Acanthosis nigricans (AN) is the term proposed by Unna [18] to indicate a disorder characterized clinically by thickening and darkening velvety plaques symmetrically distributed on the sides of the neck, axillae and groin. These lesions may be skin-coloured or brownish and may vary between 1 mm and 1 cm [9]. The neck is involved 93% to 99% of the time [4,23,24]. Less often it affects eyelids, palms, soles of the feet, nipples and phalanges and rarely the mucosa of the mouth, respiratory mucosa and genital region [4,23,24] (Figs. 1, 2).

Prevalence
The prevalence of AN varies from 7% in unselected populations to 74% in obese people (23,24). The prevalence also varies in different racial groups. For example, African Americans are 25 times more likely to have AN than patients of European descent (23,24). A study from the USA reports that the prevalence of AN is about 3% among Caucasians, 19% in Hispanics and 28% in American Indians [23,24].

Pathogenesis of AN
Biochemical mechanisms for developing this hyperplastic lesion are unclear, but likely involve local cutaneous growth factors. Insulin and insulin-like growth factor-I, and their receptors on keratinocytes are involved in the complex regulations leading to the peculiar epidermal hyperplasia [19]. At high concentrations, insulin may exert potent proliferative effects via high-affinity binding to IGF-1 receptors. In addition, free IGF-1 levels may be elevated in obese patients with hyper-insulinemia, leading to accelerated cell growth and differentiation [10].

Histologically there is papillomatosis, hyperkeratosis and acanthosis with minimal or no hyperpigmentation of the basal layer.

Table 1. A quantitative scale of AN developed by Burke et al. (modified)

<table>
<thead>
<tr>
<th>Location and score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neat severity</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Not detectable on close inspection.</td>
</tr>
<tr>
<td>1</td>
<td>Clearly present on close visual inspection, not visible to the casual observer, extent not measurable.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: limited to the base of the skull, does not extend to the lateral margins of the neck</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: extending to the lateral margins of the neck (posterior border of the sternocleidomastoid)</td>
</tr>
<tr>
<td>4</td>
<td>Severe: extending anteriorly, visible when the participant is viewed from the front.</td>
</tr>
</tbody>
</table>
Assessment

A quantitative scale of AN has been developed by Burke et al. [4]. (Table 1) This scale takes into consideration the severity of AN in the neck and axilla, neck texture and the presence or absence of AN in knuckles, elbows and knees. The scale is easy to use and correlates well with fasting insulin and body mass index (BMI). Neck AN severity is strongly associated with elevated fasting insulin and BMI in both diabetic and non-diabetic subjects, elevated fasting glucose, systolic blood pressure, and diastolic blood pressure, and with decreased high density lipoprotein (HDL) in non-diabetic subjects. Therefore, the observation of AN would help to diagnose insulin resistance (IR).

Table 2. AN and related medical conditions

1. Type 1: Hereditary benign acanthosis nigricans
2. Idiopathic onset during childhood or puberty
3. Obesity resulting in insulin resistance
4. Diabetes mellitus
5. Androgen excess (hyperandrogenism)
6. Cushing’s syndrome
7. HAIR-AN syndrome
8. Hypogonadism
9. Addison’s disease
10. Hypothyroidism
11. Type 3: Pseudo-acanthosis nigricans
12. Seen in patients with darker pigmentation
13. Type 4: Drug-induced acanthosis nigricans
14. Glucocorticoids
15. Niacin
16. Protease inhibitors
17. Oral Contraceptive
18. Malignant acanthosis nigricans
19. Causes
20. Paraneoplastic tumors (adenocarcinoma)
21. Lymphoma

Types of AN

Currently, 8 types of AN have been identified, according to Schwartz [19] (Table 2):

1. Obesity-associated AN: This is the most common type of AN. Lesions may appear at any age but are more common in adulthood. The dermatosis is weight dependent and lesions may completely regress with weight reduction. Insulin resistance is often present in these patients; however, it is not universal.

Other endocrine disturbances associated with AN are Cushing’s disease, polycystic ovary syndrome (PCOS), thyroidopathies, hirsutism, Addison’s disease and acromegaly. Some of these disorders occur along with insulin resistance [17].

2. Unilateral AN: Lesions are unilateral in distribution and may become evident during infancy, childhood, or adulthood. Lesions tend to enlarge gradually before stabilizing or regressing. It is believed to be inherited as an autosomal dominant trait.

3. Familial AN: The lesions typically begin during early childhood but may manifest at any age and the condition often progresses until puberty, at which time it stabilizes or regresses. It seems to be genetically transmitted.

