement caused after an eye loss causes significant physical and psychological disturbance to the patient. Psychological distress can be reduced by timely replacement with suitable ocular prosthesis (stock or custom) [2] Prosthetic replacement of lost eye presents with many challenges one of which being accurate positioning of iris [3]. Any asymmetry in positioning causes a squinted eye appearance which leads to unaesthetic results. Various techniques have been described in literature regarding the proper positioning of the iris each having their own merits and demerits. [4] These include use of pupilometer [4], ocular locator [5], facial landmarks, visual assessment [6], and graph grid [7,8], facebow [9], pupillary distance ruler [10], laser pointer apparatus [11]. The present article describes a simple technique to accurately locate the symmetric position of iris disk assembly while fabricating the prosthesis.

2. CASE REPORT

a. A 46 years old male patient was referred to the department of Prosthodontics with a defect in the right eye. Case history revealed that patient lost his right eye two years back due to traumatic accident.
b. On examination, the defect had a properly healed mucosa and sufficient area that would retain the prosthesis. Hence it was decided to fabricate the custom ocular prosthesis.
c. Conventional steps of fabrication were followed till the try in of wax pattern. The wax pattern onto which the iris had to be placed was well finished to have a pleasing contour with the eyelid.
d. A suitable stock eye having an iris that matches the size and shade of contra lateral eye was selected. The stock eye was trimmed to eliminate the scleral portion and the iris was obtained.
e. A used spectacle frame devoid of glasses was selected for the patient.
f. The transparent graph grid was then fabricated by photocopying paper graph grid on a transparent projector sheet.
g. Transparent graph grid was cut into two equal cutouts such that they fit precisely into the spectacle frame and the size and markings were equal on both the cutouts. (Horizontal and vertical lines on both transparent grid cutouts were coincident to each other.)
h. The cutout grids were then attached to the eyewear frame using cynoacrylate glue.

[1]*Department of Prosthodontics, Goa Dental College and Hospital, India.*
**Corresponding author: E-mail: manjitaprb9@gmail.com;*

i. The patient was asked to look forward and hold the position of the left eye at a normal conversational gaze after wearing the eyewear.
j. The medial and lateral borders of iris of the left eye were marked on the grid. A vertical line was marked through the centre of pupil on the grid using an indelible ink marker. The outline of the iris was then traced. The vertical line was then extended onto the skin of forehead of the patient. A similar line was drawn on the contra lateral side at the exact position after counting the vertical and horizontal lines on the grid.
k. A horizontal line was drawn on the grid through the centre of pupil extending to the contra lateral side grid and on the skin laterally. These horizontal extensions also provide reference points to suitably align the eyewear frame to a constant position repeatedly (Fig. 1).
l. The eyewear was removed and the vertical and horizontal lines were extended to meet on the wax sclera blank which gave the exact position of centre of the iris (Fig. 2).
m. The Iris disk was positioned in the wax scleral blank and confirmed by wearing the eyewear again such that the position of the iris corresponded to the markings made on the grid.
n. The eyewear was removed and position of the iris was checked for symmetry with patient engaged in conversational gaze (Fig. 3A).
o. The prosthesis was flasked, polymerized, finished, polished, stained and delivered to the patient. (Fig. 3B).

3. DISCUSSION

An ocular prosthesis should mimic the natural eye as far as possible, especially the iris. Care has to be taken to obtain the correct interpupillary distance and positioning with respect to the natural eye. Mc Arthur described the technique of using ocular locator for proper positioning of an artificial eye in orbital prosthesis. He also advocated relating the pupil of prosthetic eye to existing natural pupil by facial measurements [6]. Roberts described the use of Pupilometer [5]. Benson suggested the use of visual assessment as a method of choice [7]. The method described here is a simple procedure and is a modification of previously described methods for positioning of the iris. Reference points used here are both vertical and horizontal lines marked on the skin extending through the centre of pupil and hence act as a better guide in comparison to inner can thus of eye alone as used previously in literature [3].

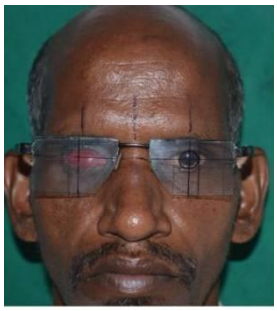


Fig. 1. Vertical and Horizontal extensions marked on the face with the use of eyewear markings

Fig. 2. Markings transferred on the wax scleral blank for iris positioning

Fig. 3. a. Iris positioning confirmed on the wax blank; b. Prosthesis delivered to the patient.

Advantages of the present technique are:

a. It is a simplified technique requiring less chair side time and armamentarium.
b. The use of a transparent graph grid gives accurate position of iris compared to relying on visual assessment.
c. There are less chances of error due to stability of graphic grid by the use of eyewear compared to conventional graphic grid technique.
d. No assistant is required to hold graphic grid.
e. The use of vertical and horizontal reference lines gives the exact location of the iris on the wax scleral blank.
f. The horizontal reference line extending on the skin provides stable and clear reference point for the alignment of eyewear at constant position.

4. CONCLUSION

The method described here has provided good results in terms of patient esthetics, acceptance, and satisfaction. The method is simple to use, less demanding, accurate, and stable in comparison to previously used techniques.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bartlett OS, Moore JD. Ocular prosthesis: a physiologic system. J Prosthet Dent. 1973;29(4): 450-459.
2. Kale E, Mese A, Izgi AD. A Technique for Fabrication of an Interim Ocular Prosthesis. J Prosthodont. 2008;17(8):654-661.
3. Pai UY, Ansari NA, Gandage DS. A Technique to Achieve Predictable Iris Positioning and Symmetry in Ocular and Orbital Prostheses. J Prosthodont. 2011;20(3):244-246.
4. Sathe S, Pisulkar S, Nimonkar SV, Belkhode V, Borle A. Positioning of iris in an ocular prosthesis: A systematic review. J Indian Prosthodont Soc. 2020;20:345-52
5. Roberts AC. An instrument to achieve pupil alignment in eye prosthesis. J Prosthet Dent. 1969;22(4):487-489.
6. McArthur. Aids for positioning prosthetic eyes in orbital prostheses. J Prosthet Dent. 1977;37(3): 320-326.
7. Benson P. The fitting and fabrication of a custom resin artificial eye. J Prosthet Dent. 1977;38(5): 532- 538.
8. Guttal SS, Patil NP, Vernekar N, Porwal A. A simple method of positioning the iris disk on a custom made ocular prosthesis a clinical report. J Prosthodont. 2008;17(3):223-227.

9. Shetty PP, Chowdhary R, Yadav RK, Gangaiah M. An iris positioning device and centering approach: A technique. J Prosthet Dent. 2018;119(1):175-177.
10. Bhochhibhoya A, Mishra S, Mathema S, Acharya B, Maskey B. Alternative Technique of Iris Orientation in a Custom-Made Ocular Prosthesis. J Prosthodont. 2019;28(5):601-604.
11. Belkhode VM, Nimonkar SV, Chaudhary SC, Hakkepatil A, Nimonkar P, Prajapat J. An Innovative Method for Iris Positioning in a Prosthetic Eye. J Contemp Dent Pract. 2020;21(7):815-818.

Biography of author(s)

Dr. M. P. Manjita
Department of Prosthodontics, Goa Dental College and Hospital, India.

She has completed her B.D.S. degree course in 2014 and M.D.S. degree course in 2017 both from Goa Dental College and Hospital, Bambolim, Goa and is working in the same institute from past 2 years. She has many research and review papers in National and International Journals and national level scientific paper presentations. She has also been awarded for many of the paper presentation for the same and also a runner up awardee for the bitein award 2016 held in Mumbai, India.

Dr. A. A. Meena
Department of Prosthodontics, Goa Dental College and Hospital, India.

She has completed her B.D.S degree course in 1983 and M.D.S. degree course in 1987 both from Government Dental College and Hospital, Mumbai Maharashtra. She is currently Professor and Head of the Department of Prosthodontics, Goa Dental College and Hospital, Bambolim, Goa and has been in service at this same institute for the past 34 years. She has several research and review papers in National and International Journals and has several State and National level scientific paper presentations. Her areas of interest include Removable Prosthodontics, Fixed Prosthodontics and Implant prosthodontics.

Dr. C. Vidya
Department of Prosthodontics, Goa Dental College and Hospital, India.

She completed B.D.S. degree course in 1987 from the Goa Dental College and hospital, Goa and M.D.S course from the Government Dental College and Hospital, Mumbai. She is currently Professor in the Department of Prosthodontics at Goa Dental College and has been in service at this institute for 30 years. She is a post- graduate student guide. Among her other publications in accredited journals, she has presentations and publications on the evidence surrounding Face-bow use in prosthodontics and the significance of negative horizontal condylar inclination readings during Face-bow transfer to her credit.

Dr. R. Praveen
Department of Prosthodontics, Goa Dental College and Hospital, India.

He completed his BDS in 2001 and MDS in 2005, both from the Goa Dental College and Hospital, Bambolim. He has a teaching experience of over 16 years and is currently serving as Assistant Professor in the Department of Prosthodontics, Goa Dental College and Hospital. He has over 20 publications in various national and international peer reviewed journals to his credit. His areas of interest include biomaterials and maxillofacial prosthodontics.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
J Dental Sci, 2(1): 000121,2017.

Chapter 14
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Study about Wound Healing, Evolution of Cancer and War on Cancer

Ming C. Liau[1*] and Linda Liau Baker[1]

DOI: 10.9734/bpi/rdmmr/v8/2652E

ABSTRACT

This review highlights the impact of wound onto the evolution and therapy of cancer. The objective of this review is to explore the mechanism of wound healing and its relationship to the evolution and therapy of cancer. Wound healing requires the proliferation and the terminal differentiation (TD) of progenitor stem cells (PSCs), which are the precursors of cancer stem cells (CSCs).Healing wound is not a big deal. If the functionality of chemo-surveillance is intact such as healthy people who can maintain a steady level of wound healing metabolites functioning as differentiation inducers (DIs) and differentiation helper inducers (DHIs).Wounds are always successfully healed without having to put up any effort, just to let the nature to do the healing. Medications such as suture and antibiotics are subsidiary to speed up the healing or to prevent infection. Acute wound affects the functionality of chemo-surveillance only temporarily, which is quickly recovered to return to the normal state. It is the chronic wound such as persistent infectious diseases or exposure to toxic chemicals including carcinogens for a long time that produces damaging effect on the functionality of chemo-surveillance.Chronic wound prompts the production of inflammatory cytokines to cause excessive urinary excretion of wound healing metabolites to affect wound healing. Without sufficient wound healing metabolites to terminate the proliferation of PCSs, it is very easy for PSCs to evolve into CSCs. It takes only a single hit to silence TET-1 enzyme to complete the transition, which is well within the reach of PSCs equipped with abnormally active methylation enzymes (MEs).CSCs can then progress to faster growing cancer cells by the activation of oncogenes or the inactivation of (AML). Cancer due to wound not healing properly is not unique to MDS and AML. It is rather a common phenomenon. War on cancer can be easily won if the battle is conducted following the nature's course to heal the wound, just like the success of wound healing without having to put up any effort in healthy people. Therefore, the best strategy to win the war on cancer is to restore the functionality of chemo-surveillance by the employment of DIs and DHIs and to prevent the loss of wound healing metabolites through anti-cachexia chemicals such as phenylacetylglutamine. Then the nature will take its course to stop the proliferation of cells with abnormal MEs that include CSCs, PSCs, and all cancer cells. Destruction strategy to kill cancer cells is definitely counter indication. It creates more damages to the functionality of chemo-surveillance to stop the growth of cells with abnormal MEs. Inability of destruction strategy to put away CSCs is a deciding factor to deny the success of destruction strategy to win the war on cancer.

Keywords: Wound healing; Change to; evolution of cancer; war on cancer; chemo-surveillance; abnormal methylation enzymes; differentiation inducers; differentiation helper inducers.

1. INTRODUCTION

Wound healing is closely related to the evolution of cancer [1,2,3], because wound healing requires the proliferation and the TD of PSCs, and the evolution of cancer is due to the transition of PSCs to become CSCs. Therefore, if wound is successfully healed, then the transition of PSCs to CSCs scan be avoid. But if wound is not successfully healed, then the transition of PSCs to CSCs is a very likely possibility. MacCarthy-Morrogh and Martin [3] highlight how tissue repair and cancer share cellular

[1]CDA Therapeutics, Inc, 3308 Sky Run Court, Missouri City, TX 77459, USA.
**Corresponding author: E-mail: mingliau@yahoo.com;*

and molecular processes that are regulated in a wound but misregulated in cancer. From sustained proliferative signaling and the activation of invasion and angiogenesis to the promoting role of inflammation, there are many obvious parallels through which one process can inform the other. For some hallmarks, the parallels are more obscure. An analogy between the functions of polyploid cells in normal and malignant tissues and discuss the idea that cell polyploidy is an evolutionary conserved source of tissue regeneration also exploited by cancers as a survival factor. In addition, polyploid cells are highlighted as a promising therapeutic target to overcome drug resistance and relapse [4]. This review examines the issues involved in wound healing and the evolution of cancer. Wound healing is not a big deal. Wounds are always successfully healed without having to put up any effort in healthy people. We can also rely on the same successful wound healing processes to avoid cancer and to win the war on cancer. On the other hand, wounds may not be healed under pathological conditions that result in the loss of wound healing metabolites. Likewise, without the help of wound healing metabolites, cancer cannot be put away. Destruction strategy of cancer therapy is following the course that fails to heal the wound, which can never be able to win the war on cancer.

2. WOUND HEALING

PSCs and CSCs are very much alike on cell features and biological missions. It is very likely that CSCs are originated from PSCs. In the transition, TET-1 enzyme is silenced, which marks the critical difference between PSCs and CSCs [5,6]. PSCs are still able to carry out differentiation programs, relying on TET-1 enzyme to achieve DNA hypomethylation required for the cell to undergo TD [7]. The differentiation capability of CSCs and cancer cells is completely blocked. PSCs are the most primitive cells to give rise to the organs or tissues during embryonic development of the fetus. A small portion of these primitive cells are retained in the organs or tissues to meet the need of expansion or the repair of damage. PSCs and CSCs express ATP binding cassette pumps that can effectively exclude toxic chemicals [8], and have anti-apoptosis programs that can negate apoptosis signals activated by DNA damaging radiation [9]. PSCs and CSCs normally reside dormantly in acidic and hypoxic microenvironment hard to reach by the blood. PSCs and CSCs express chemotactic receptors, thus sensitive to signals calling for the expansion or repair. MEs of PSCs are abnormal like cancer cells due to the association with telomerase [10], making differentiation hard to proceed. Hindrance of differentiation may be a critical mechanism to buildup cell mass for PSCs and CSCs to repair the wound. The proliferation and the TD of PSCs are the most important biological processes for wound healing. Since we do not know how to handle these biological processes, we let the nature to take its course to heal the wound. Wound incites biological response and immunological response. The biological response involves the breakdown of membrane bound phospholipid to release arachidonic acid (AA) for the synthesis of prostaglandins (PGs) [1], which are active DIs good for wound healing to terminate the proliferation of PSCs [11]. Inability to terminate the proliferation of PSCs always runs a risk for PSCs to evolve into CSCs simply by a single hit to silence TET-1 enzyme, which is well within the reach of PSCs equipped with abnormal MEs, and then to progress to faster growing cancer cells by the activation of oncogenes or the inactivation of suppressor genes. The immunological response prompts the production of inflammatory cytokines which are bad for wound healing. Among these cytokines, tumor necrosis factor (TNF) is the most damaging [12]. TNF causes the apoptosis of unipotent stem cells on one hand, and causes the symptom of cachexia on the other hand to result in the collapse of chemo-surveillance, which is a natural defense mechanism to prevent the buildup of cells with abnormal MEs such as PSCs and cancer cells [13]. The metabolites responsible for chemo-surveillance are the metabolites involved in wound healing [11,14]. Therefore, the perfection of wound healing is the natural defense mechanism to avoid cancer [15].

Healing wound is not a big deal. Wounds are always successfully healed without having to put up any effort, just to let the nature to do the healing. Medications such as suture and antibiotics are subsidiary to speed up the healing or to prevent infection. If chemo-surveillance is intact such as healthy people who can maintain a steady level of wound healing metabolites functioning as DIs and DHIs [13,14], then a spike of PGs produced in response to wound can promote perfect wound healing to avoid cancer. Chemo-surveillance metabolites are made up by DIs and DHIs. DIs are chemicals that can eliminate telomerase from abnormal MEs and DHIs are chemicals inhibitory to the enzymes of ternary MEs consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)- S-adenosylhomocysteine hydrolase (SAHH) [16]. SAHH is a steroid hormone receptor, very responsive

to steroid hormones and other growth factors. MEs of cells expressing telomerase such as PSCs and cancer cells are abnormal due to the association with telomerase as above described [10]. The abnormal MAT-SAHH isozyme pair display Km values 7-fold higher than the normal isozyme pair [10,16]. The higher Kmvalues enable cancer cells to maintain larger pool sizes of S-adenosylmethionine (AdoMet) and S- adenosylhomocysteine (AdoHcy), which are the reasons why abnormal MEs are exceptionally stable because AdoMet can protect protein against protease digestion [17]. Stable and active MEs are essential for the promotion of malignant growth. It has been shown by Chiba et al. [18] that the pool sizes of AdoMet and AdoHcy shrunk greatly when cancer cells were induced to undergo TD. Thus, destabilization of abnormal MEs is a critical mechanism to terminate proliferation of cells with abnormal MEs. DIs are more important than DHIs for the induction of TD. DHIs are totally ineffective without DIs [19]. However, DHIs are also essential for the completion of the induction of TD. TD induced by DIs alone is often incomplete due to damages caused by DIs to interrupt differentiation process [11,19]. The damages are very likely due to the conversion of MTs into nucleases when ternary MEs are destabilized to dissociate into monomeric enzymes. Such damages can be prevented in the presence of DHIs to achieve completion of TD. Completion of TD is important for the therapy of cancer, because the damages to interrupt differentiation can be repaired to result in recurrence.Therefore, combination of DIs and DHIs is essential for the formulation of good cell differentiation agents (CDA).

The membrane hyperpermeability triggered by wound is a necessary evil to allow the release of DIs and DHIs, which function as a brake to prevent the proliferation of PSCs, from inside of PSCs so that PSCs can proliferate to work on the repair. Localized inflammatory response is helpful for the wound healing. The very active DIs of PGs synthesized definitely are the nature's design for the wound healing. PGs plus sufficient chemo-surveillance metabolites are good enough to heal the wound perfectly. Although inflammatory cytokines are also produced in the process, the bad effect of cytokines is usually overwhelmed by the good effect of wound healing metabolites. Therefore, when the functionality of chemo-surveillance is intact, the outcome is always perfect wound healing. But if the functionality of chemo- surveillance has been compromised due to existing pathological conditions, then the bad effect of TNF prevails to interfere TD of PSCs, so that wound cannot be healed as expected. PSCs keep on proliferating to evolve into CSCs and then to faster growing cancer cells [15].

3. CANCER ARISES AS A CONSEQUENCE OF WOUND NOT HEALING PROPERLY

Acute wound affects chemo-surveillance only temporarily, which is quickly recovered to return to the normal state. It is the chronic wound such as persistent infectious diseases or exposure to toxic chemicals including carcinogens for a long time that produces damaging effect on chemo-surveillance to affect wound healing. This is exactly the case of MDS. MDS often starts with a display of an immunological disorder [20], which prompts the production of inflammatory cytokines. Among such cytokines, TNF is the critical factor related to the development of MDS [12]. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets, and neutrophils. TNF is also named cachectin, because of its causation of cachexia symptom commonly shared by cancer and inflammatory patients. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites because of vascular hyperpermeability caused by TNF [21,22]. As a consequence, chemo-surveillance normally operating in healthy people to keep PSCs in check becomes dysfunctional, allowing PSCs to buildup in order to replenish unipotent stem cells wiped out by TNF. The high level of telomerase in the peripheral and bone marrow leukocytes in MDS patients is an indication of the widespread multiplication of PSCs [23,24]. During the course of MDS progression, mutations affecting enzymes are frequently observed [25-27], which may play significant roles on the evolution of PSCs to become CSCs [28]. As anemia in MDS patients becomes worse, chromosomal abnormalities such as translocations and deletions characteristic of cancer cells arise to accelerate replication, eventually pushing MDS patients to progress to AML [29-32].

Cancer due to wound not healing properly is not unique to MDS and AML. It is rather a common phenomenon. We have previously observed that the protection of the integrity of chemo- surveillance by Antineoplaston A10, namely phenylacetylglutamine, could effectively prevent chemical

carcinogenesis [33,34], and achieve effective therapy of early stage cancer [13]. These observations strongly support our hypothesis that cancer arises due to wound not healing properly [15]. We have also observed that abnormal MEs were detectable in preneoplastic hyperplastic nodules before the appearance of carcinomas during chemical hepatocarcinogenesis [35]. This was an indication that carcinomas were derived from cells expressing abnormal MEs in the preneoplastic stage, which were very likely PSCs. So the occurrence of human cancer and experimental animal cancer all suggests that cancer is originated from PSCs because of the failure of wound healing.

4. WAR ON CANCER

President Nixon declared war on cancer in 1971 [36,37]. A presidential project is either to solve a catastrophic national crisis such as the Manhattan Project of President Roosevelt to develop atomic bomb to finish World War II, or to establish a monumental national honor such as the Apollo Project of President Kennedy to send the people to the moon and back. Apparently, President Nixon considered solution of cancer a monumental national honor to declare war on cancer. It was a big challenge to the health profession. But unfortunately the health profession failed the challenge to put cancer away during the 5 years of intensive presidential support and the following 45 years of almost entire national support allocated to cancer. Destruction that includes cytotoxic chemotherapy and radiation therapy was the choice of cancer establishments to combat cancer in the past but failed to put cancer away. Destruction actually is inappropriate for the therapy of a disease arising due to wound not healing properly. It is following the course that fails to heal the wound. It creates more wounds to aggravate the already bad situation. It can kill sensitive cancer cells and stem cells, but the damages it created promote the proliferation of CSCs and PSCs to work on the repair. The end result is to replace sensitive cancer cells with tough untreatable CSCs and the buildup of PSCs to evolve into additional cancer. The transition of the tumor to one containing predominantly CSCs is now thought to be a primary course of treatment failure [38-42]. Many biological characteristics that enable cancer progression are attributable to CSCs, including angiogenesis, metastasis, and drug resistance. Early stage patients may benefit if the treatment does not fatally damage chemo-surveillance. The recovered chemo-surveillance capability may still be able to subdue CSCs which destruction therapy definitely cannot put away. There is no hope for the cure of advanced patients. The inability to put away CSCs and the contribution to destroy chemo-surveillance lay the ground for inevitable recurrence and fatality even the patients are fortunate to achieve complete remission. So cancer mortalities remain at old time high worldwide. Obviously, killing the majority of sensitive cancer cells cannot win the war on cancer. Some modifications must be done. Modifications to include agents effective on CSCs and to restore chemo-surveillance are very urgent to eliminate the deficiency of destructive agents to win the war on cancer [2,14,36,37,43,44].

War on cancer can be easily won if the battle is conducted following the nature's course to heal the wound, just like the success of wound healing without having to put up any effort in healthy people. The key to the success of wound healing is the completion of TD of PSCs, which can be achieved with sufficient wound healing metabolites functioning as DIs and DHIs to destabilize abnormal MEs. Apparently, metabolites involved in wound healing are readily accepted into PSCs and CSCs protected by drug resistance mechanisms, which are most suitable agents for the termination of cells with drug resistance mechanisms. The success of cancer therapy depends greatly on the eradication of CSCs [37,44,4]. At present wound healing metabolites are the best hope to win the war on cancer [2,14,19].

5. CDA-2 AS A PERFECT CANCER DRUG

Perpetual cell replication is the hallmark of cancer. There are multiple issues involved to make cancer cells to replicate perpetually: the breakdown of cell membrane to become hyperpermeable because of destruction insults due to accidental injuries, surgery, infections, or toxic chemicals including carcinogens; the breakdown of chemo-surveillance due to membrane hyperpermeability sustained because of destruction insults to manifest cachexia symptom leading to the collapse of chemo-surveillance; the failure of wound healing due to the collapse of chemo-surveillance resulting in the evolution of PSCs to become CSCs; and the activation of oncogenes or inactivation of suppressor genes to progress to faster growing cancer cells. A perfect cancer drug must be the one that can

resolve all issues involved in the evolution of cancer. CDA-2 is such a perfect cancer drug. CDA-2 was the invention of Liau [45], which was a preparation of natural wound healing metabolites purified from freshly collected male urine of college students by reverse phase chromatography employing XAD- 16 as the adsorbent. It contains AA as a major DI, pregnenolone, steroid metabolites, and uroerythrin as DHIs, and phenylacetylglutamine as an active anti-cachexia chemical [14,45]. DIs and DHIs solve the blockade of differentiation to promote TD of cancer cells. By promoting TD, it also put to rest the issues of oncogenes and suppressor genes. Afterall oncogenes and suppressor genes are cell cycle regulatory genes. These genes have important roles to play when cells are in cell cycle replicating. But if replicating cells have exited cell cycle to undergo TD, they have no roles to play. Therefore, induction of TD is an easy solution of gene abnormalities which are otherwise very difficult to solve. Phenylacetylglutamine takes care of cachexia problem to prevent the loss of surveillance metabolites. So CDA-2 can take care of all important issues contributing to the development of cancer to qualify as a perfect cancer drug.

CDA-2 has been approved by the Chinese FDA for the therapy of MDS in 2017. MDS is a disease attributable entirely to CSCs [28]. In comparison to vidaza and decitabine, the two drugs approved by the FDA of USA, CDA-2 has a slightly better therapeutic efficacy based on cytological evaluation, and marked better therapeutic efficacy based on hematological improvement evaluation [2,46]. Cytological evaluation is based on the assessment of circulating cancer cells, and hematological improvement evaluation is based on the requirement of blood transfusion. Additionally, CDA-2 is devoid of serious adverse effects, whereas vidaza and decitabine are proven carcinogens [47], and very toxic to DNA [48-50]. Obviously, CDA-2 is the drug of choice for the therapy of MDS.

The therapeutic endpoint of CDA formulations is the TD of cancer cells. This endpoint is the same endpoint for the evaluation of hematological cancers undergoing destruction therapy. There is no problem for the acceptance of CDA- formulations for the therapy of hematological cancers. As for the therapy of MDS, these preparations should be considered as the standard of care, because the therapy of MDS requires the differentiation of pathological CSCs to become functional cells. The acceptance of CDA-formulations for the therapy of solid tumors is a problem, because the evaluation of the therapeutic endpoint is not available. Disappearance of tumor mass is not a valid therapeutic endpoint for CDA formulations. At present, they can be accepted for the therapy of untreatable cancers enriched with CSCs such as malignant brain tumors, pancreatic cancer, and melanoma. But for other more popular cancers, we can only hope to use CDA formulations as complementary therapy to assist whatever destruction therapy cannot accomplish such as the problems of CSCs, membrane hyperpermeability, cachexia, and chemo- surveillance. If surviving tumor mass is a fearful concern, combination therapy may be a solution. A combination with surgery is a perfect combination. Surgery to remove surviving tumor mass can eliminate fearful concern, and the application of CDA formulations can assure quick recovery of the surgical wound and the prevention of possible metastasis. Treatment alternately with cytotoxic chemotherapy may be another winning combination for both, relying on cytotoxic drugs to eliminate tumor mass and CDA-formulations to eradicate CSCs and to restore chemo-surveillance. The combination with immunotherapy may be another winning combination. CSCs are PSCs minus TET-1 enzyme [5-6]. The immunity of CSCs is almost the same as that of PSCs, which is tolerable to the immune system. So even a successful immunotherapy is developed for cancer therapy, it may need CDA formulations to subdue CSCs. Therefore, CDA formulations are very helpful to assist other therapies to win the war on cancer.

6. CONCLUSION

Wound healing requires the proliferation and the TD of PSCs which are the precursors of CSCs. It takes only a single hit to silence TET-1 enzyme to convert PSCs to CSCs, which is well within the reach of PSCs equipped with abnormally active MEs. Therefore, the success of wound healing is very critical to avoid the evolution of cancer. Healthy people produce a steady level of chemo-surveillance metabolites active as DIs and DHIs, which are actually wound healing metabolites to ensure the success of wound healing. Wound healing metabolites acts on abnormal MEs to promote TD. When the functionality of chemo-surveillance is intact, wound healing can always be assured to avoid cancer. But if the functionality of chemo- surveillance is damaged due to chronic wound causing excessive urinary excretion of wound healing metabolites, then it is very likely that wound cannot be

healed properly to let the proliferation of PSCs to continue beyond what is necessary to complete wound healing and to evolve into CSCs and then to progress to more faster growing cancer cells. The perfection of wound healing by the employment of wound healing metabolites active as DIs and DHIs and the prevention of the loss of wound healing metabolites with anti-cachexia chemicals such as phenylacetylglutamine is the best strategy to win the war on cancer. Destruction strategy to kill cancer cells definitely is inappropriate for cancer therapy. It creates more wounds to further damage the functionality of chemo-surveillance to the extent beyond restoration. Its inability to eradicate CSCs is a deciding factor to deny the success of destruction strategy to win the war on cancer.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ho ATV, Palla AR, Blake MR, Yual ND, et al. Prostaglandin E2 is essential for efficacious skeletal muscle stem cell function, augmenting regeneration and strength. Proc Natl Acad Sci USA. 2017;114:6675-6684.
2. Liau MC, Kim JH, Fruehauf JP. Destabilization of abnormal methylation enzymes to combat cancer: Nature's choice to win the war on cancer. Lambert Academic Publishing. 2020;978-620-2- 66889-7.
3. MacCarthy-Morrough L, Martin P. The hallmarks of cancer are also the hallmarks of wound healing. Since Signaling. 2020;13:648.
4. Moein S, Adibi R, de Silva Meirelles L, Nardi NB, et al. Cancer regeneration: Polyploid cells are the key drivers of tumor progression. Biochim Biophy Acta-Reviews on Cancer. 2020;188408.
5. Kudo Y, Tateishi K, Yamamoto K, Yamamoto S, et al. Loss of 5- hydroxymethylcytosine is accompanied with malignant cellular transformation. Cancer Sci. 2012;103(4):670-676.
6. Ficz GM, Giben JG. Loss of 5- hydroxymethylcytosine in cancer: Cause or consequence? Genomics. 2014;104(5):352-357.
7. Liau MC, Lee SS, Burzynski SR. Hypomethylation of nucleic acids: A key to the induction of terminal differentiation. Intl J Exptl Clin Chemother. 1989;2:187-199.
8. Zhou S, Shultz JD, Bunting KD, Calapietro KM, et al. The ABC transporter Bcrp/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side population phenotype. Nat Med. 2001;7(9):1028-1034.
9. Zhang M, Atkinson RI, Rosen JM. Selective targeting of radiation resisting tumor initiation cells. Proc Natl Acad Sci USA. 2010;107(8):3522-3527.
10. Liau MC, Zhuang P, Chiou GCP. Identification of the tumor factor of abnormal methylation enzymes as the catalytic subunit of telomerase. Chin Oncol Cancer Res. 2010;7(2):86-96.
11. Liau MC, Kim JH, Fruehauf JP. Arachidonic acid and its metabolites as surveillance differentiation inducers to protect healthy people from becoming cancer patients. Clin PharmacolToxicol Res. 2021;4(1):7-10.

12. Boula A, Voulgarelis M, Grannouli S, Katrinakis G, et al. Effect of cA2 antitumor necrosis factor-antibody therapy on hematopoiesis of patients with myelodysplastic syndromes. Clin Cancer Res. 2006;12(10):3099-3108.
13. Liau MC, Szopa M, BurzynskiB, Burzynski SR. Chemo-surveillance: A novel concept of the natural defense mechanism against cancer. Drug Exptl Clin Res. 1987;13(Suppl 1):77-82.
14. Liau MC, Fruehauf PA, Zheng ZH, Fruehauf JP. Development of synthetic CDA formulations for the prevention and therapy of cancer via targeting of cancer stem cells. J Cancer Stu Ther. 2019;4(1):1-19.
15. Liau MC, Baker LL. Cancer arises as a consequence of wound not healing properly. Thus, perfection of wound healing must be the most appropriate strategy to win the war on cancer. Adv Complement Alt Med. 2021;6(2):ACAM 000637.2021.
16. Liau MC, Chang CF, Saunder GF, Tsai YH. S-Adenosylhomocysteine hydrolases as the primary target enzymes in androgen regulation of methylation complexes. Arch Biochem Biophys. 1981;208:262-272.
17. Prudova A, Bauman A, Braun A, Vitvitsky V, et al. S-Adenosylmethionine stabilize-cystathionase and modulate redox capacity. Proc Natl Acad Sci USA. 2006;103(17):6489-6494.
18. Chiba P, Wallner C, Kaizer E. S- Adenosylmethionine metabolism in HL-60 cells: Effect of cell cycle and differentiation. Biochim Biophys Acta. 1988;971(1):38-45.
19. Liau MC, Kim JH, Fruehauf JP. Potentiation of ATRA activity in HL-60 cells by targeting methylation enzymes. Pharmacol Pharmaceu Pharmacovigi. 2019;3(1):9-17.
20. Williamson PJ, Kruger AR, Reynolds PJ, Hamblin TJ, et al. Establishing the incidence of myelodysplastic syndromes. Br J Haemato. 1994;87(4):743-745.
21. Itkin T, Rafii S. Leukemia cells "gas up" leaky bone marrow blood vessels. Cancer Cell. 2017;32(3):276-278.
22. Passaro D, Di Tullio A, Abarrategi A, Rouault-Pierre K, et al. Increased vascular permeability in the bone marrow microenvironment contributes to disease propression and drug response in acute myeloid leukemia. Cancer Cell. 2017;32(3):324-341.
23. Counter CM, Gupta J, Harley CB, Leber B, et al. Telomerase activity in normal leukocytes and hematological malignancies. Blood. 1995;85(9):2315- 2320.
24. Fu C, Chen Z. Telomerase activity in myelodysplastic syndrome. Chin Med J (Eng). 2002;115(10):1475-1478.
25. Larsson CA, Cote G, Quintas-Cardama A. The changing mutational landscape of acute myeloid leukemia and myelodysplastic syndrome. Mol Cancer Res. 2013;11(8):815-827.
26. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, et al. Clinical and biological implication of driver mutations in myelodysplastic syndromes. Blood. 2013;124(17):2705-2712.
27. Kennedy JA, Ebert BL. Clinical implication of genetic mutations in myelodysplastic syndrome. J Clin Oncol. 2017;35(9):967- 974.
28. Woll PS, Kjallquist U, Chowdhury O, Doolittle H, et al. Myelodysplastic syndromes are propagated by rare and distinct human cancer stem cells in vivo. Cancer Cell. 2014;25(6):794-808.
29. Maeck L, Haase D, Schoch C, Hiddemann W, et al. Genetic instability in myelodysplastic syndrome: detection of microsatellite instability and loss of heterozygosity in bone marrow sample with karyotype alteration. Br J Haemato. 2000;109(4):842-846.
30. Xie D, Hefmann KW, Mori N, Miller CW. Allotype analysis of the myelodysplastic syndrome. Leukemia. 2001;14:805-810.
31. Kuramoto K, Ban S, Oda K, Tanaka H, et al. Chromosomal instability and radiosensitivity in myelodysplastic syndrome. Leukemia. 2002;16(11):2253-2258.
32. Takada A, Goosby C, Yaseen NR. NUP98-HOXA9 induces long term proliferation and blocks differentiation of primary human CD34+ hematopoietic cells. Cancer Res. 2006;66(13):6628-6637.
33. Kampalath BN, Liau MC, Burzynski B, Burzynski SR. Chemoprevention by Antineoplaston A10 of benzo-pyrene- induced pulmonary neoplasia. Drug Exptl Clin Res. 1987;13(Suppl. 1):51-56.
34. Kampalath BN, Liau MC, Burzynski B, Burzynski SR. Protective effect of Antineoplaston A10 in hepatocarcinogenesis induced by aflatoxin B1. Intl J Tiss React. 1990;12(Suppl.):43- 50.
35. Liau MC, Chang CF, Becker FF. Alteration of S-adenosylmethionine synthetases during chemical hepatocarcinogenesis and in resulting carcinomas. Cancer Res. 1979;39:2113-2119.
36. Liau MC, Fruehauf JP. It has been half a century since President Nixon declared war on cancer:

Destabilization of abnormal methylation enzymes has the blessing of the nature to win the war on cancer. Adv Complement Alt Med. 2020;6(1):ACAM.000630.2020.
37. Liau MC, Baker LL. Eradication of cancer stem cells to win the war on cancer. Nov Res Sci. 2021;6(5):NRS.000647,2021.
38. Jordan CT, Guzman ML, Noble M. Cancer stem cells. N Eng J Med. 2006;355(12):1253-1261.
39. Vermueulen L, Sprick MR, Kemper K, Strassi G, et al. Cancer stem cells-old concepts, new insights. Cell Death Differ. 2008;15(6):947-958.
40. Zabierowski SE, Herlyn M. Melanoma stem cells the dark seed of melanoma. J Clin Oncol. 2008;26(17):2890-2894.
41. Hemmings C. The elaboration of a critical framework for understanding cancer: the cancer stem cell hypothesis. Pathology. 2010;42(2):105-112.
42. Magee JA, Piskounova E, Morrison SJ. Cancer stem cells: Impact, heterogeneity, and uncertainty. Cancer Cell. 2012;21(3):283-296.
43. Liau MC, Fruehauf JP. Restoration of the chemo-surveillance capability is essential for the success of chemotherapy and radiotherapy to put cancer away. Adv Complement Alt Med. 2019;5(4):ACAM.000617.2019.
44. Liau MC, Fruehauf JP. The winner of the contest to eradicate cancer stem cells wins the contest of cancer therapies: The winner is cell differentiation agent formulations. Adv Complement Alt Med. 2020;5(4):ACAM.000620.2020.
45. Liau MC. Pharmaceutical composition inducing cancer cell differentiation and the use for treatment and prevention of cancer thereof. US Patent. 2007;7232578B2.
46. Ma J. Differentiation therapy of malignant tumor and leukemia. CSCO Treaties on the Eduction of Clinical Oncology. 2007;480-486.
47. Prassana P, Shack W, Wilson VI, Samid D. Phenylacetate in chemo-prevention of 5- aza-2'-deoxycytidine induced carcinogenesis. Clin Cancer Res. 1995;1(18):865-871.
48. Palii SS, van Emburgh BO, Sankpal UT, Brown KD, et al. DNA methylation inhibitor 5-aza-2'-deoxycytidine induced reversible DNA damages that is distinctly influenced by DNA methyltransferase 1 and 3B. Mol Cell Biol. 2008;28(2):752-778.
49. Kizietepe T, Hideshima T, Catley I, Raje N. 5-Azacytidine, a DNA methyltransferase inhibitor, induces ATR-mediated DNA double strand break responses, apoptosis, and synergistic cytotoxicity with doxorubicine and bortezomib against multiple myeloma cells. Mol Cancer Ther. 2007;6(6):1718-1727.
50. Yang Q, Wu F, Wang F Cai K, et al. Impact of DNA methyltransferase inhibitor 5-aza-cytidine on cardiac development of zebrafish in vivo and cardiomyocyte proliferation, apoptosis, and the homeostasis of gene expression in vitro. J Cell Biochem. 2019;120(10):17459-17471.

Biography of author(s)

Ming C. Liau
CDA Therapeutics, Inc, 3308 Sky Run Court, Missouri City, TX 77459, USA.

He completed Ph. D. in Biochemistry in 1966 at Baylor College of Medicine. He discovered abnormal methylation enzymes of cancer cells during his tenure as assistant and associate professor at MD Anderson Cancer Center, and later identified the tumor factor of abnormal methylation enzymes as the catalytic subunit of telomerase. Abnormal methylation enzymes are responsible for the blockade of terminal differentiation, thus enabling cancer cells to replicate perpetually, which is the hallmark of cancer. He brought up chemo-surveillance as a natural defense mechanism against cancer at Burzynski Research Institute, which was in fact a natural mechanism to ensure wound healing to avoid cancer. Metabolites responsible for chemo-surveillance are wound healing metabolites to direct terminal differentiation of progenitor stem cells. Progenitor stem cells and cancer stem cells are very much alike, thus, wound healing metabolites are the most ideal drugs to take out cancer stem cells. He is now affiliated with the University of California Irvine Medical Center to develop perfect cancer drugs that can take out both cancer stem cells and cancer cells to accomplish a permanent cure of cancer.

Linda Liau Baker
CDA Therapeutics, Inc, 3308 Sky Run Court, Missouri City, TX 77459, USA.

She completed her Bachelor of Science Degree in Pharmacy at Texas Southern University in Houston, Texas in 1994. She worked as a pediatric hematology-oncology pharmacist at Texas Children's Hospital from 1994 through 2001. From there, she remained at Texas Children's Hospital as an Assistant Director of the Pharmacy department from 2001 to 2017. Over the years, she managed many areas of the pharmacy operations, including the inpatient and outpatient oncology unit, bone marrow unit, and cancer center clinic.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
International Research Journal of Oncology, 4(3): 13-20, 2021.

Reviewers' Information
(1) Angel Ramon Sanchez Delgado, Universidade Federal Rural do Rio de Janeiro, Brazil.
(2) Prado, Carina Aline, USP, Brazil.

Chapter 15
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Lectin-positive Spherical Deposits (SPD) in Molecular Layer of Hippocampal Dentate Gyrus of Dementia, Down's Syndrome, and Schizophrenia: Mini Review

Keiko Ikemoto[1*] and Akiyoshi Nishimura[2]

DOI: 10.9734/bpi/rdmmr/v8/5249F

ABSTRACT

Lectins are proteins which specifically bind (or crosslink) carbohydrates. Recent studies have shown the importance of glycosylation in pathogenesis of diseases. We detected lectin-positive spherical deposits (SPD), 3-10 micron in diameter, in the molecular layer of dentate gyrus of hippocampus in dementia, Down' s syndrome, and schizophrenia. The present study is aimed at elucidating the nature and significances of SPD in etiology of neuropsychiatric illnesses. In schizophrenia, SPD was observed without exception, regardless of having history of pharmacotherapy. By using multi-labeling histochemical methods, single strand DNA was co-localized in hippocampal SPD of schizophrenia with lectin, including GSI-B4 for galactose, and UEA-I for fucose, suggesting that SPD formation in schizophrenia is related to apoptotic processes. The molecular basis of SPD formation should further be investigated in brains with neuropsychiatric illnesses.