4. Syndromic AN is the name given to AN that is associated with a syndrome. Familial and syndromic forms have been subdivided into insulin-resistance syndromes and fibroblast growth factor defects.

Insulin-resistance syndromes include those with mutations in the insulin receptors (i.e., leprechaunism, Rabson-Mendenhall syndrome), peroxisome proliferator-activated receptor gamma (i.e., type 1 diabetes with acanthosis nigricans and hypertension), 1-acylglycerol-3-phosphate O-acyl transferase-2 or seipin (Berardinelli-Seip syndrome), lamin A/C (Dunnigan syndrome), and Alstrom syndrome gene [10,19,20].

Fibroblast growth factor defects include activating mutations in FGFR2 (Beare-Stevenson syndrome), FGFR3 (Crouzon syndrome with acanthosis nigricans, thanatophoric dysplasia, severe achondroplasia with developmental delay, and acanthosis nigricans [SADDAN]). Familial cases of acanthosis nigricans with no other syndromic findings have also been linked to FGFR mutations [3,21].

Type A syndrome: Also termed HAIR-AN syndrome (hyperandrogenemia, insulin resistance and AN). The lesions of AN may arise during infancy and progress rapidly during puberty. This syndrome is often familial, affecting primarily young women (especially black women). It is associated with polycystic ovaries or signs of virilization (e.g. hirsutism, clitoral hypertrophy). High plasma testosterone levels are common. Early detection, diagnosis, and treatment can help reduce further morbidity, improve self-esteem, and have a positive impact on the quality of life of these patients.

Type B syndrome: Generally occurs in women who have uncontrolled diabetes mellitus, ovarian hyperandrogenism, or an autoimmune disease such as systemic lupus erythematosus, scleroderma, Sjögren syndrome, or Hashimoto thyroiditis. Circulating antibodies to the insulin receptor may be present. In these patients, the lesions of AN are of varying severity.

Besides these variants there are other numerous syndromes, the most well known of which are Hirschowitz syndrome, which is familial, characterized by early onset, deafness and gastrointestinal disorders; and Lawrence-Seip syndrome [15,20] with lipodystrophy associated with AN.

Skeletal dysplasias: AN has been reported in association with severe skeletal dysplasias due to activating mutations in FGFR3. The development of AN in patients with skeletal dysplasias is not due to insulin insensitivity or treatment with recombinant human growth hormone. Whether the AN
is due to altered melanocyte function in these individuals remains to be elucidated [2].

5. Acral AN: The hyperkeratotic velvety lesions are most prominent over the dorsal aspects of the hands and feet. It occurs in patients who are in otherwise good health. Acral AN is most common in dark-skinned individuals, especially those of African American descent.

6. Drug-induced AN, although uncommon, may be induced by several medications, including nicotinic acid, insulin, systemic corticosteroids and oral contraceptives. The lesions of drug-induced AN may regress following the discontinuation of the offending medication.

7. Malignant AN is associated with internal malignancy, particularly gastric adenocarcinoma. It is characterized by sudden onset and it is sometimes associated to other cutaneous markers of malignancy such as eruptive seborrheic warts, florid cutaneous papillomatosis and hyperkeratosis of the palms and soles. In the case of malignant AN, multiple growth factors including transforming growth factor α, insulin-like growth factor, and fibroblast growth factor have been implicated. These factors most likely act by exerting an insulin-like effect on keratinocytes and dermal fibroblasts.

In approximately one third of cases of malignant acanthosis nigricans, patients present with skin changes before any signs of cancer. In another one third of cases, the lesions of acanthosis nigricans arise simultaneously with the neoplasm. In the remaining one third of cases, the skin findings manifest sometime after the diagnosis of cancer [10].

Warning flags that should trigger a careful evaluation for malignancy in patients presenting with acanthosis nigricans include unintentional weight loss and rapid onset of extensive AN [19]. Mucosal AN is more common in patients who have AN in association with a malignancy, as are tripe palms, florid cutaneous papillomatosis, and the sign of Leser-Trélat [19].

8. Mixed-type AN refers to those situations in which a patient with one of the above types of AN develops new lesions of a different etiology. An example of this would be an overweight patient with obesity-associated AN who subsequently develops malignant AN.

**Laboratory assessment**

The following investigations are recommended in subjects with AN:
1) serum glucose and insulin
2) lipid profile
3) glycosylated hemoglobin level, and in selected cases oral glucose tolerance test.