Keywords: Sugar chain; postmortem brain; apoptosis; dentate gyrus; hippocampus; schizophrenia.

1. INTRODUCTION

Hippocampal neuropathology, as a result of pathognomonic procedures of molecular basis related to memory and cognitive disturbance, has been described in mental disorders such as schizophrenia [1,2]. Glycoconjugates have been implicated to play a major role in the process of cell-cell recognition of development during embryogenesis, and increasing number of diseases came to be known abnormalities in the biosynthesis of sugar chains [3,4]. Abnormal accumulation or deposition of sugar chains in brains of patients with neurodegenerative diseases has been reported [5,6,7]. Recently, lectin-involved pathogenesis of schizophrenia have been described [8,9,10].

Lectin staining is able to reveal several kinds of carbohydrate-related depositions in addition to the conventional degenerative changes including senile plaques, neurofibrillary tangles and corpora amylacea (Table.1, Fig. 1) [6]. According to an old definition,"Lectins are multivalent carbohydrate-binding proteins or glycoproteins except for enzymes and antibodies." As a significant number of exceptions are evident now, such a narrow definition, however, seems no longer relevant. For today, "lectins are defined as proteins which specifically bind (or crosslink) carbohydrates." Previously, we reported lectin-positive spherical deposits (SPD) in the molecular layer of hippocampal dentate gyrus of schizophrenia (Figs. 1, 2, 3), dementia, and Down's syndrome (Fig. 4) [6]. In the present mini-review, possible nature and pathophysiological significance of SPD is shown.

[1]Department of Psychiatry, Iwaki City Medical Center, Iwaki, 973-8555, Japan.
[2]Department of Forensic Medicine, Health Bioscience Institute, University of Tokushima Graduate School, Tokushima, 770-8503, Japan.
**Corresponding author: E-mail: kemoto@iwaki-kyoritsu.iwaki.fukushima.jp;*

2. SPHERICAL DEPOSITS (SPD) IN THE MOLECULAR LAYER OF HIPPOCAMPAL DENTATE GYRUS

Lectin immunohistochemistry using various antibodies that detect sugar chains (Table. 1), combined with conventional staining methods, revealed SPD, 3-10 micron in diameter, in the molecular layer of the dentate gyrus of the hippocampal formation (Figs. 1, 2, 3) from patients with dementia of Alzheimer type, dementia with tangles, Down' s syndrome and schizophrenia, and aged individuals (Fig. 4) [6].

The lectin-positive SPD did not show immunoreactivity for antibodies against ubiquitin and tau-protein, though the corpora amylacea showed clear immunoreactivity for these substances (Fig. 1D-b) [6]. The SPD contained fucose (α-Fuc), galactose (α-Gal) (Figs. 2C, 6), N-acetyl galactosamine (α-GalNAc) (Fig. 5), N-acetyl glucosamine (GlcNAc), sialic acid, mannose (Man) and chondroitin sulfate, suggesting that there might be unusual glycometabolism (Table 1), possibly related to the process of neurogenesis in the molecular layer of hippocampal dentate gyrus (Figs. 5, 6, 7).

3. LECTIN-POSITIVE SPD IN SCHIZOPHRENIA

In brains of patients with schizophrenia, lectin-positive SPD was observed in the molecular layer of dentate gyrus of hippocampal formation, without exception, regardless of previous medication of antipsychotics (Fig. 8). In the lectin-positive SPD, partially disrupted nucleus with decreased staining properties by mean of SYBR Green, a marker of DNA, were detected. Single strand DNA and lectin, including BSI-B4 for galactose (Fig. 7B-a, 7B-b), UEA-I for fucose (Fig. 7C-a, 7C-b), and DBA for N-acetylgalactosamine (Fig. 7A-a, 7A-b) were co-stained in the portion of partially disrupted nucleus (Fig. 7, Table 1). In immuno-electron microscope method, lectin-positive structures were also detected in the portion of partially disrupted nucleus (Figs. 5, 6, 7A-b, 7B-b, 7C-b). These lectin-positive SPD might be produced in a process of apoptosis (Fig. 7) [5,7]. Some experimental studies reported that a kind of therapeutic products of major tranquillizers induced neuron apoptosis [11], whereas, Boiadzhian et al. showed increase rate of apoptosis in case of first-episode neuroleptic free schizophrenia patients [12].

Table 1. Interaction between lectins and antibodies, abbreviation and carbohydrate bindings specificity

Lectin and antibodies	Abbreviation	Carbohydrate binding specificity
Archis hypogaea agglutinin	PNA	Gal(β1,3)GalNAc
Canavalia ensiformis agglutinin	Con A	Branched α-Man (Manα1-6 (Manα1-3) Man)
Datura stramonium	DSA	GlcNAc
Dolichos biflorus agglutinin	DBA	α-GalNAc
Erythrina cristagalli	ECA	Gal(β1,3)GlcNAc
Glycine max agglutinin	SBA	GalNAc(α1,3)Gal
Griffonia simplicifolia iso agglutinin I-B4	GSI-B4	α-Gal
Pisum sativum agglutinin	PSA	Fuc(α1,6)Glc, α-Man
Triticum vulgare	WGA	Manβ(1,4)GlcNAc(1,4)GlcNAc
Ulex europaeus agglutinin	UEA-I	α-Fuc

Interaction between lectins and antibodies, abbreviation, and the carbohydrate binding specificity is shown.

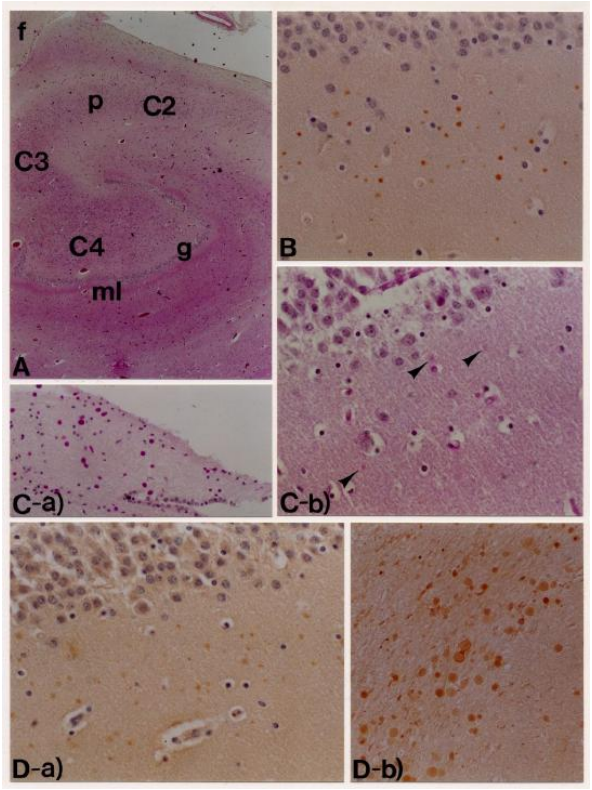


Fig. 1. A: The hippocampal formation stained by Hematoxilin Eosin. g: granular layer, p: pyramydal neuron. ml: molecular layer, f: fimbria; B: SPDs detected by lectin stains. GSI-B4. C-a: Corpora amylacea are intensely stained by PAS. C-b: SPDs are weakly stained by PAS. D-a: SPDs show intense reactivity with anti-chondroitin sulfate. D-b: Corpora amylacea show intense reactivity with anti-tau protein antibody

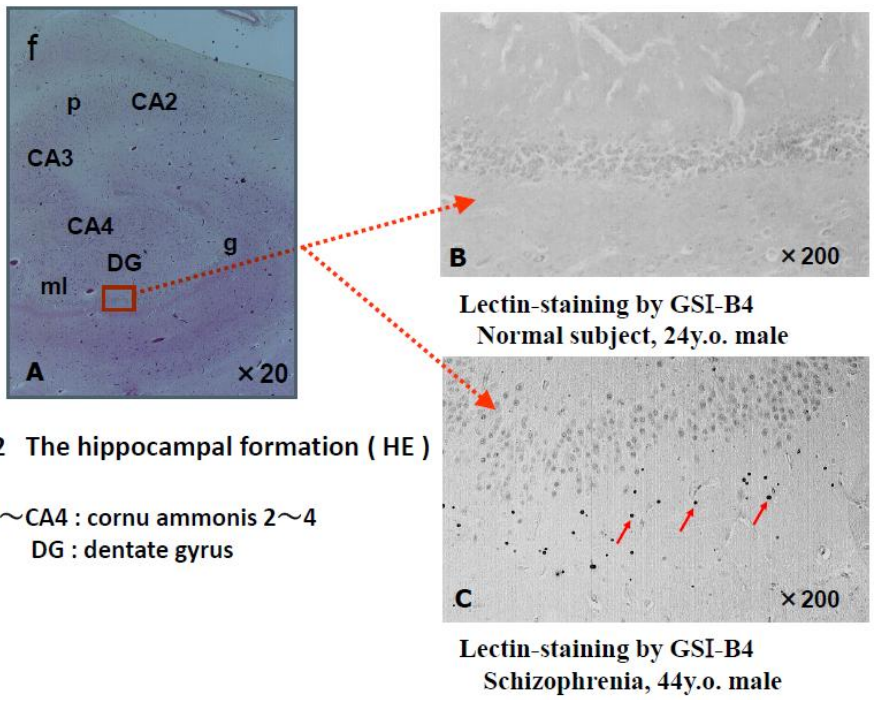


Fig. 2 The hippocampal formation (HE)

CA2～CA4 : cornu ammonis 2～4
DG : dentate gyrus

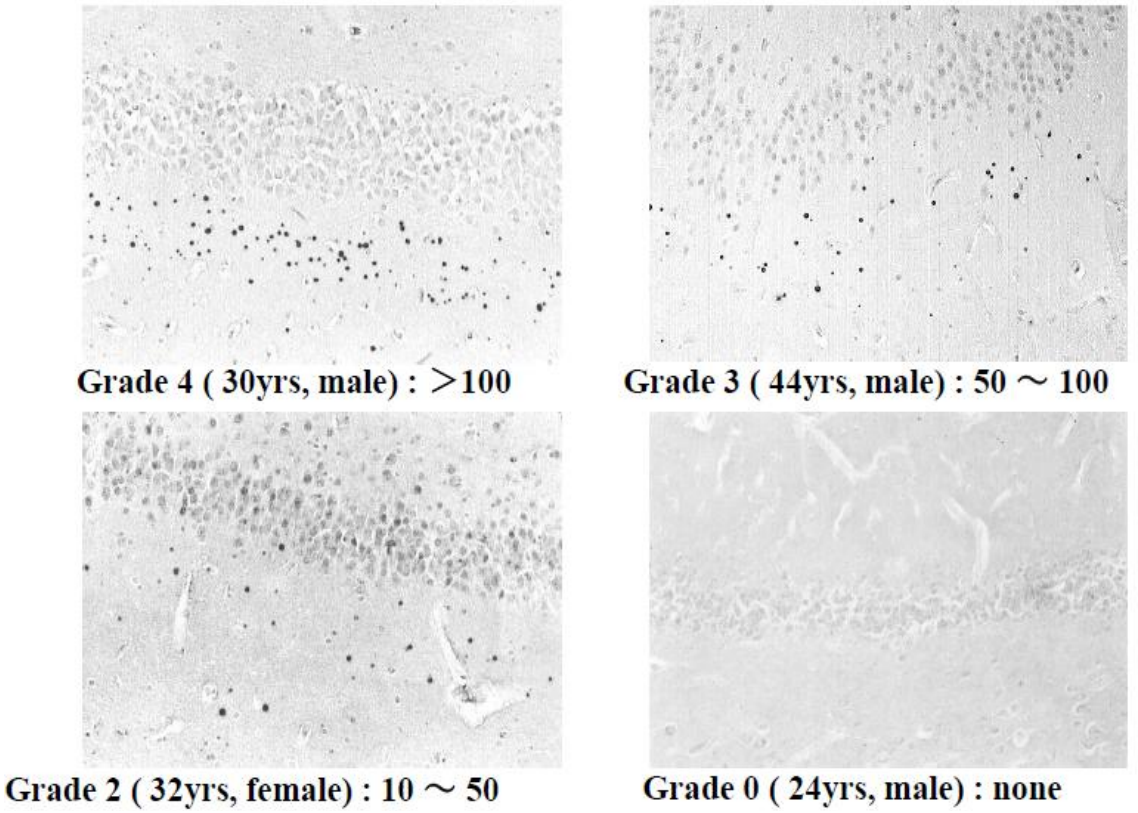


Fig. 3. Frequency (Grade 1～4) of SPD appearance in molecular layer of hippocampal dentate gyrus

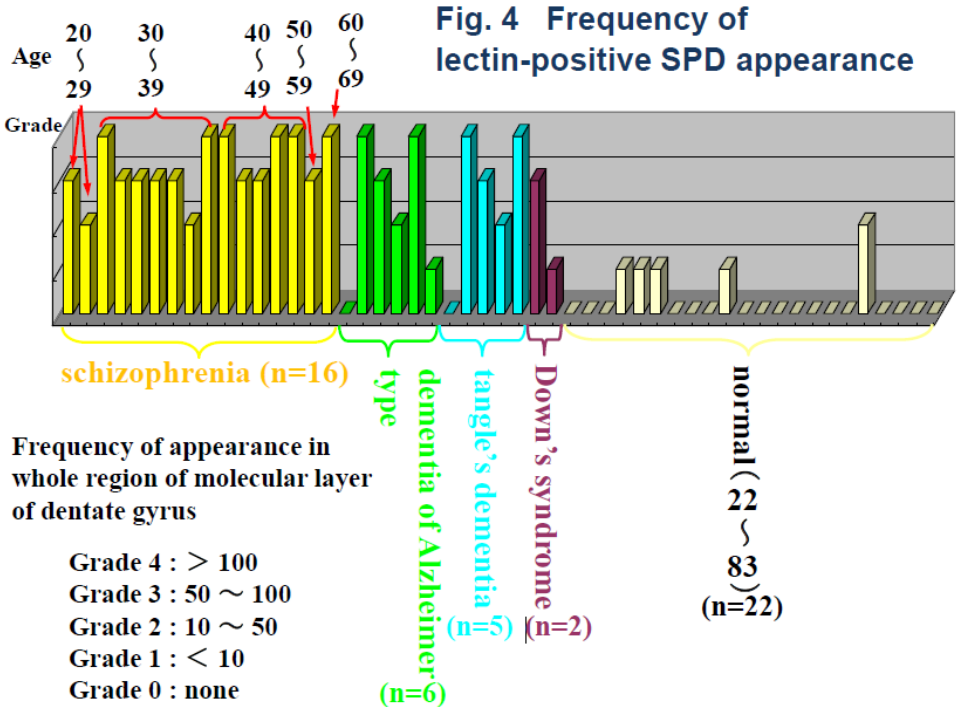


Fig. 4. Frequency of lectin-positive SPD apperance

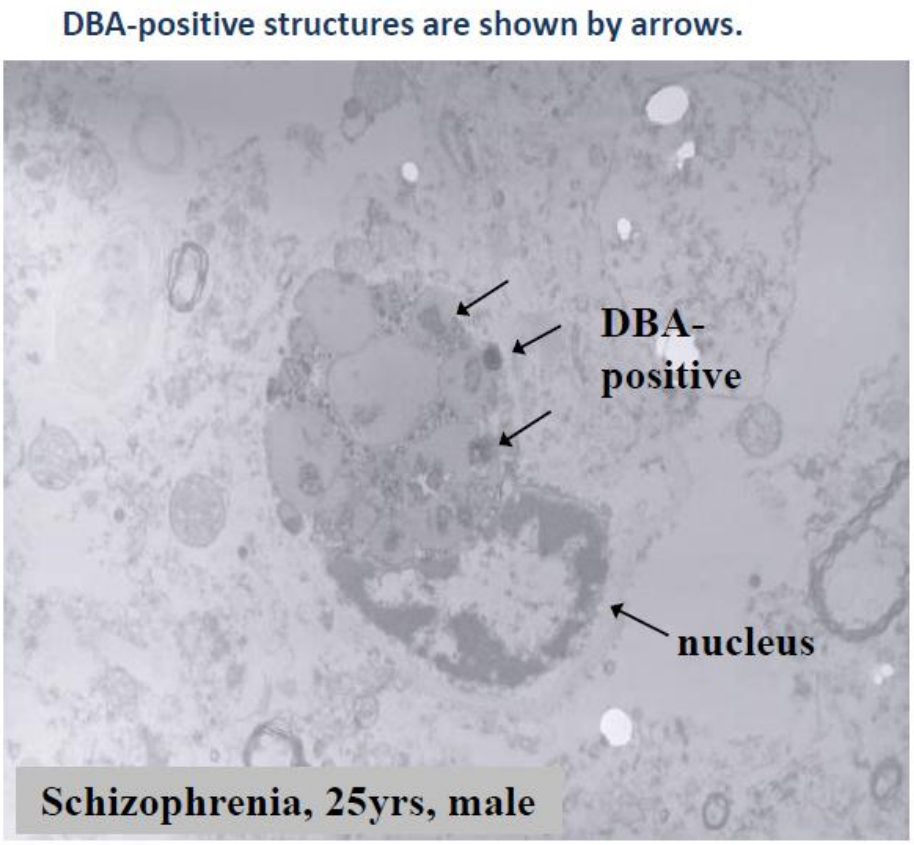


Fig. 5. Ultrastructure of a lectin-stained cell DBA staing for N- acetyl galactosamine (X-GalNAc)

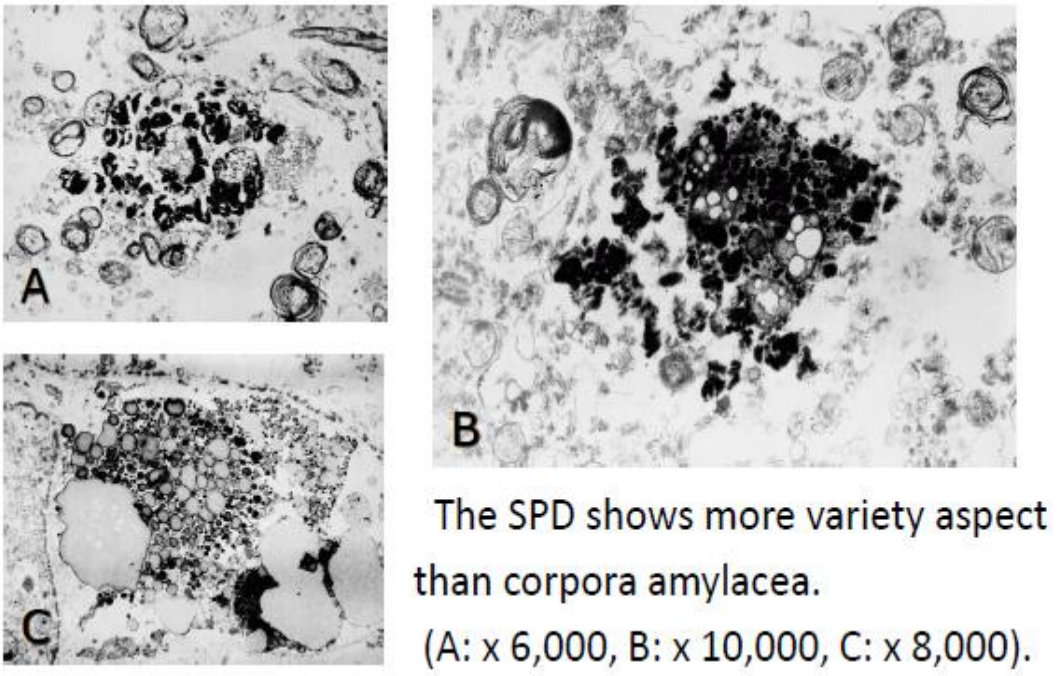


Fig. 6. Ultrastructure of SPD stained by GSI-B4

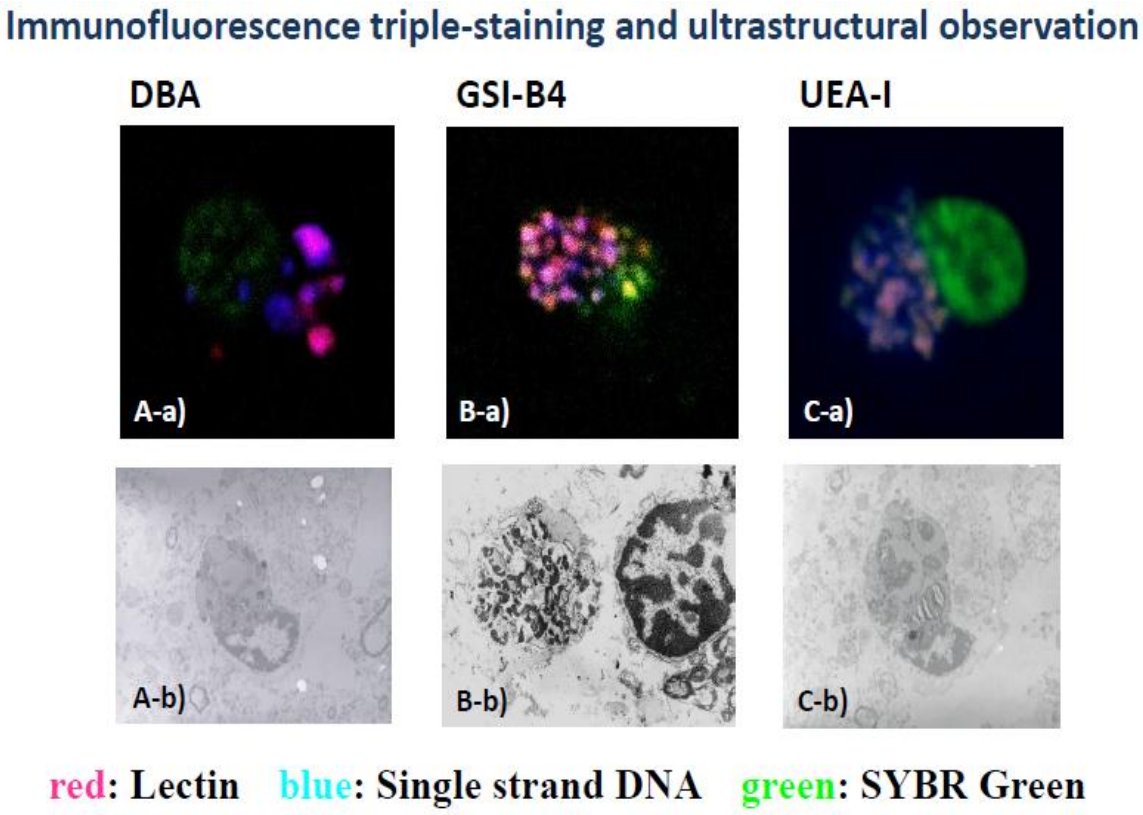


Fig. 7. Lectin-positive SPD in hippocampus of schizophrenia (25 y.o. male)

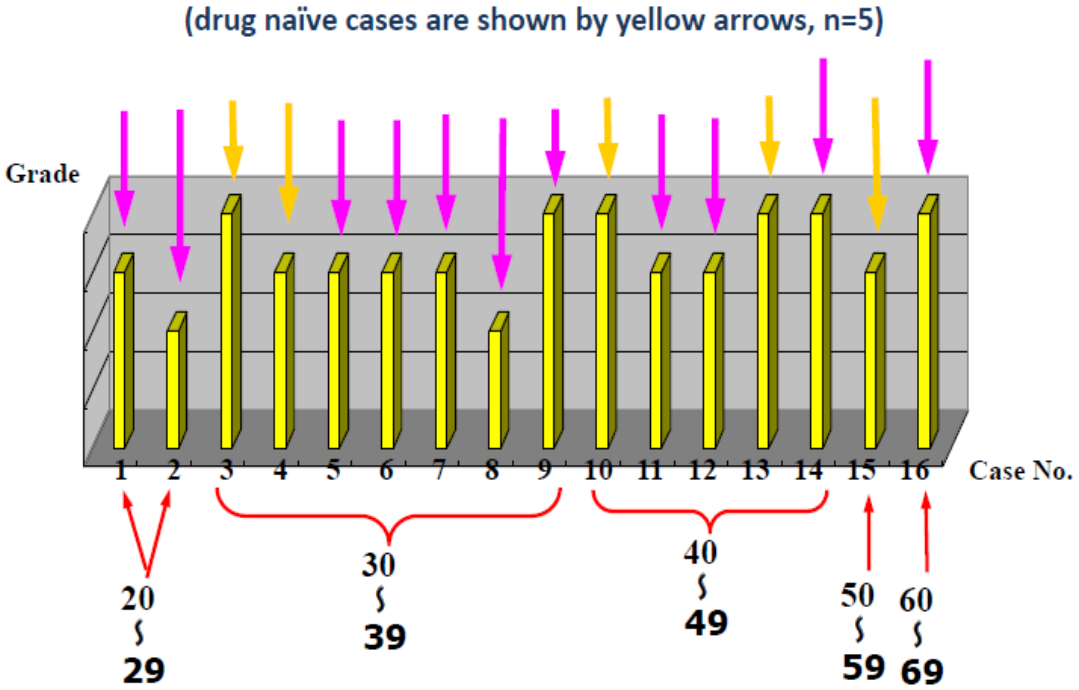


Fig. 8. Lectin-positive SPD was detected both in medicated and drug naïve cases of schizophrenia

4. LECTIN-POSITIVE SPD IN DEMENTIA

In dementia with Alzheimer type, and tangle's dementia, some cases did not contain hippocampal lectin-positive SPD, being different from schizophrenia (Fig. 4). The chemical nature or formation procedures of lectin-positive SPD in dementia, as degenerative disorders, and the distinction between that in natural aging processes also remain to be investigated.

5. DISCUSSION

Recent studies have shown more and more importance of the involvement of altered glycosylation in pathological procedures of neuropsychiatric diseases. In the superior temporal gyrus, altered N-glycosylation of GABAA receptor has been shown in schizophrenia [13]

In our study, it should be noticed that lectin-positive SPD in the molecular layer of dentate gyrus of hippocampal formation in patients with schizophrenia, observed in drug naïve cases, is in accordance with the results in first-episode neuroleptic free schizophrenia patients [12]. The molecular basis of lectin-positive SPD formation of schizophrenia, linked with apoptotic process should further be elucidated [9].

As novel therapeutic strategies, some pharmacodynamic studies have recently shown usefulness of exogenous lectin for brain delivery of intranasally administered drugs of neuropsychiatric diseases such as schizophrenia [14] and Parkinson's disease [15], Studies on lectin physiology as well as lectin pathology would be needed to establish novel methods for diagnoses and treatment of neuropsychiatric illnesses.

6. CONCLUSION

To clarify the pathophysiology of degenerative disorders including Parkinson's disease as well as dementia of Alzheimer type, and to detect newly established biomarkers of neurodegeneration, the nature of lectin-positive SPD should further be analyzed.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kolomeets NS, Uranova N. Ultrastructural abnormalities of astrocytes in the hippocampus in schizophrenia and duration of illness: a postortem morphometric study. World J Biol Psychiatry. 2010;11:282-292.
   DOI: 10.1080/15622970902806124
2. Chung C, Tallerico T, Seeman P. Schizophrenia hippocampus has elevated expression of chondrex glycoprotein gene. Synapse. 2003;50:29-34,
3. Kobata A. A retrospective and prospective view of glycopathology. Glycoconj J. 1998;15:323-331,
4. Tone K, Stappers MHT, Willment JA, Brown GD. C-type lectin receptors of the Dectin-1 cluster: Physiological roles and involvement in disease. Eur J Immunol. 2019;49:2127-2133.
5. Nishi K, Tanegashima A, Yamamoto Y, Ushiyama I, Ikemoto K, Yamasaki S, Nishimura A, Rand S, Brinkmann B. Utilization of lectin-histochemistry in forensic neuropathology: Lectin staining provides useful information for postmortem diagnosis in forensic neuropathology. Leg Med. 2003;5:117-131.
6. Nishimura A, Ikemoto K, Satoh K, Yamamoto Y, Rand S, Brinkmann B, . The carbohydrate deposits detected by histochemical methods in the molecular layer of the dentate gyrus in the hippocampal formation of patients with schizophrenia, Down's syndrome and dementia, and aged person. Glycoconj J. 2000;17: 815-822.

7. Nishimura A. Are lectin positive spherical deposits detected in molecular layer of the hippocampal formation related with neuronal apoptosis? J Med Invest. 2010;57:183-189.
8. Ohi K, Hashimoto R, Yasuda Y, Yoshida T, Takahashi H, et al. The chitinase 3-like 1 gene and schizophrenia: Evidence from a multi-center case-control study and meta-analysis. Schizophr Res. 2010;116:126-132.
9. Aytac HM, Oyaci Y, Yazar MS, Erol A, Pehlivan S. Association of MIF and MBL2 gene polymorphisms with attempted suicide in patients diagnosed with schizophrenia or bipolar disorder. J Clin Neurosci. 2020;78:264-268.
10. Petralia MC, Ciurleo R, Bramanti A, Bramanti P, Saraceno A, et al. Transcriptomic data analysis reveals a down-expression of *Galectin-8* in schizophrenia hippocampus. Brain Sci. 2021;11:973.
DOI: 10.3390/brainsci11080973
11. Abekawa T, Ito K, Nakagawa S, Nakato Y, Koyama T. Effects of aripiprazole and haloperidol on progression to schizophrenia-like behavioural abnormalities and apoptosis in rodents. Schizophr Res. 2011;125:77-87.
DOI: 10.1016/j.schres.2010.08.011
12. Boiadzhian AS, Chavushian AC, Zakharian RV, Mkrtchian GM. Markers of apoptotic dysfunction in schizophrenia. Mol Biol (Mosk). 2013;47:674-680.
13. Mueller TM, Haroutunian V, Meador-Woodruff JH. N-Glycosylation of GABAA receptor subunits is altered in Schizophrenia. Neuropsychopharmacology. 2014;39:528-537.
DOI: 10.1038/npp.2013.190
14. Piazza J, Hoare T, Molinaro L, Terpstra K, Bhandari J, Selvaganapathy PR, Gupta B, Mishra RK. Haloperidol-loaded intranasally administered lectin functionalized poly(ethylene glycol)-block-poly(D,L)-lactic-co-glycolic acid (PEG-PLGA) nanoparticles for the treatment of schizophrenia. Eur J Pharm Biopharm. 2014;87:30-39.
DOI: 10.1016/j.ejpb.2014.02.007
15. Wen Z, Yan Z, Hu K, Pang Z, Cheng X, Guo L, Zhang Q, Jiang X, Fang L, Lai R. Odorranalectin-conjugated nanoparticles: Preparation, brain delivery and pharmacodynamic study on Parkinson's disease following intranasal administration. J Control Release. 2011;151:131-138.
DOI: 10.1016/j.jconrel.2011.02.022

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
J Neurol Neurophysiol, 6(6): 2015.

Chapter 16
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Prenatal Maternal Stress Due to Repeated Exposure to Cold Environment Affects Development of Catecholamine Neurons in Rat Offsprings

Keiko Ikemoto[1*], Teruko Uwano[2], Taketoshi Ono[2] and Hisao Nishijo[2]

DOI: 10.9734/bpi/rdmmr/v8/5250F

ABSTRACT

Using 8-day-old pups and tyrosine hydroxylase (TH) immunohistochemistry, we investigated the influence of maternal recurrent cold stress (RCS) on catecholamine neuron development in offsprings. Between day 10 to 20 day following fertilisation, RCS was loaded into pregnant rats. The frontal and cingulate cortices tended to contain fewer TH-immunoreactive (-ir) fibers, and density of TH-ir varicosities with a large size (more than 7 μm in diameter) was significantly ($p<0.05$) lower in rats prenatally exposed to RCS than controls. In prenatal RCS rats, locus coeruleus neurons had decreased TH immunoreactivity than controls. In the medullary C1/A1 catecholaminergic field, RCS rats had smaller TH-ir neurons and fewer TH-ir fibers, however the differences were not significant. We found no variations in TH-ir structures between the two groups in originating and projection regions of the midbrain dopaminergic system. Prenatal RCS hampered development of catecholaminergic neurons, particularly noradrenergic neurons in pups, according to these studies.

Keywords: Cerebral cortex; locus coeruleus; medulla oblongata; prenatal stress; noradrenaline; development; immunohistochemistry.

1. INTRODUCTION

Prenatal stress affects on emotional and behavioral development of offspring [1,2], and a cause of mental disorders, including schizophrenia and depression [3]. Catecholamines (CA) are neurotransmitters that are thought to be involved in emotion, behaviour, and pathogenesis of psychoses [4]. In postmortem brains of patients with psychoses, histological findings of the catecholamine neuronal system have been reported [5-7]. Maternal repeated cold stress (RCS) also influences on physiological [8-11] or immune functions [12,13] of offsprings.

Based on these facts, morphological changes in brains of prenatally stressed rats were hypothesized. The present study is aimed at investigating developmental effects on CA neurons of offsprings of prenatal RCS loaded mother rats using tyrosine hydroxylase (TH) immunohistochemistry [14, 15].

2. EXPERIMENTAL PROCEDURES

The study adhered current RIGOR guidelines [16,17].

Two female Wistar rats were randomizely selected for loading RCS between day 10 to 20 following fertilization. The treatment group was composed of total of 24 pups (prenatally RCS rats) borne and fostered by the RCS- loaded mother rats. Another female Wistar rat was randomizely selected, and 10 pups borne and fostered by the latter mother rat composed control group.

[1]Department of Psychiatry, Iwaki City Medical Center, Japan.
[2]System Emotional Science, Graduate School of Medicine, University of Toyama, Japan.
**Corresponding author: E-mail: ikemoto@iwaki-city-medical-center.jp;*

The SART (specific alteration of rhythm and temperature) stress apparatus (modified M-9000 apparatus made by Advantec Toyo) consisted of a built-in heater and cooler that could be controlled by an adjustable self-timer. The size of the interior of apparatus was 120 cm in height and 105 X 65 cm in width [8]. Environmental temperature in this apparatus was altered from 24℃ to -3℃ at 1 cycle / 2 h from 10:00 to 18:00 by switching heater and cooler and was kept at -3℃ from 18:00 until 10:00 the following morning [8]. This sequence was repeated four times between 10:00 and 18:00. The lighting was maintained on a 12: 12 light-dark cycle (light, 7:00 to 19:00; dark, 19:00 to 7:00). RCS was loaded to 2 pregnant Wistar rats between day 10 to 20 after fertilization.

A total of 24 prenatal RCS rats (= treatment group) and 10 control rats (= control group) were examined. At postnatal day 8, under deep anesthesia with 10mg / kg of sodium pentobarbital (Nembutal, Dainippon Pharm.), each neonate rat was perfused through the cardiac ventricle with 5 ml of saline (0.9% of NaCl) followed by 20 ml of fixative containing 4% paraformaldehyde or 5% glutaraldehyde [14]. Thirty or 50 μm thick cryostat coronal sections were made from each brain. Detailed procedures for TH immunohistochemistry have been described elsewhere [14].

Details of production, characterization and specificity of TH antiserum have been described elsewhere [15]. Some sections were counterstained with neutral red. Neurons immunoreactive for TH were observed under a light microscope. The atlas by Hokfelt et al. [18] was used to determine anatomical localization of TH-positive neurons.

Image analyses were performed using a software, Win ROOF (version 5.0, Mitani Corporation, Japan) and a self-made PC program to quantify size, and number of varicosities and neural fibers.

3. RESULTS

Average body weights of 8-day-old pups were 13.6±1.32g (n=10) for control rats and 9.90±1.54g (n=24) for prenatal RCS rats, and wet weights of brains were 0.67±0.07g (n=10) for controls and 0.66±0.06g (n=24) for prenatal RCS rats, but there were no significant differences in either body or brain weight (t-test, $p<0.05$). Although there were some individual differences between findings in RCS rats and controls, some evident differences between the two groups were noted.

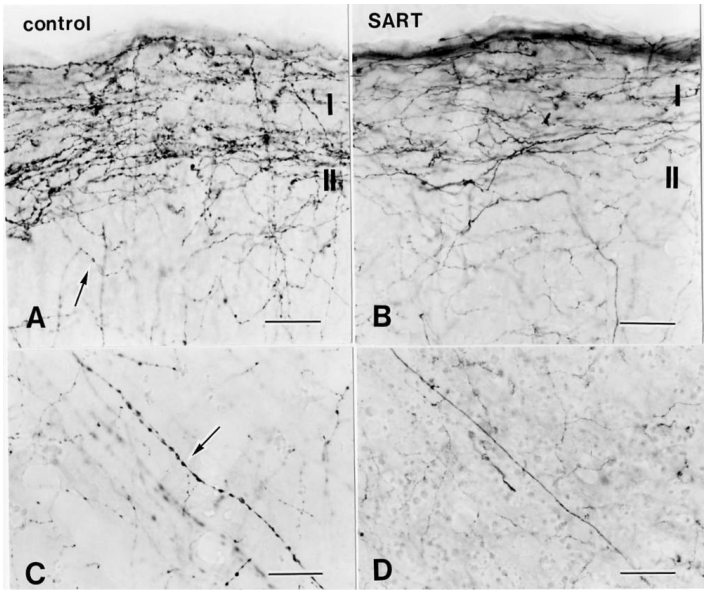


Fig. 1. TH-immunoreactive (-ir) fibers in the frontal cortex, area 2 of 8-day-old pup following maternal exposure to RCS. (A, C) Control rat. (B, D) Prenatal RCS rat. Amount of TH-ir fibers is lower in prenatally RCS rat, especially in layers II and III. Cortical TH-ir fibers of RCS show a reduced number of large varicosities. An arrow indicates a varicose fiber of the control rat. Bar: 25μm

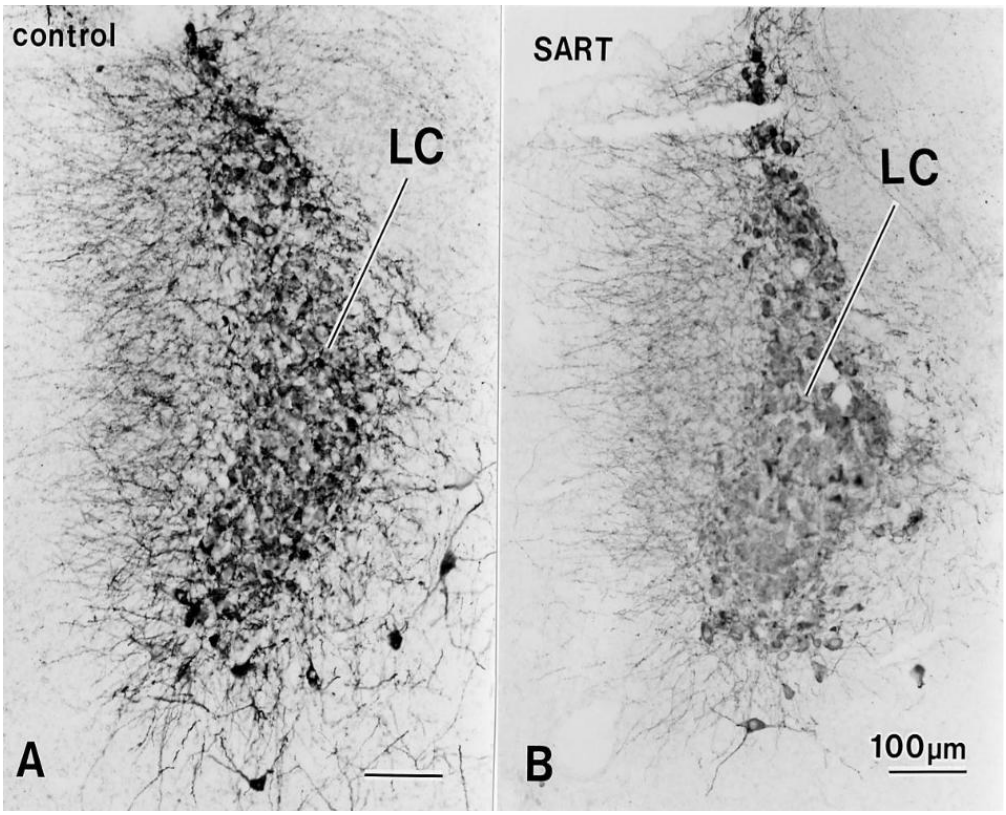


Fig. 2. The LC (A6) neurons of prenatally RCS rats showed lower TH immunoreactivity

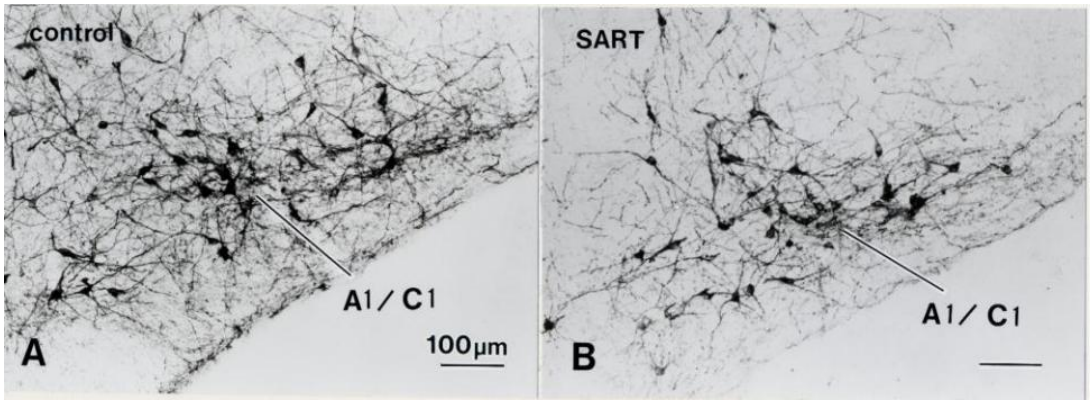


Fig. 3. The medullary A1/C1 region (ventrolateral medulla) of a RCS rat demonstrated small TH-ir neuronal cell bodies and fewer TH-ir fibers

The frontal and cingulate cortices of prenatal RCS rats, especially layers II and III, contained fewer TH-immunoreactive (-ir) fibers than controls (Fig. 1A, B), though there were no significant differences. In these areas, TH-ir fibers demonstrated apparently less TH-ir varicosities (Fig. 1C, D). Image analysis demonstrated that density of large varicosities (more than 7μm in diameter) in TH-ir fibers was significantly ($p<0.05$) less in prenatal RCS rats than in controls.

In the substantia nigra (SN, A9) and ventral tegmental area (VTA, A10), originating nuclei of midbrain dopaminergic system, and in the striatum, their major projection field, there were no apparent differences in stainability or cellular sizes between the two groups. The locus coeruleus (LC), the originating nucleus of noradrenergic neurons, of the prenatal RCS rats showed less intense TH immunoreactivity (Fig. 2A, B).