These data are useful tools for baseline screening and follow-up of subjects at risk for type 2 diabetes mellitus, hypercholesterolemia and hypertension.

In 2000, the American Diabetes Association established acanthosis nigricans as a formal risk factor for the development of diabetes in children [22].

Insulin resistance (IR) is a metabolic disorder in which target cells fail to respond to normal levels of circulating insulin, which results in compensatory hyperinsulinemia in an attempt to obtain an appropriate physiological response [1,12].

In order to assess insulin resistance, insulin secretion and insulin sensitivity, methods based on the hyperglycaemic clamp have been validated both in obese and normal adults [5,25]. In children, the euglycaemic clamp procedure is cumbersome, time consuming and technically difficult to perform especially on a large group.

**HOmeostasis Model Assessment of IR index (HOMA-IR):**

\[
\text{HOMA-IR} = \frac{\text{fasting insulin in mU/l} \times \text{fasting glucose in mmol/l}}{22.5}
\]

**QUantitative Insulin-sensitivity ChecK Index (QUICKI):**

\[
\text{QUICKI} = \frac{1}{\log10 \text{fasting plasma insulin in mU/l} + \log10 \text{glucose in mg/dl}}
\]

Normal percentiles values (from the 2.5th to the 97.5th) of HOMA-IR, HOMA-b% and QUICKI for the adolescent Italian population are available in the literature [8].

One hundred and forty-nine overweight and obese children were screened for AN by Dubnov-Raz et al. [7]. Twenty-two (14.8%) children had AN. Children with AN had greater weight, height, BMI, waist circumference, waist-to-height-ratio, triceps skinfold thickness, and total and truncal body fat percentage, compared to those without AN. After adjustment for age and BMI, no adiposity measure was increased in children with AN. The authors concluded that overweight and obese children with AN basically have greater overall and central adiposity than those without it.

A large-scale screening of fifth-grade students in West Virginia explored the prevalence of metabolic syndrome among 676 male and female participants who had mild to severe AN. Children with AN who were classified as obese or morbidly obese were at significantly increased odds of having metabolic syndrome [11].

**Treatment**

Treatment is directed towards management of the underlying cause that includes either weight reduction, discon-
continued off-therapy of offending drugs, correction of the endocrine abnormality or therapy of the underlying malignancy.

Emollients, keratolytics, calcipotriol, systemic retinoids, CO2 laser ablation, and long-pulsed laser may improve appearance. In the setting of AN with obesity, weight loss with appropriate dietary and lifestyle modifications should be encouraged [10]. Oral metformin is a first choice drug in the treatment of AN associated with obesity and insulin resistance [6]. Follow up care should be coordinated with the patient’s primary care physician and should include periodic measurements of body weight and blood insulin levels.

Conclusions

Acanthosis nigricans is a lesion affecting localized areas of the skin in persons with obesity and/or hyperinsulinemia. Biochemical mechanisms for developing this hyperplastic lesion are unclear, but likely involve local cutaneous growth factors. Clinicians should recognize acanthosis nigricans because it heralds disorders ranging from endocrinologic disturbances to malignancy. AN in association with high BMI (at or above the 85th percentile) is a sensitive screening tool for identifying children and youth with IR who are at increased risk for developing type 2 diabetes and other features of the metabolic syndrome [11].

REFERENCES

ACANTHOSIS NIGRICANS IN ADOLESCENTS: A PRACTICAL APPROACH


Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy; Department of Pediatrics, Hamad Medical Center (HMC), Doha, Qatar; Pediatric Unit, Rimini, Italy; Pediatrician, Forlì, Italy; Pediatrician, Imola, Italy; Pediatric Unit, Faenza, Italy; Dermatologist, Quisisana Hospital, Ferrara, Italy

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Keywords: Acanthosis nigricans, adolescents.

SUMMARY

ACANTHOSIS NIGRICANS IN ADOLESCENTS: A PRACTICAL APPROACH


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REZIOME

AKANTOKERATODERMIA У ПОДРОСТКОВ: ПРАКТИЧЕСКИЙ ПОДХОД


Квисисанский госпиталь, амбулаторная клиника детей и подростков, Феррара, Италия; Хамадский медицинский центр, отделение детского здравоохранения, Доха, Катар; Педиатрический центр, Римини, Италия; Амбулатория аллергологии и педиатрии, Форли, Италия; Педиатрический центр, Имола, Италия; Педиатрический центр, Фаенца, Италия; Квисисанский госпиталь, дерматолог, Феррара, Италия

Акантокератодермия (Acanthosis nigricans – AN) – поражение локализованных участков кожи, встречающееся у лиц с ожирением и/или гиперинсулинемией. Биохимические механизмы этих гиперпластических изменений неясны, возможно, определенную роль играют факторы роста кожи. AN ассоциируется с ожирением, эндокринопатиями (резистентность к инсулину, сахарный диабет, болезни Кушинга и акромегалии), а также с злокачественными опухолями внутренних органов. Клиницисты должны уметь распознавать AN, так как она может предвещать ряд нарушений – от эндокринопатий до опухолей. Раннее распознавание этого состояния весьма важно для идентификации детей с высоким риском развития сахарного диабета типа 2 и дальнейших метаболических нарушений.

Адератоза. Акантоэритродермия: практический подход


Квисисанский госпиталь, амбулаторная клиника детей и подростков, Феррара, Италия; Хамадский медицинский центр, отделение детского здравоохранения, Доха, Катар; Педиатрический центр, Римини, Италия; Амбулатория аллергологии и педиатрии, Форли, Италия; Педиатрический центр, Имола, Италия; Педиатрический центр, Фаенца, Италия; Квисисанский госпиталь, дерматолог, Феррара, Италия

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GROWTH HORMONE DEFICIENCY IN ADULTS WITH THALASSEMAIA: AN OVERVIEW AND THE I-CET RECOMMENDATIONS

1Soliman A., 2De Sanctis V., 3Elsedfy H., 4Yassin M., 5Skordis N., 6Karimi M., 7Sobti P., 8Raiola G., 9El Kholy M.

Although growth hormone (GH) is secreted throughout life, its role in adulthood has been mainly studied in the last two decades.

GH is an important growth-promoting factor that has been shown to have metabolic, inflammatory and immunologic importance [15,33]. Adults with GH deficiency (GHD) experience lack of positive wellbeing, depressed mood, feelings of social isolation, decreased energy, and an overall poorer quality of life when compared with controls [4,33]. Their bone mineral density (BMD) is also reduced, resulting in increase in bone fracture rate [40,43,49,52].

Moreover, experimental studies suggest that GH and IGF-1 have stimulatory effects on myocardial contractility, possibly mediated by changes in intracellular calcium handling [21].

Short-term GH replacement therapy in adults has been associated with beneficial effects on body composition, fat distribution, cardiac function, BMD and quality of life [11]. It remains to be determined, however, whether or not chronic GH replacement therapy can indeed have beneficial effects on morbidity and mortality [57].

Significant barriers to treatment of adults who have GHD exist. These include a perceived difficulty in making a secure diagnosis, non standardized strategies for dosing and treatment monitoring, a lack of awareness or acceptance of data supporting efficacy, concern regarding the relationship of GH to side effects or complications, cost and need for daily injections.

This review paper provides a summary of the current state of knowledge regarding GHD in adults and gives some recommendations for the diagnosis and treatment of GHD in adult patients with thalassaemia major (TM).

GHD in adult TM patients

Adults with TM have several clinical manifestations comparable to those with GHD: muscle wasting, weakness and cramps, neuromuscular abnormalities, cardiomyopathy and cardiac complications, decreased bone density and osteoporosis associated with an increased risk of fracture, decreased muscle mass, abnormal fat metabolism, increased prevalence of impaired glucose tolerance or diabetes, decreased insulin sensitivity and premature senescence of cells (lymphocytes) [25,35,43,44,54].

Although anemia and chronic iron overload are important etiologic factors, other complications such as chronic liver diseases and endocrinopathies (hypothyroidism, hypoparathyroidism, insulin dependent diabetes, GH and insulin like growth factor 1 (IGF-1) deficiency may actively contribute to these clinical manifestations [28].

GHD or neurosecretory GH dysfunction, as well as reduced IGF-1 production, have been reported in children and adults with TM [16,50,51]. The documented GH-IGF-1 alterations in adult TM patients could be a continuation of the childhood GHD state or a newly developed deficiency with age [42,44,45,48,50-52].

In adult TM patients, the prevalence of GHD and/or IGF-1 deficiency is relatively high and varies from 8% to 44% in different centres (Table). De Sanctis et al. [19] sent a questionnaire to 29 centres treating a total of 3817 TM patients. Thirty-six per cent of patients were over the age of 16 years. Short stature was present in 31.1% of males and 30.5% of females, and the prevalence GHD was on average 7.9% in males and 8.8% in females. Analysis of these results indicate that GHD in TM patients probably is an age-related phenomenon and the risk of pituitary and/or hypothalamic dysfunction remains high in adult TM patients, despite improvements in the care of hematologic problems and treatment of iron overload.