In the medullary A1 / C1 catecholaminergic region (VLM: vetrolateral medulla) of prenatal RCS rats, TH-ir neurons were likely to be smaller (major axis: 11～30μm) than those in controls (major axis: 15～33μm), and

TH-ir fibers were fewer as shown in Fig. 3A, B. However, comparison of total areas of TH-ir structures in A1 / C1 CA fields in each section by image analysis did not show any significant differences between the two groups ($p<0.05$).

4. DISCUSSION

By examining TH-ir structures of 8-day-old pups, we demonstrated that maternal stress by repeated exposure to a cold environment affected development of fetal CA neurons. This is the first morphological evidence showing developmental influence of prenatal stress on the central nervous system.

In prenatal RCS group, LC and VLM, originating nuclei of noradrenalinergic neurons showed decreased TH-immunoreactivity, smaller TH-ir cell bodies and decreased TH-ir neural fibers, suggesting that prenatal exposure to RCS affects development of fetal noradrenalinergic neurons. The SN and VTA, major originating nuclei of dopamine (DA) neurons, and the striatum, projection field, did not show apparent morphological differences between the two groups. This suggested that prenatal RCS impaired development of noradrenaline (NA) neurons rather than that of DA neurons in pups.

Findings in frontal and cingulate cortices of prenatal RCS pups, such as reduction of TH-ir fibers in all layers, especially in layers II～III, morphologically coincide with those of NA neurons in LC and VLM [19]. Reduction of large TH-ir varicosities (more than 7μm in diameter) in RCS pups implied impaired CA neuronal functions. Such morphological changes in CA neurons of RSC pups were not likely transient, but are to have long-term functional influences [20]. A recent report using restraint stress showed that intense prenatal stress reduced reactivity of NA neuronal systems for stress in adulthood [21]. Alteration of noradrenergic modulation of LTP in hippocampal slice by prenatal stress has also been shown [22].

Though numerous animal studies on prenatal stress using various methods including restraint stress have focused on metabolism and / or turn over of monoamines [20,21,23], to the authors' knowledge, there are no other studies focused on morphological changes in CA neuronal systems.

Our recent studies demonstrated that prenatal RCS rats showed altered emotional development [2], and significantly smaller cingulate cortices on coronal plane (unpublished data) similar to morphological findings in schizophrenia [24]. The cingulate cortex is a brain area vulnerable to prenatal stress, related to pathogenesis of psychoses [25] or developmental deficits [26].

In the present study, analyses were limited only in 8-day-old pups. It remains to be demonstrated whether these changes persist until an adolescent or adult stage. The genetic and/or epigenetic involvement producing present findings should also be investigated.

5. CONCLUSION

Prenatal RCS hampers the development of catecholaminergic neurons particularly noradrenalinergic neurons in pups.

ACKNOWLEDGEMENTS

This study was supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Takahashi LK, Turner JG, Kalin NH. Prenatal stress alters brain catecholaminergic activity and potentiates stress-induced behavior in adult rats. Brain Res. 1992;574:131-137.
2. Tazumi T, Hori E, Uwano T, Umeno K, Tanabe K, et al. Effects of prenatal maternal stress by repeated cold environment on behavioral and emotional development in the rat offspring. Behav Brain Res. 2005;162:153-160.
3. Mednick SA, Cannon TD, Barr CE, Lyon M. Longitudinal perspectives in schizophrenia research: Fetal neural development and adult schizophrenia, Cambridge University Press, Cambridge; 1991.
4. Toru M, Nishikawa T, Mataga N, Takashima M. Dopamine metabolism increases in post-mortem schizophrenic basal ganglia. J Neural Transm. 1982;54:181-191.
5. Akil M, Pierri JN, Whitehead R, Edgar CL, Mohila C, et al. Lamina-specific alterations in the dopamine innervation of the prefrontal cortex in schizophrenic subjects. Am J Psychiatry. 1999;156:1580-1589.
6. Akil M, Edgar CL, Pierri JN, Casali S, Lewis DA. Decreased density of tyrosine hydroxylase-immunoreactive axons in the entorhinal cortex of schizophrenic subjects. Biol Psychiatry. 2000;47:361-370.
7. Benes FM, Todtenkopf MS, Taylor JB. Differential distribution of tyrosine hydroxylase fibers on small and large neurons in layer II of anterior cingulate cortex of schizophrenic brain. Synapse. 1997;25:80-92.
8. Hata T, Kita T, Higashiguchi T, Ichida S. Total Acetylcholine content, and activities of choline acetyltransferase and acetylcholinesterase in brain and duodenum of SART-stressed (repeated cold-stressed) rat. Jpn J Pharmacol. 1986;41:475-485.
9. Hori T, Fukuda M, Suzuki H, Yano S, Ono T. SART stress effects on lymphocyte in the thymus and spleen of normal, adrenalectomized, and sympathectomyzed mice. Clin Immun and Immunopath. 1993;68:243-255.
10. Kawanishi C, Fukuda M, Tamura R, Nishijo H, Ono T. Effects of repeated cold stress on feeding, avoidance behavior, and pain-related nerve fiber activity. Physiol Behav. 1997;62:849-855.
11. Tagoh H, Nishijo H, Uwano T, Kishi H, Ono T, et al. Reciprocal IL-1b gene expression in medial and lateral hypothalamic areas in SART-stressed mice. Neurosci Lett. 1995;184:17-20.
12. Veru F, Laplante DP, Luheshi G, King S. Prenatal maternal stress exposure and immune function in the offspring. Stress. 2014;17:133-148.
13. Lian S, Guo J, Wang L, Li W, Wang J, et al. Impact of prenatal cold stress on placental physiology, inflammatory response, and apoptosis in rats. Oncotarget. 2017;8:115304-115314.
14. Ikemoto K, Satoh K, Maeda T, Fibiger HC. Neurochemical Heterogeneity of the primate nucleus accumbens. Exp Brain Res. 1995;104:177-190.
15. Nagatsu I, Kondo Y, Inagaki S, Karasawa N, Kato N, et al. Immunofluorescent studies on tyrosine hydroxylase: Application for its axoplasmatic transport. Acta Histochem Cytochem. 1977;10:494-499.
16. Lapchak PA. Recommendations and practices to optimize stroke therapy: Developing effective translational research programs. Stroke. 2013;44:841-843.
17. Landis SC, Amara SG, Asadullah K, Austin CP, Blumenstein R, et al. A call for transparent reporting to optimize the predictive value of preclinical research. Nature. 2012;490:187-191.
18. Hokfelt T, Johansson O, Goldstein M. Central catecholamine neurons as revealed by immunohistostochemistry with special reference to adrenaline neurons. In Handbook of Chemical Neuroanatomy. Vol. 2, Classical transmitters in the CNS, Part 1, A. Bjorklund, T. Hokfelt, ed. Elsevier; Ireland. 1984;157-276.
19. Berger B, Verney C, Febvret A, Vigny A, Helle, KB. Postnatal ontogenesis of the dopaminergic innervation in the rat anterior cingulate cortex (area 24). Immunocytochemical and catecholamine fluorescence histochemical analysis. Brain Res. 1985;353:31-47.

20. Berger MA, Barros VG, Sarchi MI, Tarazi FI, Antonelli MC. Long-term effects of prenatal stress on dopamine and glutamate receptors in adult rat brain. Neurochem Res. 2002;27:1525-1533.
21. Hashimoto M, Watanabe T, Fujioka T, Tan N, Yamashita N, et al. Modulating effects of prenatal stress on hyperthermia induced in adult rat offspring by restraint or LPS-induced stress. Physiol Behav. 2001;73:125-132.
22. Grigoryan G, Segal M. Prenatal stress alters noradrenergic modulation of LTP in hippocampal slices. J Neurophysiol. 2013;110:279-285.
23. Muneoka K, Mikuni M, Ogawa T, Kitera K, Kamei K, et al. Prenatal dexamethasone exposure alters brain monoamine metabolism and adrenocortical response in rat offspring. Am J Physiol. 1997;273:1669-1675.
24. Goldstein JM, Goodman JM, Seidman LJ, Kennedy DN, Makris N, et al. Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. Arch. Gen Psychiatry. 1999;56:537-547.
25. Grodin EN, Cortes CR, Spagnolo PA, Momenan R, et al. Structural deficits in salience network regions are associated with increased impulsivity and compulsivity in alcohol dependence. Drug Alcohol Depend. 2017;179:100-108.
26. Vogt BA. Cingulate impairments in ADHD: Comorbidities, connections, and treatment. Handb Clin Neurol. 2019;166:297-314.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
J Neurol Neurophysiol, 6(1), 2015.

Chapter 17
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Yogic Help for Anorexia Nervosa: A Recent Study

Mrunmayee Kulkarni[1*]

DOI: 10.9734/bpi/rdmmr/v8/5256F

ABSTRACT

Anorexia nervosa is considered as eating disorder which affects a person mentally. It is more often seen in young generation these days who have the fear of gaining weight which thus affects them psychologically. This can be treated either with medication but the following article encourages about how the disorder can be treated using various yoga asanas or positions.

Keywords: Yoga; anorexia; psychiatric disorders; osteoporosis.

1. INTRODUCTION

Anorexia nervosa is an eating disorder caused by a variety of environmental factors. This causes the person to become overly conscious of the weight he gains, resulting in excessive weight loss. It is more common in females than males and is most prevalent in the middle and upper classes of society [1]. It is seen as a result of societal pressure and the desire to look good in order to achieve certain goals. Anorexia nervosa is also known as "unstoppable dieting," because the person believes he or she is fat even after losing a lot of weight.

1.1 Symptoms of Anorexia Nervosa [2]

Person suffering with anorexia nervosa may experience; Dizziness, stiffness of joints, anxiety and feeling of guilt, low blood pressure, muscle weakness, abdominal pains, early morning waking, abnormal menstrual cycles and constant depression or irritated mood [3].

It has the highest mortality rate in the psychiatric disorders and is not only socially-bound but can also be genetic [4].

Recent studies say that first degree relatives of an individual with AN have approximately ten fold greater life time risk of having AN than the relatives of an unaffected individual. Many times a pregnant women in the fear of gaining weight due to the baby bump takes up excessive dieting, this condition is called pregorexia.

People suffering from anorexia nervosa experience the following:

1. Osteoporosis

Excessive weight loss or not eating proper nutrient food may reduce the bone density leading to osteoporosis.

2. Heart problems

Anorexia nervosa results in reduction of muscle mass which also affects the cardiac muscle. Severe anorexia nervosa can also lead to cardiac failure.

[1]Sigma institute of Physiotherapy, Vadodara, Gujrat, India.
**Corresponding author: E-mail: mrunmayeek8@gmail.com;*

3. Infertility

Most common effect of Anorexia nervosa on a women. The loss of excessive fat leads to less or no production of estrogen necessary to stimulate ovulation.

4. Brain damage

Anorexia nervosa leads to nerve damage with further leads to nerve damage conditions like confusion, cold sensations and anxiety.

5. Blood disorders

Anorexia nervosa can reduce the blood supply and deficiency of various vitamins can lead to anemia (pernicious anemia because of vitamin B12). Can also lead to life threatening conditions like pancytopenia.

1.2 Treatments

Along with the professional help from medical world, yoga has always been the most essential and pocket friendly remedy for all the disorders especially mental illness. Yoga can always boost the inner confidence and help in finding peace which is necessary for all the mental health patients.

Practicing yoga by anorexic patients can secure them the ability to gain confidence for accepting themselves for who they are and get rid of the anxiety.

Yoga can be the most useful kit for any anorexia nervosa patient as the physical yogic activity or asanas help in gaining strength and develop metabolism whereas various types of meditation and breathing exercises can help in gaining the inner peace and confidence to reduce anxiety.

1.3 Breathing Exercises in Yoga [5]

1. Breath retention (kumbhaka pranayama)
2. Channel cleaning breath (nadi shodhana pranayama)
3. Conqueror breath (ujjayi pranayama)
4. Deer seal (mrigi mudra)
5. Lion pose (blowing off steam from mouth)
6. Single nostril breath (surya/Chandra bedhana pranayama) 7. Skull shining breath (kapalbhati pranayama)

1.4 Physical Strengthening Poses of Yoga for Anorexia Nervosa [6]

Crab pose:

-Stimulates respiratory and endocrine system.
-Builds arm, leg and core body strength.
-Helps building a hold and control over body.

Pigeon pose:

-Provides deep stretch for buttocks and outer thigh muscles.
- There are several variations such as forward bend, reclining, seated pigeon etc.

Locust pose:

-Build lower back and strengthen spine.
-Precursor to all the flexibility poses.

Mountain pose:

-Idealized as preparatory or resting phase.
-Strengthens thighs knees and ankles.
-Tones muscles near abdomen and buttocks.

Goddess pose:

- Great for centering your breathing.
- Helps gaining focus.

Squat pose:

-Helps gaining concentration, coordination and balance.
-Eases tension from lower back.

2. CONCLUSION

Before practicing the physical yogic activities, a patient should always begin with the breathing exercises. Many patients due to certain contraindications cannot perform certain asana, hence beginning with meditation can be essential for everyone. Various breathing exercises in yoga can benefit in relaxation, cleansing and reduction of stress from the body but not all should be practiced together initially. For An anorexia nervosa patient, the heart rate and muscle strength are already relatively low, therefore the exercise should be minimal initially and gradually increased. Along with the exercises certain therapies like psychotherapy, nutritional rehabilitation, and behavioral therapy should be taken. Also for breathing exercises, certain contraindications like lung disorders and current medication should be taken care of.

FUNDING

This article received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Pranayama (Breathing) Exercises & Poses - Yoga Journal.
2. The Physical Effects of Anorexia.
   Retrieved from: newbridge-health.org.uk
3. Pinheiro AP, Root T, Bulik CM. The genetics of anorexia nervosa: Current findings and future perspectives. International Journal of Child and Adolescent Health. 2009;2(2):153–164.
4. Editors YJ. Beginner's Guide to Pranayama.
   Available:https://www. yogajournal.com/how-to/pranayama/
5. Yoga for Anorexia.
   Available:https://www.indianmirror.com/games/ yoga/yoga-anorexia.html
6. Rizzuto L, Hay P, Noetel M, Touyz S. Yoga as adjunctive therapy in the treatment of people with anorexia nervosa: a Delphi study. Journal of Eating Disorders; 2021.
   Mirauda DC, Cruzat-Mandich C, Moore C, Ugarte ML, Díaz-Castrillón F. Kundalini yoga in women with anorexia nervosa and bulimia nervosa: A qualitative research. Revista mexicana de trastornos alimentarios. 2017;8(1):82-94.

Biography of author(s)

Ms. Mrunmayee Kulkarni
Sigma Institute of Physiotherapy, Vadodara, Gujrat, India.

She is a Student at Sigma institute of Physiotherapy, Gujarat, India. She has done a research in anorexia nervosa. Her research interest falls on Biomedical sciences. She has 2 published papers: Yogic help in anorexia nervosa: International online medical council; and World's need for covid vaccine: Model United Nations ebook of WHO. She is also the author of the book "struggle stories "

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Primary Health Care: Open Access, 10(6): 357, 2020.

Chapter 18
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Determination of Clinical Profile of Childhood Extrapulmonary Tuberculosis

Dhara K. Gosai[1*], Jigar B. Gosai[2] and Omprakash S. Shukla[3]

DOI: 10.9734/bpi/rdmmr/v8/13884D

ABSTRACT

Background: Tuberculosis is the world's second leading cause of death from an infectious disease, being second only to AIDS. There is a lack of good data on the prevalence of all types of tuberculosis among children in India; most surveys have focused on pulmonary tuberculosis. The current study aimed to investigate the clinical profile of various types of childhood EPTB. The current study sought to investigate the clinico-epidemiological profile of various forms of childhood EPTB.
Objectives: To observe the agewise distribution of various forms of extrapulmonary tuberculosis in children and to analyse demographic profile and different clinical presentations of childhood extrapulmonary tuberculosis .
Methods: Retrospective analysis of clinical profile of 100 patients of childhood EPTB in the age group of 6 months to 12 years.
Results: In our study, 62 percent of the cases were aged 0-5 years, 38 percent were aged 5-12 years (P = 0.041), with a male to female ratio of 1.9:1. 96 percent (P = 0.016) of the patients belonged to the lower socioeconomic class (P = 0.01). The distribution of EPTB was - TBME (46%), disseminated TB (21%), pleural effusion (12%), abdominal TB (10%), TB lymphadenitis (7%), Osteoarticular (4%). 28% of the patients had mild to moderate malnutrition (PEM Grade-I,II) and 46% (PEM Grade-III,IV) were severely malnourished. 66% of the patient were BCG vaccinated & history of Koch's contact were present in 28% of the all cases. Fever was present in 97 percent of CNS tuberculosis patients, followed by altered sensorium and convulsion in 80%, tonic posturing in 60%, and abnormal movements in 4%. The most common sign was tonic posturing in 60%, with the crack pot sign positive in 41%. Fever (100%), anorexia (90%), weight loss (80%), abdominal pain (50%), and hepatomegaly were common findings in 100% of cases of abdominal tuberculosis.
Conclusion: Childhood EPTB is most common in children over the age of one year, those from lower socioeconomic classes, and those who are severely malnourished. CNS tuberculosis is characterised by fever, altered sensorium, convulsions, and abnormal movements, whereas abdominal tuberculosis is characterised by fever, anorexia, weight loss, and abdominal pain.

Keywords: Clinical profile; childhood; extra pulmonary tuberculosis.

1. INTRODUCTION

Tuberculosis is one of the ancient diseases. It is mentioned in the Vedas and the Ayurvedic Samhitas. Tuberculosis was first described in Greek literature around the time of Hippocrates (460-377 BC), and the term phthisis first appeared in Greek literature around 460 BCE [1]. Tuberculosis is one of the most serious infectious diseases in the world. It is the world's second leading cause of death from infectious disease, being second only to HIV/AIDS. In 2009, out of estimated global annual incidence of 9.4 million TB cases, 1.98 million were estimated to have occurred in India, thus accounting for a fifth of the global burden of TB [2]. Tuberculosis still is one of the deadliest diseases in the world killing nearly 2 million people every year [3]. Tuberculosis, the only infectious disease to be declared a

[1]Department of Pediatrics, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India.
[2]Department of Emergency Medicine, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India.
[3]Department of Pediatrics, Baroda Medical College and S. S. G. Hospital, Vadodara, Gujarat, India.
**Corresponding author: E-mail: drdharagosai@yahoo.co.in;*

'global emergency' by the WHO, is major cause of death in adult and children worldwide but the brunt is borne by developing countries with 95% of cases and 98% of deaths.[4] In India, two deaths occur every three minutes from tuberculosis [4]. It is estimated that about one third of current global population is infected asymptomatically with tuberculosis [5].

The definition of EPTB disease under the RNTCP follows the international classification. EPTB is defined as TB of organs other than the lungs, such as pleura, lymph nodes, abdomen, genito-urinary tract, skin, joints, bones, tubercular meningitis, tuberculoma of the brain, etc. The problem of EPTB is still high, both in developing and developed countries. In India, EPTB forms 10 to 15 percent of all types of TB, in comparison to 25 percent in France and 50 percent in Canada, partly due to the dual infection of TB with human immunodeficiency virus (HIV) [6].

Since the global strategy has shifted to achieving 'Zero death by TB', this obviously cannot happen without adding focus to TB in children. Countries are reporting on average 7% cases of TB among children, mostly clinically diagnosed and EP. Numbers may be low as many children are treated outside National TB programmes. RNTCP treats children reporting to them and has introduced child - friendly dispersible FDC medication in 2017 to ensure treatment compliance. Consistently about 6-7% of all patients treated under RNTCP annually are children with TB [7].

The conventional Mycobacterium tuberculosis detection techniques based on microscopic examination of acid fast specimens are relatively insensitive. Cartridge based nucleic acid amplification test (CBNAAT)/ Gene Xpert MTB/RIF have been the game changer as they have far higher sensitivity than smear and it almost reaches the culture. CBNAAT is real-time PCR rapid technique for diagnosis of TB and detection of rifampicin-resistance conferring mutations within 2 hours. Performed on both respiratory and non-respiratory specimens (GA, BAL, IS, pleural fluid, CSF, lymph node aspirate etc), now recommended in all children for diagnosis of TB. Sensitivity and specificity of CBNAAT in sputum samples is around 98% and 99% for smear positive patients and 72% for smear negative culture positive patients. The sensitivity and specificity on GA have been 68% and 99% respectively [7].

2. OBJECTIVES

To observe the agewise distribution of various forms of extrapulmonary tuberculosis in children and to analyse demographic profile and different clinical presentations of childhood extrapulmonary tuberculosis.

3. METHODS

This study was conducted in the department of pediatrics, Shri Sayaji general hospital and medical college Baroda, between December '08 to June'10 for a period of one & half years including OPD & ward patients. The total numbers of 100 patients in the age group 6 months to 12 years were included in this study and all of them presented with clinical features of extra pulmonary tuberculosis. This is retrospective analytic study with simple randomization with sample size of 100 with prior informed consent of parents of children of our study. A detailed clinical history including presenting symptoms, family history of contact with Koch's disease, history of BCG vaccination of each child was recorded. Socioeconomical status of children was classified according to modified Prasad classification. A complete examination was carried out and findings regarding the general and systemic examination were recorded in each patient. The nutritional status was assessed and classified according to IAP classification of under nutrition.