These functional abnormalities of the GH/IGF-1 axis, in patients with TM, are accompanied by structural abnormalities of the pituitary gland (pituitary siderosis and atrophy) and its stalk [1,2].

The presence of hepatic siderosis with cirrhosis and the high incidence of chronic liver disease due to chronic hepatitis can explain in part the defective synthesis of IGF-1 in the liver [51,52].
<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>GH provocative test</th>
<th>GHD %</th>
<th>IGF-1 %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poggi et al (38)</td>
<td>28</td>
<td>Arginine + GHRH</td>
<td>32%</td>
<td>Low</td>
<td>The group affected by GHD showed a worse bone profile</td>
</tr>
<tr>
<td>Cavallo et al (7)</td>
<td>29</td>
<td>Clonidine and ITT</td>
<td>45%</td>
<td>Low</td>
<td>The reduction of GH reserve is more frequently due to a hypothalamic than to a pituitary dysfunction</td>
</tr>
<tr>
<td>Scacchi et al (42)</td>
<td>94</td>
<td>GHRH + arginine</td>
<td>41.4%</td>
<td>Low</td>
<td>80% of patients with normal GH reserve had low IGF-1 SDS. The reduced liver synthetic activity and low GH secretion are major determinant of low IGF-1 production. Biosynthetic GH replacement therapy in GHD thalassaemic adults is worth considering</td>
</tr>
<tr>
<td>Scacchi et al (43)</td>
<td>64</td>
<td>GHRH + arginine</td>
<td>42.1%</td>
<td>*Low</td>
<td>Analysis pointed to both GH peak and IGF-1 SDS as predictors of femoral T-score. Mean femoral T-score was significantly lower in patients with severe GHD than in those with normal GH</td>
</tr>
<tr>
<td>Pincelli et al (37)</td>
<td>25</td>
<td>GHRH + arginine</td>
<td>8%</td>
<td>72%</td>
<td>Patients with hepatitis C virus infection showed lower IGF-1 concentrations than uninfected subjects despite a normal GH reserve, suggesting partial GH insensitivity at the post-receptor level</td>
</tr>
<tr>
<td>La Rosa et al (30)</td>
<td>16</td>
<td>GHRH + arginine</td>
<td>19%</td>
<td>low</td>
<td>GH status should be retested in adult thalassaemic patients with childhood-onset GHD. If the diagnosis of adult GHD is established, GH treatment may be considered as it could contribute to improved heart function and BMD</td>
</tr>
<tr>
<td>Vidergor et al (58)</td>
<td>16</td>
<td>GHRH + arginine</td>
<td>25%</td>
<td>69%</td>
<td>The clinical benefits of GH therapy need to be determined. GH alone does not account for the high prevalence of reduced IGF-1 in adult β thalassaemia</td>
</tr>
<tr>
<td>De Sanctis et al (16)</td>
<td>33</td>
<td>Glucagon (GST)</td>
<td>44%</td>
<td>Low</td>
<td>86.6% of patients with normal GH response to GST had low IGF-1 level, indicative of a relative resistance to GH. 9% (n =3) of patients with GHD and normal T2* were found to have reduced LVEF</td>
</tr>
</tbody>
</table>

*IGF-1 < -1.88 SDS (54.6%)

The relevance of the defective GH-IGF-1 axis to the pathogenesis of cardiovascular disease in thalassemia
Cardiomyopathy remains the leading cause of death in patients with TM [15,33]. Despite regular transfusions, these patients have larger ventricular volumes, higher cardiac outputs and lower total vascular resistances. These hemodynamic findings may be related to chronic anemia and/or severe iron overload [39,47]. However, endocrinopathies like GH-IGF-1 deficiency, hypothyroidism and hypoparathyroidism may contribute to the heart pathology [55].

The role of GH and IGF-1 as modulators of myocardial structure and function are well established [6]. Receptors for both GH and IGF-1 are expressed in cardiac muscles [21]. Therefore, GH may act directly on the heart or via the induction of local or systemic IGF-1. In patients with GHD, GH administration dramatically improves cardiac function. The first case report of reversible severe heart failure associated with GHD due to primary pituitary failure improved within days on 12 IU daily of subcutaneous GH (14). Furthermore, in a GHD patient with severe dilated cardiomyopathy, and reduced left ventricular ejection fraction (LVEF), intramuscular treatment with 4 IU of GH daily resulted in a marked improvement in myofibrillar content of myocardiocytes [24].

Limited information are available in the literature of TM patients with GHD and cardiac dysfunction.
A 21-year-old woman with TM developed end-stage heart failure within 3 months after withdrawal of GH. Intensive treatment with digoxin, angiotensin-converting enzyme inhibitor, diuretics and intensive iron chelation therapy with desferrioxamine did not improve her progressive heart failure. A myocardial biopsy excluded myocarditis and showed moderate iron deposit in the heart. GH was restarted and her heart failure reversed. One year later her cardiac function normalized [22].

The second case was an Italian 23-year-old man with GHD, insulin-dependent diabetes mellitus, hypogonadism and enlarged left ventricle. He was treated with GH and six months later physical examination, laboratory and cardiologic evaluation showed a reduction in abdominal waist adiposity, an amelioration of gluco-metabolic control, a reduction of LVEF and an improvement of ventricular motility [46].

In summary, the fact that untreated GHD, in the context of varying degrees of hypopituitarism, is associated with an adverse cardiovascular risk profile provides circumstantial evidence for a causative role of GHD in mediating increased rates of a cardiac dysfunction [36].

Therefore, clinicians taking care of TM patient should consider GHD as a potential risk factor for cardiac failure and should evaluate the potential favorable effect on cardiac performance of GH treatment in TM patients.

The relevance of the defective GH-IGF-I axis to the pathogenesis of bone disease in thalassemia

Decreased bone mineral density (BMD) is a recognized phenomenon in adult hypopituitary patients and is associated with an increased fracture risk [15,33]. Measurements of markers of bone formation and bone resorption are consistent with a low bone turnover state in GHD. Deficits in bone mineral content and density are more striking in adults with childhood-onset GHD. Failure to achieve peak bone mass has important implications for the future development of osteoporosis and fracture risk.

Despite the extraordinary improvements carried out in diagnostic and therapeutic management of thalassemia major osteoporosis in TM still represents a prominent cause of morbidity [43].

The pathogenesis of bone disease in TM is multifactorial and complex [29,56]. Peak bone mass is achieved shortly after completion of puberty and normally remains stable until the third decade of life when age-related bone mass begins.

GH and sex steroids play a crucial role in bone remodeling and in the maintenance of skeletal architecture during adult life. GH and insulin like growth factors have anabolic effect in bone formation. Sex steroids act probably by increasing the expression of RANKL by osteoblastic cells and alterations in the RANK/RANKL/OPG system in favor of osteoclasts [56].

In TM patients, like in panhypopituitarism, impaired GH secretion and lack of sex steroids due to pituitary damage contribute to failure of achieving optimal peak bone mass [20]. In addition, available evidence indicates that qualitatively similar changes in BMD are found in adult-onset isolated GHD as in panhypopituitarism, therefore supporting a role for GHD in the pathogenesis. Furthermore, these abnormalities in bone metabolism and bone density are favorably influenced by GH replacement therapy [8].

Considering the relatively high prevalence of GHD among children and adult TM patients, the possible role of GH-IGF-I abnormalities in the pathogenesis of the osteopenia/osteoporosis of this disease is raised and investigated in children with TM. In two different studies on 30 and 29 TM children the BMD at femoral neck and lumbar vertebrae was highly correlated with the circulating concentrations of IGF-1 and IGFBP3, as well as with the auxological parameters [31,49,52].

A study on the relation between GH secretion and BMD in 61 adult TM subjects confirmed the high prevalence of both osteopenia/osteoporosis and GH-IGF-1 deficiency in these patients and indicated that defective GH secretion and diminished serum IGF-1 levels may contribute to femoral demineralization [43]. Another study showed progressive decrease of BMD with progression of age in TM patients (osteopenia increased from 20% in age group 17-20 years; to 40% in age group 21-25 years and 100% in age group 26-30 years) [29].

In summary, the relative high frequency of bone disease associated with GH-IGF-1 axis abnormalities and the evidence of a positive effect of GH on bone accretion in adult GHD endorse GH therapy as a preventive and therapeutic tool for low BMD. However, it is important to note that the effects on fractures are not yet fully proven. Therefore, randomized trials that compare homogenous groups of GHD patients are still needed.

The relevance of the defective GH-IGF-I axis to the pathogenesis of impaired glucose tolerance in thalassemia

GH reduces insulin sensitivity (IS), whereas IGF-1 increases it. IGF-1 seems to be critical for the development of the β-cells, and impaired IS has been reported in GHD. The frequency of changes in insulin sensitivity varies considerably and is associated with age and abdominal adiposity. GH replacement therapy has often been proposed to restore IS in these patients [33,53].