4. RESULTS

Age distribution in our study showed that 62% cases falling in the age group 6 months - 5 years and 38% cases in the age of 5-12 years with P value = 0.041 which shows higher incidence in children <5 years.

Male to female ratio in our study was 1.9:1 with P value = 0.016, statistically higher incidence in male. In our study, 96% belonged to lower socioeconomical class. 28 % of the patients had mild to moderate malnutrition (PEM Grade- I,II) & 12% under nutrition, and 46% (PEM Grade-III,IV) were severely malnourished. 46% of patients were severely malnourished.

66% patients were immunized with BCG vaccine and only 34% did not receive any BCG vaccine. 69% of TBME, 71% of TB lymphadenitis, 25% of osteoarticular TB, 75% of TB pleural effusion, 60% of abdominal kochs, 61% of disseminated TB cases were BCG vaccinated.

History of Koch's contact was positive in 28 % children (P=0.00001). BCG scar was present in 66% cases (P=0.001), which was significant to reduce incidence of extrapulmonary tuberculosis.

Distribution of EPTB was - TBME (46%), disseminated TB (21%), pleural effusion (12%), abdominal TB (10%), TB lymphadenitis (7%), osteoarticular (4%).

Table 1. Age wise distribution of various forms of extrapulmonary tuberculosis

Type of TB	<1 year	1-5 years	5-12 years	Total
TBME	11	23	12	46
Disseminated TB	5	4	12	21
Abdominal TB	2	6	2	10
Pleural effusion	0	7	5	12
TB lymphadenitis	0	5	2	7
Osteoarticular TB	0	0	4	4
Total	18	45	37	100

In CNS tuberculosis, fever was the most common symptom, present in 97% patients followed by altered sensorium & convulsion in 80%, history of tonic posturing in 60% & abnormal movements in 4%. Most common neurological finding was tonic posturing in 60%, crack pot sign positive in 41%, hemiplegia in 26%, facial palsy 23%, quadriplegia in 15%, abducens palsy in 13%, abnormal movements in 6%, occulomotor palsy in 6%.

Table 2. Clinical signs of CNS tuberculosis

Signs	%
Motor paralysis	
Hemiplegia	26
Quadriplegia	15
Cranial nerve involvement	
(VII) Facial	23
(VI) Abducens	13
(III) Oculomotor	6
Other cranial nerves	0
Crack pot sign (Macewan sign)	41
Tonic posturing	60

Common symptoms of abdominal tuberculosis were - fever (100%), anorexia (90%), weight loss (80%) abdominal pain (50%), followed by abdominal distension (40%), vomiting (40%) & diarrhea (30%). Hepatomegaly was the most common physical finding observed in 100%, followed by doughy feel of abdomen on palpation in 60%, splenomegaly in 50% & abdominal distension in 40% in our study. Consolidation was most common chest X ray finding seen in 73%.

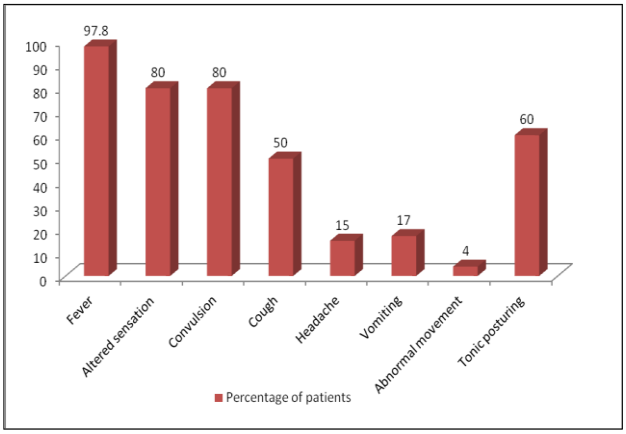


Fig. 1. Clinical symptoms of CNS tuberculosis

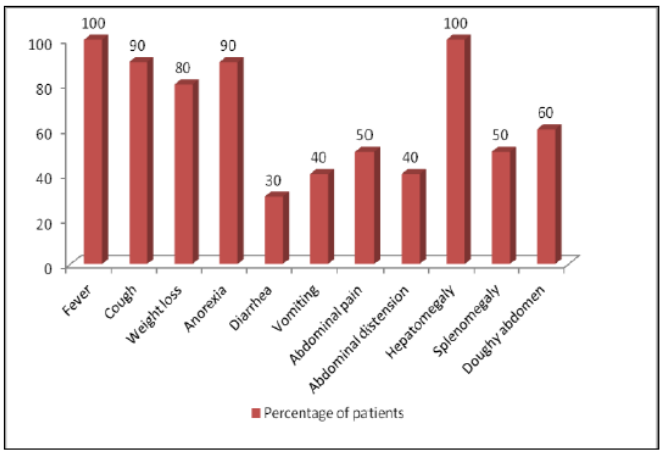


Fig. 2. Clinical profile of abdominal tuberculosis

5. DISCUSSION

The present study assessed clinicoepidemiological profile in patients of extra pulmonary childhood tuberculosis. We aimed to assess age wise distribution of the various forms of EPTB in children. We aimed to know common presenting symptoms & signs of various forms of EPTB with special reference to CNS & abdominal tuberculosis. We aimed to assess various predisposing factors like malnutrition, lower socioeconomical status, children who had not received BCG vaccine.

Age distribution in our study showed that 62% cases falling in the age group 6 months -5 years and 38% cases in the age of 5-12 years with P value = 0.041 which shows higher incidence in children <5 years while study by Van Well GT et al. 82% of TBME cases were <5 years [6] & Cherry Lyn P et al. showed 16.5% were less than 1 year old; 33% were 1 to 5 years old; 22% were 11 to 15 years old and majority of pediatric TB occurred in children less than 5 years of age [8]. In the study by Anis- ur-Rehman, at Ayub medical college, Abbottabad, Pakistan, 8% of the patients were below 3 years and 22% of the patients belonged to 3-6 years and 48% of the patients were between 6-12 years [9]. In the study by Garg P, at department of pediatrics, Shanti Manglik hospital, Agra, maximum number of children were seen in the age groups 3-5 years (48.8%) followed by 21.4% in the 5-7 years age group [10].

Male to female ratio in our study was 1.9:1 with P value= 0.016, statistically higher incidence in male as compared to 0.94 :1 by Fawzia et al. [11] & 1.6:1 by Tahmeed et al. [12] In our study, 96% belonged to lower socioeconomical class in comparison to 73% by Thilothammal et al. [13].

96% of the patients belonged to the lower socio- economic class of III, IV, and V of Modified Prasad's classification (P =0.01) .73% belonged to lower socio- economic status in the study of N. Thilothammal et al. [13]. Anis-ur-Rehman at Ayub medical college, Abbottabad, Pakistan, showed that TB is common problem of poor community, majority of the cases belonged to backward district [9]. Poverty, ignorance, over-crowding decreases immunity in growing children making them more vulnerable to TB. High incidence of TB in children aged 0-5 years in an area of South Africa correlated with lower level of parental education, low annual household income [14].

28% of the patients had mild to moderate malnutrition (PEM Grade- I,II) & 12% under nutrition, and 46% (PEM Grade-III,IV) were severely malnourished. 46% of patients were severely malnourished in comparison to 52.3% by Cherry Lyn P et al. [8].

66% patients were immunized with BCG vaccine and only 34% did not receive any BCG vaccine. 69% of TBME, 71% of TB Lymphadenitis, 25% of Osteoarticular TB, 75% of TB pleural effusion, 60% of abdominal Koch's, 61% of disseminated TB cases were BCG vaccinated.

History of Koch's contact was positive in 28% children (P = 0.00001). In the study by Nooshin Baghaie et al. pediatric respiratory disease research centre, Tehran, Iran, family history was positive in 28% of EPTB, Which coincides with our study [15]. In the study by Vimlesh Sheth, AIIMS, New Delhi, positive family history present in 17% cases [16]. In the study by Matloob Azam et al. J. Ayub medical college, Abbottabad, Islamabad, 41% cases had positive family history [9]. Schaaf et al. at Baylor college of medicine, Houston, Texas showed that contact with infectious tuberculosis adult was recorded in 49.5% [17]. Garg P. at Agra showed that history of contact with tuberculosis was given by only 13.1% relatives [6]. Lower history of adult contact reflects social stigma attached to the disease. Tahmeed Ahmed et al. at Dhaka, Bangladesh, had found the history of contact with TB patient in only 40% of cases [12].

BCG scar was present in 66% cases (P = 0.001), which was significant to reduce incidence of extrapulmonary tuberculosis while it was 41% in study by Matloob Azam, et al. [18] Nelson et al. showed that the efficacy of BCG vaccination in the prevention of TB has varied from 0% to 80%; its overall effect is 50%, the effect being greatest in preventing TB meningitis and Miliary TB or disseminated TB [19]. Therefore, even if it cannot reduce the disease burden in general, the vaccine can reduce severity of disease. For this reason, the WHO continues to recommend BCG vaccination of infants [20].

Distribution of EPTB was - TBME (46%), disseminated TB (21%), pleural effusion (12%), abdominal TB (10%), TB lymphadenitis (7%), osteoarticular (4%). while in the study by Fawzia, Al Otaibi Malek et al., most common sites were lymph nodes (42%), Osteoarticular (13.7%), abdominal (13.3%), pleural (12.1%), CNS (4.4%), urogenital (3.6%), milliary (2.1%), paravertebral abscess (1.2%) [11]. In study of V. Sheth, et al., distribution of EPTB was TBME (4%), TB lymphadenitis (78%), osteoarticular (4%), disseminated TB (8%) & others (6%) [19]. In study of V. Sheth, AIIMS, New Delhi, distribution of EPTB was TBME (4%), TB lymphadenitis (78%), osteoarticular (4%), disseminated TB (8%) & others (6%) [21]. As we had done study at higher centre so percentages of severe forms of EPTB like TBME, disseminated TB & abdominal TB are higher.

In CNS tuberculosis, fever was the most common symptom, present in 97% patients followed by altered sensorium & convulsion in 80%, history of tonic posturing in 60% & abnormal movements in 4%. Van Well GT et al., study showed that most common symptom was altered sensorium & convulsion in 96% followed by fever, weight loss & anorexia 91% [8]. Most common neurological finding was tonic posturing in 60%, crack pot sign positive in 41%, hemiplegia in 26%, facial palsy 23%, quadriplegia in 15%, abducens palsy in 13%, abnormal movements in 6%, occulomotor palsy in 6% as compared to, motor deficit in 63%, signs of meningeal irritation 98%, signs of raised ICT 23%, brainstem dysfunction 39%, and cranial nerve palsy 27% in study of Van well GT et al. [8].

Common symptom of abdominal tuberculosis were - fever (100%), anorexia (90%), weight loss (80%) abdominal pain (50%), followed by abdominal distension(40%),vomiting (40%) & diarrhea (30%) & In the study by Yadav K. et al., shows that most common symptom was weight loss (84%), abdominal

pain (81%), anorexia (77%), fever (68%), cough (57%), vomiting (31%), bowel disorder (23%) [22]. Hepatomegaly was the most common physical finding observed in 100%, followed by doughy feel of abdomen on palpation in 60%, splenomegaly in 50% & abdominal distension in 40% in our study. Garg P at Agra observed commonest presentation of Abdominal Koch's as ascites, [10] which matches with our study. Consolidation was most common chest X ray finding seen in 73% as compared to 20% in the study by Cherry Lyn P. et al. [8].

6. CONCLUSION

We concluded from our study that childhood extra pulmonary tuberculosis is common in pediatrics population, more common in children <5 years of age. Extrapulmonary tuberculosis is commonly seen in lower socioeconomical class, with moderate to severe malnutrition. BCG vaccine is recommended to reduce severe forms of EPTB. In our study, TBME, disseminated TB & abdominal TB were commonly seen as we had done our study at higher centre. The diagnosis of tuberculosis is usually based on high index of suspicion with supportive evidence of clinical symptoms. & signs, & contact history.

ETHICAL APPROVAL

The study was approved by the institutional ethics committee

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Park K. Health programs in India. In: K Park, eds. Park's Textbook of Preventive and Social Medicine, 20th ed. Jabalpur: Banarsidas Bhanod publication. 2009;305-319.
2. Balachandra A, Shiv Bolan S, Govrishankar MC, Childhood TB. Current Scenario. Indian J of Pract Pediatr. 2007;3:6-9.
3. Ministry of Health & Family Welfare & Experts of IAP. Management of pediatrics tuberculosis under RNTCP - Joint statement of central TB division, Directorate general of health services; 2003.
   Available:http://tbcindia.nic.in/pdfs/consensus%20statement.p df
4. Ministry of Health & Family Welfare. TBC India directorate general of health service; 2010.
   Available:http://www.tbcindia.org/
   Accessed March 2010.
5. The Government of India. Case finding policy for National TB control programme. Indian J Tub. 1998;45:3-7.
6. Van Well, et al. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the western cape of South Africa. Netherlands, Neoreviews official J American Acad Pediatr. 2009;123:e1-8.
7. Draft updated IAP RNTCP Ped TB Guidelines; 2019
   Available:http://tbcindia.gov.in
8. Cherry Lyn. P. Clinical profile of culture proven Tuberculosis cases among Filipino Children aged 30 months to 18 years. Phil J Microb Infect Dis. 2001;30(4):133-43.
9. Rehman Anis-or, Idris Mahammad. Comparison of Mantoux test with diagnostic BCG in pediatric patients with pulmonary tuberculosis. J Ayub Med Coll Abottabad. 2005;17:6-8.
10. Garg P. Childhood tuberculosis in a community hospital from a region of high environmental exposure in North India. J clin diagnost Res. 2003;2(4):634-8.
11. Fawzia Al Otaibi Malak, et al. King Khalid University Hospital: Study on extra pulmonary TB in Saudi Arabia. Saudi Arabia. 2010:227-31.
12. Tahmeed Ahmed, Farzara Sobhan. Childhood Tuberculosis a review of epidemiology. Diagnosis & Management. Infect Dis J Pakistan. 2008;17:52- 60.
13. Thilothammal PV, Krishna Murthy, Basu K, Ratnam SR. Tuberculosis meningitis in children,

clinical profile mortality & morbidity of bacteriologically confirmed cases. Indian Pediatr. 1995;32:641-6.
14. Van Rie A, Byers N, Gie R, Kunneke M., Zeitsman L, Donald P. Childhood tuberculosis in an urban population in South Africa: Burden & NSK factor : Arch Dis Child. 1999;80:433-7.
15. Nooshin Baghaie, Soheila Khalilzade. Extra pulmonary tuberculosis in children: Two years study. Pediatric respiratory research centre, Tehran, Iran. Acta Medica Iranica. 2010;48(4):239-43.
16. Sheth V, Kabra SK, Jain Y, Semwal OP. Study on EPTB. Inst Med Sci. 1994;31:1585-93.
17. Schaaf H, Marais BJ, Whitelow Andrew, Anneke C Hesseling, Eleg Brian Husseg GD, Donald PR. Culture-confirmed childhood tuberculosis in Cape Town, South Africa: a review of 596 cases**.** BMC Infect Dis. 2007;7:140.
18. Matloob Azam, et al. Intracranial tuberculoma & caries spine: study in children's hospital Islamabad. J Ayub Med College, Abbottabad, Islamabad. 2004;16(4):7-11.
19. Nelson L J, Wells Co. Global epidemiology of Childhood tuberculosis. Inst. J Tub Lung Dis. 2004;8(5):636-47
20. Agrawal RK. To be or not to be and TB or not TB? Indian Pediatr. 2008;45:259-60.
21. Sheth V, Kabra SK, Jain Y, Semwal OP. Study on EPTB. Inst Med Sci. 1994;31:1585-93.
22. Yadav MS, et al. A comparative study of DOTS & Non - DOTS interventions in tuberculosis cure, Kasturba medical college, Mangalore. Indian J Community Med. 2004;29:1.

Biography of author(s)

Dr. Dhara K. Gosai
Department of Pediatrics, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India.

She is an Assistant Professor of Pediatrics in B J Medical college, Ahmedabad, 380016,India. She has Total 12 years of teaching and administrative experience. She Contributed in many publications in the field of pediatrics and neonatology in the indexed national and international journals and also reviewed articles. She is a National instructor of Neonatal Resuscitation Programme and trainer for many trainings like Essential New Born Care Training, Facility Based New born Care Training, IMNCI,FIMNCI etc. She Completed various scientific courses about Biomedical Research and Medical Education. She Participated in various research projects. She is a University recognized under graduate and post graduate teacher. She Guided many PG students for their dissertation and research studies. She is also an Examiner (UG and PG) and at various Universities.

Dr. Jigar B. Gosai
Department of Emergency Medicine, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India.

He is an Assistant Professor of Emergency Medicine Department in B J Medical college, Ahmedabad, India He has Total 12 years of teaching and administrative experience. He contributed in many publications in the field of emergency medicine, anaesthesia and pediatrics in the indexed national and international journals and also reviewed articles. He is an International instructor for the course Hospital preparedness for emergencies (HOPE), University recognized under graduate and post graduate teacher. He completed various scientific courses about Biomedical Research and Medical Education. He Guided many PG students for their dissertation and research studies. He is also an Examiner (UG and PG) and DNB at various Universities.

Dr. Omprakash S. Shukla
Department of Pediatrics, Baroda Medical College and S. S. G. Hospital, Vadodara, Gujarat, India.

He is a Professor of Pediatrics, Govt Medical College Baroda-390001, Gujarat, India. He has Total 30 years of teaching and administrative experience. He is a PG teacher since 23 years. He has PG examinership since 18 years. He Guided around 40 PG students including MD (24) and DCH(16) students for their thesis, dissertation, short research studies. He is an Examiner (UG and PG) at various Universities of Gujarat, Rajasthan, Maharashtra, Karnataka, Punjab, Delhi, Haryana, Madhya Pradesh, Chhattisgarh, UP, Bihar including AIIMS. He is a National Trainer of NRP, FBNC, Adolescent health, IYCF, NSSK, RBSK, IMNCI, F-IMNCI, EMNC, Health Care Communication, SAM etc. He has around 35 publications in various International and National Indexed Journals.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
International Journal of Research in Medical Sciences, 2(2): 8, 2014.

Chapter 19
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Associations of Serum Fluorescent Advanced Glycation End Products, Glycemic Control, Vascular Complications and Duration of Diabetes Mellitus

Nivedita L. Rao[1*], Greeshma B. Kotian[1] and Shaheena Yasser[1]

DOI: 10.9734/bpi/rdmmr/v8/9093D

ABSTRACT

Introduction: Advanced glycation end products (AGEs), glycemic control and diabetes duration, all have roles in the development of vascular complications that are associated with morbidity and mortality in diabetic patients. Understanding the associations between serum fluorescence of advanced glycation end products, glycemic control, microvascular complications and duration of diabetes mellitus therefore, becomes vital. Significantly higher serum fluorescence of AGEs and higher incidence of microvascular complications have been found in diabetic patients of higher age with poorer glycemic control and longer diabetes duration. Poor glycemic control was associated with disease duration, hypercholesterolemia, high level of low density lipoprotein, hypertension and income level of the patients. Significant positive correlations have been found between serum fluorescence of AGEs, duration of diabetes mellitus, glycated haemoglobin and fasting glucose levels. Observations made from key study findings indicate that intensive glycemic control and therapeutic strategies that target molecular mechanisms involving AGEs are warranted in older patients with longer diabetes duration who are at higher risk of developing diabetic microvascular complications.

Keywords: Serum fluorescence; advanced glycation end products; diabetes duration; glycemic control; microvascular complications.

1. GLOBAL BURDEN OF DIABETES MELLITUS

Diabetes mellitus, a group of metabolic diseases characterized by hyperglycemia, is a major global public health problem. According to current global estimates, the disease has affected 463 million people and is set to escalate to 578 million by the year 2030 [1]. India is the second most affected country in the world after China having an estimated 77 million adults with diabetes [1-2]. Chronic hyperglycemia, microvascular and macrovascular complications of diabetes are associated with long-term damage, dysfunction, failure of various organs which are main causes of morbidity and mortality of the disease [3].

2. CHRONIC VASCULAR COMPLICATIONS IN DIABETES MELLITUS

Diabetic vascular complications are leading causes of end-stage renal failure, acquired blindness, a variety of neuropathies, cardiovascular disease that cause morbidity and high mortality rates suffered by diabetic patients. Both microvascular and macrovascular complications can arise as chronic complications of diabetes mellitus. Illustration 1.

Chronic microvascular complications of diabetes include retinopathy, nephropathy and neuropathy [4 - -7]. Diabetic retinopathy, a common microvascular complication of diabetes is estimated to be responsible for 10,000 new cases of blindness every year in the United States of America [7]. Chronic

[1]*Department of Biochemistry, Yenepoya Medical College, Yenepoya (deemed to be University), Deralakatte, Mangalore, Karnataka, India.*
**Corresponding author: E-mail: nlrdr@yahoo.com;*

macrovascular complications of diabetes are cardiovascular diseases, peripheral vascular and cerebrovascular diseases. Patients with diabetes are at two to four times increased risk of coronary heart disease, peripheral vascular disease and related deaths, than those in the general population [8].

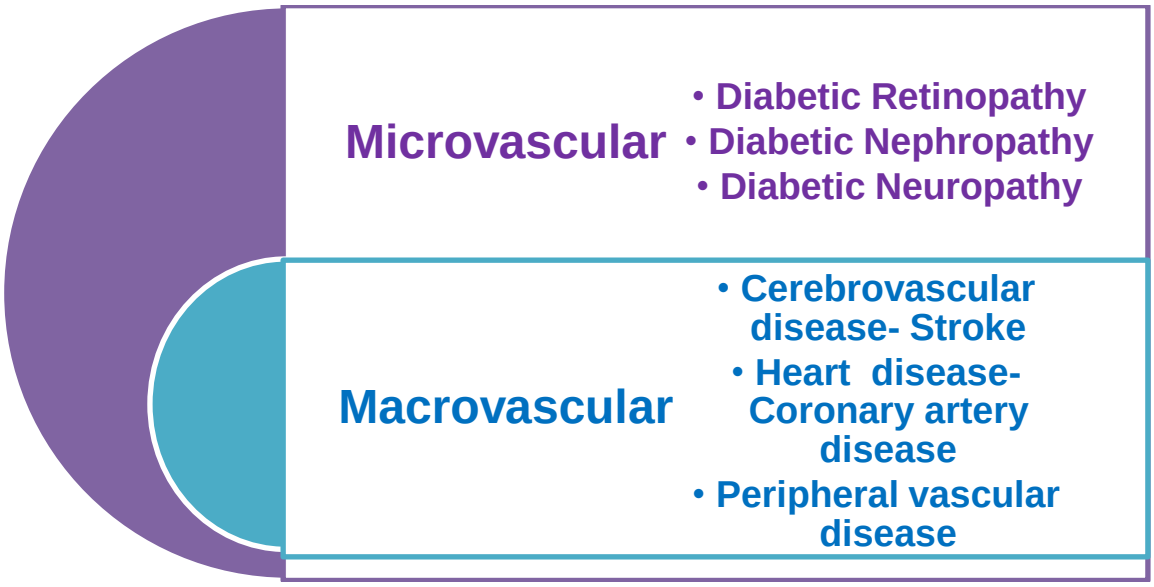


Illustration 1. Chronic vascular complications of type 2 diabetes mellitus

Impacts of age, diabetes duration and glycemic control on diabetic vascular complications: Impacts of age, age at diagnosis of diabetes and diabetes duration on subsequent vascular complications have been investigated in some studies, yielding a variety of results. Positive association of older age on the risk of myocardial infarction and stroke has been reported in diabetic patients [9]. Independent effects of duration of diabetes and greater risks have been found to be associated with early rather than late onset of diabetes [9-10]. In type 2 diabetes patients, age, age at diagnosis and diabetes duration, were all independently associated with macrovascular events and death. Diabetes duration was independently associated with microvascular events [9] Poor glycemic control was associated with disease duration, hypercholesterolemia, high level of low density lipoprotein, hypertension and income level of the patients. Age was associated with the highest percentage of complications [10]. Long duration of diabetes, poor glycemic control and hypertension, reportedly increase the chances of microvascular complications of diabetes [11].

Advanced glycation end products and diabetic vascular damages: Advanced glycation end products (AGEs) are known to be involved in the development of diabetic vascular complications. Enhanced formation, accumulation of AGEs has been linked to increased risk for both macro- and micro vascular complications of diabetes mellitus [12-14]. Intense hyperglycaemia elicited by diabetes leads to formation of Amadori products which through the Maillard reaction, form AGEs, many of which have particular fluorescence [14,15] Fig. 1.

Consequently, the expression of receptors for advanced glycation end-products (RAGEs) gets accelerated. Constant activation of the AGE-RAGE system creates long-term metabolic memory, increases reactive oxygen species (ROS) formation, accelerating oxidative stress in cells. Cytokines and growth factors secreted thereby cause inflammatory response or aggravate thrombotic tendency that leads to progression of arteriosclerosis and other vascular damages [14-16] Fig. 2.

Associations of serum fluorescent AGEs with glycemic control, diabetes duration and microvascular complications of diabetes: Although AGEs are understood to be key players in development of chronic vascular complications in diabetic patients, very few studies have simultaneously investigated the associations of AGEs levels, diabetes duration and glycemic control.

It has been reported that urinary fluorescent AGEs, years of diabetes and glycosylated/glycated haemoglobin (HbA1c) are associated with the occurrence of microvascular complications, while serum fluorescent AGEs, years of diabetes and glycosylated hemoglobin are associated with the number of complications [17]. Non-fluorescent AGEs N(ε)- carboxymethyl-Lysine (CML) too, have been found to be associated with diabetic retinopathy. Multiple regression analysis have confirmed that AGEs, length of diabetes and glycosylated haemoglobin are variables associated with diabetic complications [17]. Interesting findings of a recent study conducted on Indian diabetic patients, are presented in this chapter [18]. A previously described, simple spectrofluorometric method was employed for measuring AGE fluorescence [17]. Serum fluorescence of AGEs, diabetes duration, indicators of glycemic control- fasting blood glucose; glycated haemoglobin levels; incidence of microvascular complications-retinopathy, neuropathy and their correlations are illustrated in Tables 1, 2.

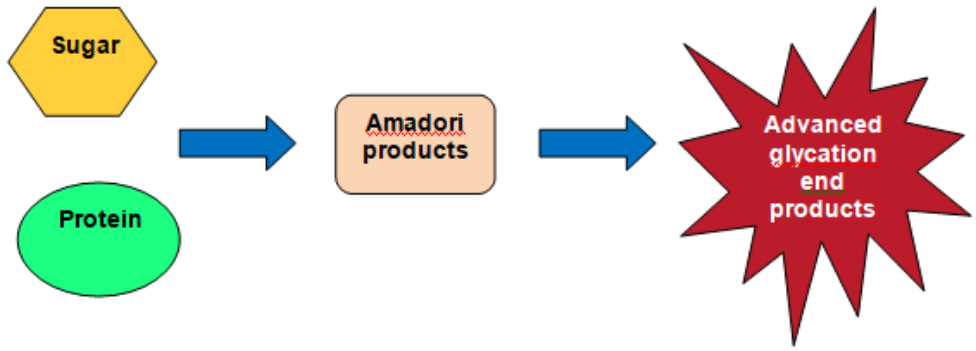


Fig. 1. Simple illustration of advanced glycation end products (AGEs) formation [14]

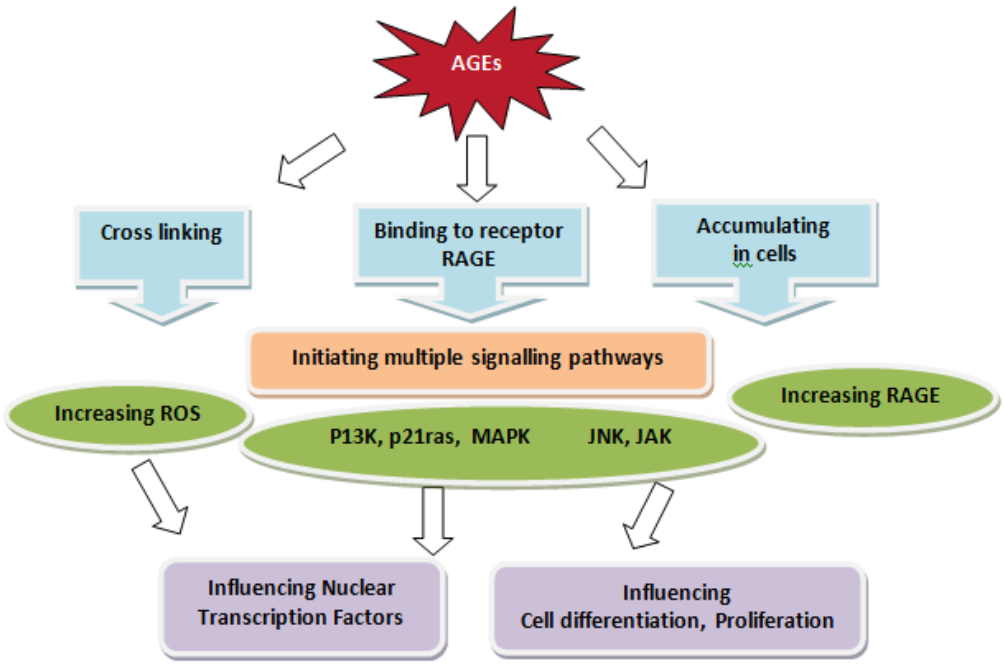


Fig. 2. AGE–RAGE interaction and activation of multiple signaling pathways [14]

Key observations from comparisons of findings between diabetes duration groups in Table 1:

- Mean age of patients of group with diabetes duration >10 years was significantly higher than that of patients with shorter diabetes duration.
  Age of patients however, did not have separate effect on the risk of microvascular events in a previous report [9].
- No significant gender influences were present.
- Although diabetes duration of one to ten years in group 1 appears to be wide compared to group 2 with duration of ten to fifteen years, majority of patients in group 1 (38 out of total 46 patients) had diabetes duration of less than five years.
- Significantly higher HbA1c values existed in patients with longer diabetes duration indicating poorer glycemic control but, their fasting blood glucose levels were not significantly higher.
- Serum fluorescence levels of advanced glycation end products were significantly higher in patients with longer diabetes duration.
- Incidence of microvascular complications in the form of retinopathy and nephropathy in diabetic patients was significantly more in patients with longer diabetes duration of more than 10 years.

  Serum fluorescence of AGEs, years of diabetes and glycosylated hemoglobin were found to be associated with the number of microvascular complications in diabetic patients of another ethic population of Chile in western South America [17].

- Compared to patients with diabetes duration 1-10 years, diabetic patients with duration of more than 10 years-15 years, had higher mean HbA1c level (poorer glycemic control) and incidence of microvascular complications in the present study.

  These findings are consistent with previous reports in which diabetes duration was associated with risk of microvascular events even after adjustment for baseline HbA1c level. [9,11]. Multiple adjusted risk of microvascular events was reported to be increased by 28% for each 5 year increase in diabetes duration [9].

- The number of patients with diabetic microvascular complications was 7.2 times more in patients with longer diabetes duration >10 -15 years than in those with shorter diabetes duration of 1-10 years, when the incidence proportions of patients with microvascular complications were compared between the two duration groups (47% and 6.5 % respectively in Table 1).

  These findings are similar to that in a previous study wherein patients with diabetes duration of >7 years were reported to be 6 times more likely to have the resulting complications [11].

Key observations from comparisons of findings between diabetes duration groups in Table 2:

- Serum fluorescence of AGEs showed significant positive correlations with diabetes duration, fasting blood glucose and glycated haemoglobin in both groups of patients with diabetes duration 1-10 years and >10 – 15 years.
- Correlation of AGEs was strongest with diabetes duration evident from the r value of .740 and $p < .001$, than with fasting blood glucose and glycated haemoglobin in patients with diabetes duration 1-10 years.
  Serum fluorescent AGEs did not correlate with age, duration of diabetes or glycosylated hemoglobin in a previous study. However, although patients below 4 years diabetes duration were excluded in that previous report, there was no data showing duration in years of the patients included in that study to compare and analyze the reason for variation from findings of the present study [17].
- Correlation of AGEs was strongest with glycated haemoglobin, evident from r value of .769 and $p < .001$ in patients with diabetes duration **>** 10 – 15 years.

Table 1. Demographic and biochemical parameters of diabetic patients grouped according to diabetes duration

Parameter	Group 1: Diabetes duration 1-10 years (n 46)	Group 2: Diabetes duration > 10 -15 years (n 49)	p value
Age (years)	Mean ± SD 52.5 ± 5.5	Mean ± SD 57.6 ± 3.6	* 0.00 S
Gender	Female Male	Female Male	0.357
Number of patients:	25 21	22 27	†NS
%:	54.3 45.7	44.9 55.1	
Diabetes duration (years)	Mean ± SD 3.72 ± 2.16	Mean ± SD 11.96 ± 1.11	*< 0.001 S
Fasting blood glucose (mg/dL)	Mean ± SD 136.59 ± 30.16	Mean ± SD 144.16 ± 37.5	0.283 †NS
Glycated hemoglobin HbA1c (%)	Mean ± SD 7.5 ± 0.84	Mean ± SD 8.2 ± 1.54	*0.006 S
Serum fluorescent AGEs (Arbitrary Units AU/g protein)	Mean ± SD 1.77 ± 1.72	Mean ± SD 4.30 ± 3.2	*<0.001 S
Microvascular complications			*0.000
Number of patients:	3	23	S
Incidence proportion:	6.5%	47%	

**p value of <0.05 indicates significant difference (S) between the groups.*
†NS is not significant. Table includes data and figures previously presented in [18]

Table 2. Correlations of serum fluorescence of AGEs with diabetes duration, fasting blood glucose and glycated hemoglobin between patients grouped based on diabetes durations

Parameters	Serum fluorescence of AGEs	
	Group 1 Diabetes duration 1-10 years (n=46)	Group 2 Diabetes duration > 10 -15 years (n=49)
Diabetes duration (years)	*r .740 P < .001 S	*r .342 P .016 S
Fasting blood glucose (FBS)	*r .307 P .038 S	*r .513 P < .001 S
Glycated hemoglobin (HbA1c)	*r .449 P .002 S	*r .769 P < .001 S

**r is the Pearson's correlation coefficient. p value of <0.05 indicates significant difference (S) between groups. Table includes data and figures previously presented in [18]*

Clinical applications of measurement of fluorescent AGEs: AGEs comprise the link between diabetes disease as cause and the effect of occurrence of microvascular complications. Toxic AGE (TAGE) formation inhibition, TAGE-RAGE interaction blockade and RAGE expression suppression, have all been reported as promising therapeutic targets against diabetic vascular complications [19,20] Fig. 3.

Simple spectrofluorometric assay to measure fluorescent AGEs could serve as a useful tool to screen for patients who may be at higher risk of developing diabetic microvascular complications at primary care settings. Prevention of associated adverse outcomes of diabetes can thereby, be enabled. AGEs should probably be considered as another therapeutic target in the effective management of diabetes mellitus.

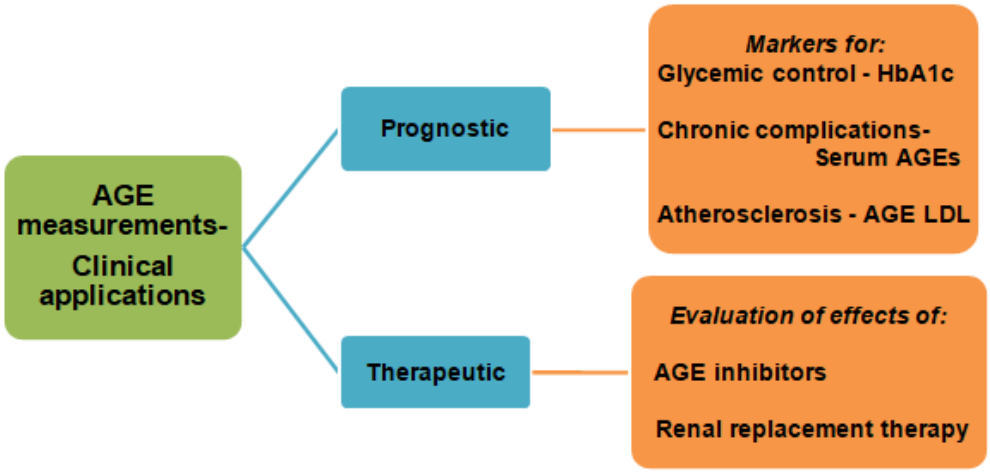


Fig. 3. Clinical applications of AGE measurements [14]

3. CONCLUSIONS

Serum fluorescence of AGEs and the incidence of microvascular complications are significantly higher in diabetic patients with longer diabetes duration, higher age and poorer glycemic control. Screening patients for fluorescent AGEs, intensive glycemic control and therapeutic strategies that target molecular mechanisms involving AGEs are therefore, warranted in older patients with longer diabetes duration to minimize the risk of microvascular complications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 9th ed- Brussels, Belgium: IDF; 2019.
   Available: http://www.diabetesatlas.org/
2. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Research and Clinical Practice. 2011;94:311-21.
3. Swerdlow AJ, Laing SP, Silva IS, Slater SD, Burden AC, Botha JL et al. Mortality of South Asian patients with insulin-treated diabetes mellitus in the United Kingdom: a cohort study. Diabetic Medicine. 2004;21(8):845–51.
4. Ozougwu JC, Obimba KC, Belonwu CD, Unakalamba CB. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. J. Physiol. Pathophysiol. 2013;4(4):46-57.
5. Katakami N. Mechanism of development of atherosclerosis and cardiovascular disease in diabetes mellitus. J Atheroscler Thromb. 2018;25(1):27–39
6. Pitocco D, Tesauro M, Alessandro R, Ghirlanda G, Cardillo C. Oxidative Stress in Diabetes: Implications for Vascular and Other Complications. Int. J. Mol. Sci. 2013;14:21525-50.
7. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. Clinical Diabetes-Diabetes Foundation. 2008;26:77-9.
8. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 2018;17:83.
   DOI: 10.1186/s12933-018-0728-6

9. Zoungas S, Woodward M, Li Q, Cooper M E, Hamet P, Harrap S et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia. 2014;57:2465–74.
10. Shamshirgaran SM, Mamaghanian A, Aliasgarzadeh A, Aiminisani N, Alamdari IM, Ataie J. Age differences in diabetes-related complications and glycemic control. BMC Endocrine Disorders. 2017;17:25.
DOI: 10.1186/s12902-017-0175-5
11. Ramnath SR. Correlation of duration, hypertension and glycemic control with microvascular complications of diabetes mellitus at a tertiary care hospital. Integrative Molecular Medicine. 2017;4(1):1-4.
DOI: 10.15761/IMM.1000272
12. Sho-ichi, Kazuo N, Tsutomu I. Advanced Glycation End Products (AGEs) and Diabetic Vascular Complications. Current Diabetes Reviews. 2005;1:93-106.
13. Zeinab H, Stephen G, Ludwig N, Mamas A. Role of advanced glycation end products in cardiovascular disease. World J Cardiol. 2012;4(4):90-102.
14. Ashraf JM, Ahmad S, Choi I, Ahmad N, Farhan M, Tatyana G, Shahab U. Recent advances in detection of AGEs: Immunochemical, bioanalytical and biochemical approaches. IUBMB Life. 2015;67: 897-913.
Available: https://doi.org/10.1002/iub.1450
15. Yamagishi S. Role of advanced glycation end products (AGEs) and receptor for AGEs (RAGE) in vascular damage in diabetes. Exp Gerontol. 2011;46:217-24.
16. Sang Youl Rhee, Young Seol Kim. The Role of Advanced Glycation End Products in Diabetic Vascular Complications. Diabetes Metab J. 2018;42:188-95.
17. Maza MP, Garrido F, Escalante N, Leiva L, Barrera G, Schnitzler S et al. Fluorescent advanced glycation end-products (ages) detected by spectro-photofluorimetry, as a screening tool to detect diabetic micro vascular complications. J Diabetes Mellitus. 2012;2(2):221-226.
18. Ali S, Rao N. Correlation of serum fluorescence of advanced glycation end products with diabetes duration and glycemic control in type 2 diabetic patients. Biomedical Research and Therapy. 2020;*7*(8):3933-3938.
19. Takeuchi M, Takino J, Yamagishi S. Involvement of the toxic AGEs (TAGE)-RAGE system in the pathogenesis of diabetic vascular complications: A novel therapeutic strategy. Curr Drug Targets. 2010;11(11):1468-1482.
20. Pinkas A, Aschner M. Advanced Glycation End-Products and Their Receptors: Related Pathologies, Recent Therapeutic Strategies, and a Potential Model for Future Neurodegeneration Studies. Chem. Res. Toxicol. 2016;29 (5):707–14.

Biography of author(s)

Dr. Nivedita L. Rao
Department of Biochemistry, Yenepoya Medical College, Yenepoya (deemed to be University), Deralakatte, Mangalore, Karnataka, India.

She is Professor (Former incharge Head) in the department of Biochemistry at Yenepoya Medical College, Yenepoya (deemed to be University), Mangalore, Karnataka, India. She holds MSc., PhD degrees in Medical Biochemistry from Kasturba Medical College Manipal, Manipal Academy of General Education. Her rich academic experience spans 22 years, teaching medical, dental, allied health undergraduate, postgraduate and doctoral students. Introducing innovations in teaching-learning-assessment methods transforming traditional classroom activities into shared experiences and value-added electives for curriculum enrichments are her career highlights. Recipient of the Best Poster Award at the 3rd International Conference of Genetic and Molecular Diagnosis in Modern Medicine and Biology, her research areas include cell calcium, saliva-diagnostics, advanced glycation end products, nutrition and healthy lifestyle. Her first report on saliva CRP in Hashimoto-Subacute thyroiditis is credited as an emerging diagnostic test in the eminent British Medical Journal (BMJ) Best Practice website. She has authored 20 publications in International-National indexed journals, chapters in International books, articles in Yenepoya Environmental Studies e-newsletter and is Associate editor of IQRA-the Yenepoya University magazine. Being an astute organizer and team-builder she, with NSS unit, organized Govt school programs- community plays to create awareness on key health issues. She has been awarded the prestigious 'Bharat Shiksha Ratan' Award from Delhi (India) in September 2021, for her achievements in promoting health and educational growth.

Dr. Greeshma B. Kotian
Department of Biochemistry, Yenepoya Medical College, Yenepoya (deemed to be University), Deralakatte, Mangalore, Karnataka, India.