The relation between GH-IGF-I deficiency and glucose homeostasis in adults with TM and GHD and the effect of GH therapy on glucose metabolism have not been studied.
One of our peripubertal patients developed an impaired glucose tolerance (IGT) [18] and one patient reported by Gallisai (unpublished data, 1994) developed IDDM during treatment with GH. Therefore, the possibility of IGT should be excluded before initiating GH treatment and blood glucose levels should be regularly monitored in order to exclude any adverse influence of treatment on glucose homeostasis.

**Growth hormone diagnosis in adults**

International consensus guidelines have focused on insulin tolerance test (ITT) and growth-hormone releasing hormone (GHRH) + arginine test as the best available tests for the diagnosis of GHD in adults [11,26,27].

When ITT is contraindicated or GHRH is not available or a hypothalamic GH deficiency is suspected, glucagon stimulation test (GST) is an alternative option [30].

The GST can also provide co-assessment of ACTH reserve. Although the GST is safe, with almost no contraindications, it causes nausea and sometimes vomiting in 15-20% of subjects [26,27].

The presence of obesity (especially abdominal), which increases with advancing age throughout adulthood, creates significant difficulties in diagnosing GHD as the obese state is associated with poor GH responsiveness to secretagogues. Corneli et al. have defined BMI-specific cut-off points for diagnosing adult onset GHD using GHRH + arginine=11.5 ng/mL for those with BMI <25 kg/m²; 8.0 ng/mL, for BMI 25-30 kg/m²; 4.2 ng/mL for those with BMI >30 kg/m² [12].

Many studies support the notion that IGF-1 levels of 1 SD below the mean for men and women at various ages in their life can be used in the context of a patient’s total clinical assessment as an indication of GHD. However, a normal IGF-1 value does not exclude the diagnosis of GHD, as a significant overlap of IGF-1 levels between normal subjects and GHD patients has been noted [11,26].

**Diagnosis of GHD in adult thalassemic patients and the I-CET recommendations**

Confirmation of persisting GHD at the time of completion of linear growth or an acquisition of GHD in adult TM patients is important for a number of reasons reported above.

Because GH treatment requires analysis of many factors, including efficacy of treatment on cardiac function, metabolic parameters, psychosocial functioning, safety, ethical considerations, financial cost and other burdens of therapy, stringent diagnostic criteria are needed. The following recommendations are suggested by the International Study Group of Endocrine Complications in Thalassaemia (I-CET) [17] for adult TM patients:

1. Selecting thalassemic patients for GH testing and possible therapy appears to be difficult because of the occurrence of many symptoms and signs in thalassemia overlap with those for adult GHD.
2. Some clinical and laboratory parameters favour performing GH stimulation test including: short stature (HtSDS < -2.5), severe and/or prolonged iron overload, presence of severe osteoporosis and/or serum IGF-I level < -2SDS for age and sex (Soliman, submitted for publication).
3. In consideration of all controversy over the best method to diagnose GHD, we believe that two stimulating tests are necessary and required for an accurate diagnosis of GHD in adult TM patients [37].
4. The ITT test has been the stimulation test used by most endocrinologists to diagnose GHD in adults. Insulin-induced hypoglycaemia, however, may pose significant risks in the setting of any known cardiovascular disease that is quite common in TM patients [39]. Therefore, alternative GH stimulation tests must be used. The co-administration of arginine and GH-RH is a powerful stimulus for GH release and glucagon stimulation test is a reliable and safe alternative choice to ITT [26,34]. Glucagon is administered intramuscularly and serum samples are taken up to 240 minutes.
5. Adults who have GHD may have normal responses to GHRH + arginine in the setting of hypothalamic GHD [50,51].
6. Adjustment of peak GH cut-off values for assay differences has been recommended by International Consensus Guidelines for the diagnosis of adult GHD [6,9,10,13]. Reference Preparation 98/574) is used in all GH assays. It should be specified if GH isoforms (e.g. 20 and 22kDa GH) or GH binding protein might interfere [9]. A GH response, to provocative stimulation test <3 ng/mL, when measured by polyclonal antibody (RIA), or less than 2.5 ng/mL, when measured by monoclonal antibody (IRMA), is suggestive of severe GHD [3,26].
7. GHD during the transition period: proposed intervals between cessation of GH treatment and re-testing of the GH axis generally range from 1 to 3 months. During this phase a cut-off level of <5 ng/L is considered as compatible with a diagnosis of GHD. We also recommend optimization of all other hormone therapies, BMI and pubertal status of patient (recognizing that the greatest amount of GH is produced during puberty) for an accurate interpretation of GH test.
8. If provocative testing demonstrates severe GH GHD, consideration of GH therapy can be raised and discussed in detail with the patient (the pros and cons).
9. GH stimulation testing is not strictly required in TM patients with cardiac failure in presence of a normal MRI cardiac T2* and/or a personal history of childhood-onset GHD.
10. In chronic liver disease, IGF-1 levels are decreased, and the circulating levels correlate to the extent of hepatocellular dysfunction.
11. Very low IGF-1 levels, especially in those patients with childhood-onset GHD, in the presence of pituitary iron deposition and/or atrophy are suggestive of GHD [5].
Each clinician must base treatment decisions for each patient on the clinician’s independent judgment, knowledge of the patient’s circumstances, and continuing developments in the field.