She obtained her MBBS degree from K.S Hegde Medical Academy, Mangalore, India and MD degree in Medical Biochemistry from Yenepoya Medical College, Yenepoya deemed to be University, Mangalore, India. She is currently working as Assistant Professor in the Dept of Biochemistry at Yenepoya Medical College, Mangalore, Karnataka, India. She has pursued PG diploma in Bioethics and Medical ethics from Yenepoya Medical College, Yenepoya deemed to be University, Mangalore, India. She has 7 years of teaching experience in medical college, teaching medical as well as allied health students. She has guided undergraduate students in their research projects. Her field of interests includes cardiovascular diseases, nutrition, obesity, research ethics and humanities. She has authored 5 publications in International indexed journals. She has keen interest in implementing innovative teaching-learning and assessment methods. She is one of the recipients of Yenepoya Teacher of year 2021 awards.

Dr. Shaheena Yasser
Department of Biochemistry, Yenepoya Medical College, Yenepoya (deemed to be University), Deralakatte, Mangalore, Karnataka, India.

She is currently working as Assistant Professor in the department of Biochemistry, Yenepoya Medical College and has teaching experience of 4 years, teaching undergraduate and post graduate students. She is experienced as deputy quality manager since 4 years in NABL- accredited Yenepoya Medical College Hospital Central Laboratory. She is a certified internal Auditor and obtained Quality Management Systems Certificate Course, conducted by Foundation for Quality (India) as per ISO 15189 - 2012. She has extensive experience within multiple areas of diagnostic and clinical biochemistry. She is currently pursuing her part time PhD on the topic Coronary Artery Disease under the guidance of Dr. Prabha Adhikari and co-guidance of Dr. Nivedita L Rao. She holds MBBS degree from Yenepoya Medical College, RGUHS and MD Biochemistry degree from Kasturba Medical College, Mangalore, MAHE. Her post graduate thesis titled “Correlation of Vitamin D status in Coronary Artery Disease with High Sensitivity C- reactive protein and first Angiographic findings” had received grant support by MAHE. She has published 13 articles including case reports and original articles in National and International indexed journals. Her research area of interest is coronary artery disease. She also guides students in research work. She was awarded best scientific poster twice in State conferences in 2018 and 2021.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Biomedical Research and Therapy, 7(8): 3933-3938, 2020.

Chapter 20
Print ISBN: 978-93-5547-060-7, eBook ISBN: 978-93-5547-068-3

Study on Antioxidants and Growth Factors in the Treatment of Alopecia with Injectables

Ana Mery Da Silva Leite[1], Marcela Sene Fiorese[2], Force Tefo Thema[3*] and E. Marcela Avelina Bataghin Costa[2]

DOI: 10.9734/bpi/rdmmr/v8/1949C

ABSTRACT

Alopecia can be caused by a variety of reasons, both intrinsic (organic) and extrinsic (environmental), including a lack of vitamin complexes, stress, hormonal abnormalities, genetic inheritance, chemical effects, and medication use. The use of antioxidant shampoos and conditioners with hair stimulation has become common practise in Brazil.The most common is androgenetic alopecia (AGA), which causes premature fillet unit ageing, follicle micro-inflammation, and hair growth inhibition. (AGA) is a slow, painless and silent micro-inflammation triggered by factors such as climbing, chemical action caused by the use of cosmetics, body stress, hormonal disorders, menstrual irregularity, weight loss, systemic disease, use of medication to treat cancer and iron deficiency.The hair fibre growth cycle is harmed (catagen, telogen and anagen). So, a low-protein, low-vitamin diet is concerning; a multivitamin supplement is required. Today, medications are regarded as a watershed in the treatment of alopecia, associating a scheduled and targeted active induction technique. When using a mix of LED and Laser therapy, microagulching is vitally crucial. Calculated as men and women's complaints upon exposure to certain aspects of everyday life, as well as a decrease in the creation of reactive elements that might cause disruption and fall. It is recommended that nutritional supplements with antioxidant and anti-fall activity, as well as the use of growth factors, be used, as well as potential in-hibitors of hair ageing and with fall and alopecia. The goal of this study was to conduct a literature review on the scientific background and how aesthetic applications of antioxidants and growth factors in the treatment of alopecia can benefit patients.

Keywords: Antioxidant nutricosmetics; growth factors for treatment of alopecia; injectables for alopecia.

1. INTRODUCTION

Hair changes that lead to alopecia can be caused by both intrinsic (organic) and extrinsic (environmental) factors, including a lack of vitamin complexes, stress, hormonal disorders, genetic inheritance, chemical actions, and drugs [1]. In Brazil, the use of shampoos and conditioners with antioxidant action to combat hair loss and stimulate hair growth has become extremely common.

The most common type is androgenetic alopecia (AGA), which causes premature ageing of the pilosebaceous unit, follicle micro-inflammation, and hair growth inhibition. (AGA) is a slow, painless, and silent micro-inflammation brought on by variables such as climate change, chemical activity from improper cosmetic use, body stress, hormonal abnormalities, menstrual irregularity, weight loss, systemic disease, cancer treatment drug, and iron deficiency. Androgenetic alopecia is not considered a life threatening disease but can have serious impacts on the patient’s psychosocial life. Genetic, hormonal, and environmental factors are considered responsible for the presence of androgenetic alopecia [2-5]. It compromises the hair fiber growth cycle (catagen, telogen and anagen). Therefore, a

[1]*Specialist in Formulation of Magistrates, Brazil.*
[2]*Department of Physiological Science, The Federal University of São Carlos, Brazil.*
[3]*Botswana University of Agriculture and Natural Resources, Botswana*
**Corresponding author: E-mail: ftthema@gmail.com;*

diet low in protein and vitamins is worrying, requiring a supplement with multivitamins [6]. Today we have injectable monodoses for the treatment of Androgenetic alopecia, Seborrheic alopecia, we have the growth factor rich intradermal actives that will perform hair nutrition, the nutricosmetics are used as a blend of Nutricosmetic actives known as pill food, and these associated actives a capillary lymphatic drainage oxygenating stimulant drainage 21.

Due to the complaints of men and women who after sun exposure and some factors of everyday life, increasing the production of reactive factors that can lead to disruption and fall. Nutricosmetic supplements with antioxidant and anti-fall action are suggested, with the potential to inhibit hair aging and hair loss and alopecia. As well as the use of growth factors associated with Led and lasers.

Thus, this study aimed to perform a literature review on the scientific foundations and aesthetic applications of antioxidants and growth factors in the treatment of alopecia.

2. MATERIALS AND METHODS

To achieve the proposed objective, a survey of relevant bibliographies in databases (Google Scholar; PubMed and in secondary sources in the Virtual Health Library (VHL) and LILACS (Latin American Literature in Health Sciences) and in SciELO (Scientific Electronic Library Online) article were used as search terms the words Antioxidants, growth factors, alopecia and were considered for this study (inclusion criteria) theses, dissertations, VictaLab site course, scientific articles, as well as books, published between 2000 and 2017 in Portuguese and English (or only in Portuguese).

3. DISCUSSION

To have healthy hair we need balanced nutrition, it is also necessary to maintain health. Some vitamins are needed daily. Vitamins C, E, A, Beta Carotene, Folates and Magnesium (important for collagen synthesis), nutrient and food intake influence the appearance of hair fiber and skin. According to Purba et al. [7] described that sun injuries are associated with poor eating habits. There are studies that ingestion of vitamin C, linoleic acid and daily use of multivitamins will improve the appearance of hair fiber. Preventive use of antioxidants will reduce hair damage by increasing the consumption of fruits, vegetables that are antioxidant energy sources.

Nutrient intake with antioxidant action plays an extremely important role in the inhibition of alopecia [8,9]. According to Cosgrove et al. [10] factors that lead to alopecia as: smoking patients, age, sun exposure, and menopause, lose body mass by fast diets, causes fall. With the use of supplements, healthy living, energy intake and multivitamin doses, vitamin C, D3, B2, K2, TGP has found excellent results in the appearance of hair fiber with fruit consumption.

Those who use fat (butter, margarine, lactides) and high carbohydrates have older skin and more damaged hair requiring supplementation of glycosamides (pool of amino acids, minerals and antioxidants). According to Cosgrove et al. [10] and Murad and Tabibian [11], the oral supplementation of nutricosmetics and injections mentioned does not replace healthy eating; the dietary supplement inhibits the capillary dehydration and the breakage or breakage of the capillary fiber 21.

The antioxidants used in the skin have been carried out numerous studies, the cutaneous application of α-lipoic acid, in order to minimize the harmful effects of UV radiation. Studies by Podda and colleagues have concluded that α-lipoic acid is effective in protecting against the loss of skin antioxidants. The authors used cultures of keratinocytes protected initially with tocopherol and ubiquinol, verifying that after exposure to UV radiation, the levels of these antioxidants decreased. Thus, in order to preserve antioxidant levels, the authors increased α-lipoic acid, observing the maintenance of antioxidant levels in cell cultures, with a decrease in the levels of reactive species present, as well as a prevention of oxidative stress.

However, studies by Segall et al. [12] Aimed at evaluating the stability of α-lipoic acid in a cutaneous formulation containing vitamin (E, A) showed that despite its low stability. In the formulation and its rapid degradation its use was effective.

According to Professor Dr Nelson Maurício, nutrient-based supplementation leads to increased yarn rate in the anagen phase and improves overall appearance in healthy women with excessive hair loss. Intake of vitamins and minerals promotes beneficial impact on the health of the hair, helping to reduce hair loss and brittle and opaque appearance [13].

Healthy looking hair is a sign of excellent overall health as well as good practice about hair care. Healthy individuals have adequate nutritional intake through their daily diet. However, many people do not have access to good nutrition, and others have pathologies that lead to predisposition to nutritional deficiency. This is often reflected in changes in the scalp and hair fiber with frequent ruptures leading to alopecia [14].

The existing antioxidant list is large, however, only a few can be used in hair-use formulations. 21 In addition to their antioxidant activity, most have other biological properties. The growth factors and peptides used in treating alopecia, (anti-aging capillary) is scientifically proven. With advancing age, cells begin to produce fewer growth factors. The use of vitamin E, vitamin C, carotenoids, (poliquartenum 6, amisosoft EC22, betaine, starch 90, emulsified amino functional silicone, neolone, glycerin, high molecular weight dimethicone, butters, mineral oils, serisea II, hydrolyzed keratin in the handling of Hair moisturizers with antioxidant action, we suggest that they are inert, nontoxic and above all should protect the hair against harmful solar action [11,15-19].

Growth factors are natural biological factors that act on the process of skin repair and regeneration, being found in various tissues undergoing healing and/or cell renewal [20-22]. They are considered protein molecules, produced by the body that binds to other cellular components to promote recovery, maintenance of skin integrity and regulation of tissues. However, with increasing age, there is a decrease in the number of these factors in the body. To produce a smaller amount of these factors impairing the communication between them and their functioning of the tissue, thus research produced the growth factors homologous to human growth factors by genetic engineering, through the process of inoculation of human genes in bacteria. As the *Escherichia coli* [21-23].

The use of growth factors in topical or injectable cosmetics acts on cell recovery regeneration, healing improvement, rejuvenation treatment (wrinkles and fine lines), hair stimulation treatment (alopecia), as well as providing health for the patient. Fabric and aesthetic beauty for the skin [22]. In industry, it was possible to produce growth factors homologous to human growth factors, ensuring that these actives when supplemented *via.* exogenous, cellular activities are reactivated and the rejuvenation process becomes much faster [24-27]. In cosmetics, we have the following growth factors and their peptides available: Copper Peptide; EGF Nano factor (Epidermal Growth Factor); Nano factor IGF (Insulin Growth Factor; Nano factor VEGF (Vascular Growth Factor); Nano factor b-FGF (Basic Fibroblastic Growth Factor) [21-24]. Following are suggestions for formulations of the protocol performed on patients with alopecia below.

3.1 Hair Loss Interruption Capsules

- Colágeno - 25 mg
- Exysnutiment - 100 mg
- Biotina - 30 mg
- Cisteína - 80 mg
- Cistina - 25 mg
- Clicocil - 25 mg
- Silicio quelado - 10 mg
- Magnésio quelaldo - 200 mg
- Boro quelado - 3 mg
- Pantotenato Cálcio - 25 mg

- Vitamina B6 - 10 mg
- Vitamina B2 - 1 mg
- Vitamina E - 3 mg
- Metionina - 200 mg
- Zinco quelado - 12 mg
- Selênio quelado - 100 mg

Suggested use: Take 1 capsule per day, 30 capsules.

3.2 Hair Loss Interruption Lotion and New Follicle Stimulation

- Minoxidil - 5%
- Cooper Peptídeo de - 1.5%
- a FGF - 1.5%
- Hair Active - 10%
- Cafeina - 5%
- VEGF - 1.5%
- Folicusan - 3%
- Locao Hidroalcoolica 20% qsp to 100 ml

Patient use suggestion: Administer up to 20 drops on scalp and massage of stimulating hair drainage Injection suggestion [25].

3.3 Hair Nutrition

- Minoxidil 0.5% to 2 ml Copper Peptídeo
- 10 mg to 2 ml Pill Food* 2 ml
- Lidocaína 2% to 2 ml

Patient use suggestion: Intradermal - 4 mm Needle 1 × Week

3.4 Androgenetic Alopecia

- Biotina 10 mg to 2 ml, Minoxidil 0.5% to 2 ml
- D -Pantenol 40 mg to 2 ml, Finasterida 0.05% to 2 ml/ Lidocaína 1% to 2 ml

Patient use suggestion: Intradermal - 4 mm Needle - 1 × Week

3.5 Alopecia c/ Fatores de Crescimento

- Biotina 10 mg to 2 ml/ D-Pantenol 40 mg to 2 ml
- Minoxidil 0.5% to 2 ml/ IGF 1% + BFGF
- 1% + VEGF 1% + Copper Peptídeo 1% - 2 ml
- Lidocaína 1% - 2ml

Patient use suggestion: Intradermal - 4 mm Needle - 1 × Week

3.6 Alopecia Seborréica

- Biotina 10 mg to 2 ml/ D-Pantenol 40 mg to 2 ml
- IGF 1% + BFGF 1% + VEGF 1% + Copper
- Peptídeo 1% - 2 ml/ Lidocaína 1% - 2 ml/Beta
- Estradiol 2 mg to 2 ml

Patient use suggestion: Intradermal - 4 mm Needle - (Apply separately) 1 × week

According to Fitzpatrick et al. [26] growth factors and peptides today for the treatment of alopecia plays an important activity, especially Androgenetic alopecia, unlike conventional hair and hair growth treatments that are based on hair nutrition and vasodilation. Growth factors and their peptides stimulating formation of new hair follicles with abundant extracellular matrix deposition: essential for the growth and permanence of the new hair (fortified root).

Control with treatment follows some studies that prove the influence of growth factors and their peptides on the hair cycle. Due to hormonal issues as well as aging, responsible cells start producing a smaller amount of growth factors, directly influencing the amount of hair on the scalp. According to Fitzpatrick et al. [26], Japanese researchers at Kyoto University conducted a study, published in Tissue Engineering, which investigated how the prolonged-release Basic Fibroblast Growth Factor (bFGF) affects rat hair growth in the anagen and telogen phases. Of the hair cycle after 10 days of application. Results show that 70 mcg of bFGF, after the given period, increased the size of hair follicles, proving its positive effects on the hair growth cycle in rats.

Copper Peptides (Copper Peptides) have been shown to act as a growth factor in cell differentiation, in addition to stimulating the proliferation of dermal fibroblasts and increasing the production of vascular endothelial growth factor. We evaluated the effect of Copper® Tripeptide (Copper® Peptide) complex on human hair growth through ex vivo study and dermal papilla® cell culture. The results showed that Copper Peptide stimulated the prolongation of live hair follicles and the proliferation of the dermal papillae of the follicle. Thus, it was concluded that Copper® Tripeptide Complex (Copper Peptide) promoted growth of hair follicles in humans, and that this effect may have occurred due to stimulation of proliferation and the prevention of hair loss.

One of the protocols carried out by Caregen in proving the efficacy of growth factors and their peptides in the treatment of alopecia is the use of a hair lotion containing Copper Peptide® associated with Insulin Growth Factor (IGF), Vascular Growth Factor (VEGF). And Basic Fibroblastic Growth Factor® (bFGF). Early in the treatment it is possible to notice the interruption of the fall thanks to the anti-5 alpha reductase action provided by the Copper Peptide [12,27,28]. After three months of use there was an increase in the hair population resulting from the actions of follicular revitalization, vasodilation and nutrition of the new hairs.

4. CONCLUSION

The use of antioxidants and growth factors in the treatment of alopecia has been shown to be efficient, and the Injectables have thus expanded the therapeutic possibilities of aesthetic treatments. It was used in this study the various procedures and techniques such as: micro-needling, intradermotherapy, Led, Laser, the PDS method and the technique of treatment of induction of assets of Dr. Alex de Souza who makes use of the technique of the British Doctor Edward Jenner (1749 to 1823).

The actives manipulated the nutricosmetics for hair stimulation; each procedure was suggested to the patient a glass of soft red wine and a glass of drinkable H20 before and after the procedure. Same procedure. This approach will be studied in our next article, together with the study of ozone-enriched autohemotherapy in the treatment of alopecia.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Pereira JM. O tricograma - Parte II - Resultados e interpretação. An Bras Dermatol. 1993;64:217-23.
2. Prie BE, Iosif L, Tivig I, Stoian I, Giurcaneanu C. Oxidative stress in androgenetic alopecia. Journal of medicine and life. 2016 Jan;9(1):79.

3. Cwynar A, Olszewska-Słonina DM, Czajkowski R. The impact of oxidative stress in androgenic alopecia in women. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii. 2020;37(1):119.
4. Erdogan HK, Bulur I, Kocaturk E, Yildiz B, Saracoglu ZN, Alatas O. The role of oxidative stress in early-onset androgenetic alopecia. Journal of cosmetic dermatology. 2017;16(4):527-30.
5. Aslani FS, Dastgheib L, Banihashemi BM. Hair counts in scalp biopsy of males and females with androgenetic alopecia compared with normal subjects. Journal of cutaneous pathology. 2009;36(7):734-9.
6. Cassia D, Souza A. A Importância do Conhecimento da Alopecia Aerata na Estética. Acesso Em. 2017;15(1):1-15.
7. Purba MB, Kouris-Blazos A, Wattanapenpaiboon N, Lukito W, Rothenberg EM, Steen BC, et al. Skin wrinkling: can food make a difference? J Am Coll Nutr. 2001;20(1):71-80.
8. Xu Q, Parks CG, Deroo LA, Cawthon RM, Sandler DP, Chen H. Multivitamin use and telomere length in women. Am J Clin Nutr. 2009;89(6):1857-64.
9. Piccardi N, Manissier P. Nutrition and nutritional supplementation: impact on skin health and beauty. Dermatoendocrinol. 2009;1(5):271-4.
10. Cosgrove MC, Franco OH, Granger SP, Murray PG, Mayes AE. Dietary nutrient intakes and skin-aging appearance among middle-aged American women. Am J Clin Nutr. 2007;86(4):1225-31.
11. Murad H, Tabibian MP. The effect of an oral supplement containing glucosamine, amino acids, minerals, and antioxidants on cutaneous aging: a preliminary study. J Dermatol Treatment. 2001;12(1);47-51.
12. Nanofactor peptídeos. Arch Pharm Res. 30(7):834.
13. Folder nanofactore peptideos; 2011.
14. Guarrera M, Seminom T, Rebora A. Quantitating hair loss in women: A critical approach. Dermatology. 1997;194:12-6.
15. Rivitti EA. Alopecia areata: Revisão e atualização. An Bras Dermatol. 2005;80:57-68.
16. Leite AMS. Intimate beautification for men and women without borders with the use of blood plasma and the use of Led and Laser. Work presented at the 3rd International Online Aesthetics Congress Ipatinga. 2017;55:121.
17. Galembeck F, Csordas Y. Cosméticos: A Química Da Beleza; 2001.
18. Saitho M, Uzuka M, Sakamoto M. Human hair cycle. J Invest Dermatol. 1970;54:65-80.
19. Nanofactor and Peptídeos. Pharma Special. 12.
20. The use of growth factors in cosmetics for skin rejuvenation; 2010.
21. Microneedling + growth factors; 2018.
22. Silva BMF, Bolda JM, França AJVBDV. O uso de fatores de crescimento em produtos cosméticos para o envelhecimento cutâneo. 2011;18(3):8-12.
23. Borges FS, Scorza As. Therapeutics in aesthetics concepts and techniques 1st.ed-São Paulo: Phorte; 2011.
24. Oliveira LP. The use of growth factors in cosmetics for skin rejuvenation. 2010;30.
25. Victa manipulation laboratory; 2019.
26. Fitzpatrick RE, Mehta RC. Endogenous growth factor as cosmeceutica. Dermatol Ther. 2007;20:350-9.
27. Droge W. Oxidative stress and aging. Adv Exp Med Biol. 2003;543:191-200.
28. Nishigori C, Hattori Y, Arima Y, Miyachi Y. Photoaging and oxidative stress. Exp Dermatol. 2003;12(Suppl 2):18-21.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Annals of Surgical Education, 1, 2020.

London Tarakeswar

Registered offices
India: Guest House Road, Street no - 1/6, Hooghly, West Bengal, PIN-712410, India, Corp. Firm Registration Number: L77527, Tel: +91 7439016438 | +91 9748770553, Email: director@bookpi.org, (Headquarters)
UK: 27 Old Gloucester Street London WC1N 3AX, UK
Fax: +44 20-3031-1429 Email: director@bookpi.org, (Branch office)