Basal evaluation, before GH treatment, should include clinical (height, weight, BMI, waist circumference, pubertal status) laboratory, instrumental and radiologic evaluation. Biochemical parameters include measurement of serum ferritin and fructosamine levels, oral glucose tolerance test, liver function tests, hepatitis screening and antitransglutaminase antibodies. Endocrine evaluation includes: measurement of serum IGF-1, TSH, FT4, cortisol and sex steroids. Cardiac evaluation includes Echocardiography and T2* MRI of the cardiac iron overload. Bone mineral density (BMD) and muscular strength, endurance and flexibility and BMD are important to assess. Evaluation of quality of life using adult GHD assessment questionnaire and energy status questionnaire is recommended [32,41].

Dose selection
The objective of treatment is to maximize benefit and minimize side-effects. Experience has shown that sensitivity to GH treatment varies considerably between individuals, with elderly individuals being the most sensitive. However, some degree of GH resistance has been reported in TM patients [17,19,48,50]. Dosing of GH replacement therapy in all patients should be individualized. It is recommended that therapy should start with a low dose (0.15-0.30 mg/day; 0.45-0.90 IU/day). The dosage should be increased gradually every one to two months, on the basis of clinical and biochemical responses. The target is achieving an optimal clinical response without any side effects. Clinically significant effects may not be seen before few months of treatment. Biochemically IGF-1 levels is adjusted to be in the upper half of the age-adjusted reference range [9,10,13,34]. Therefore, a high degree of methodological consistency in the assay and a specific reference ranges for IGF1 are essential for the interpretation of results. Furthermore, careful consideration of factors influencing IGF1 levels in adult TM patients is crucially important for correct interpretation of IGF1 levels.

The maintenance dose may vary considerably from person to person and seldom exceeds 1.0 mg/day (3 IU/day) [9,10,13,23,34]. Clinical experience has demonstrated that the variability in subcutaneous absorption and individual responsiveness to GH make dose determination based on body weight or body surface area less helpful than anticipated. Besides, some adult patients experience side-effects even with a low dose [9,10,13,23,32,34].

In accordance with the clinical practice of treating GHD children, we recommend that GH be administered as daily sc self-injections in the evening.

During puberty, adolescents with GHD typically receive GH in a wide range of doses (usually between 1.25 and 2.5
mg/day. Whereas in the transition period, patients should reduce their GH dose. If GH is already discontinued, patients can restart GH therapy in a dose of 0.2-0.5 mg/day [34].

**GHD and multiple hormone deficiencies**

Standard hormonal replacement therapy should be monitored closely when GH therapy is administered. Testosterone appears to stimulate IGF-1 production [39]. In contrast, oral administration of estrogen increases GH secretion and decreases serum IGF-1 concentration. Therefore, estrogen replacement blunts the IGF-1 response to GH replacement in women, whereas in men, androgen replacement increases IGF-1 responsiveness over time.

In patients with GH, central (secondary) hypothyroidism may first become evident or worsen during GH treatment. Therefore, patients treated with GH should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated [9,10,13,23,32,34,41].

**Follow-up**

It is recommended that TM patients with GHD receiving GH replacement should remain under long term surveillance by an endocrinologist to monitor their response as well as to detect possible long-term side-effects early. Patients may need to be seen initially by the endocrinologist as often as monthly. Once treatment is stabilized, two-three visits per year will suffice.

**GH therapy in adults with GHD and cancer risk:**

The growth promoting effects of GH and IGF-1 provide a plausible theoretical basis by which GH treatment could increase cancer risk. Overall, the published data so far do not fully suggest that GH therapy is associated with causing or accelerating recurrences of tumors. However, it is possible that some adverse events may become evident over the time and, therefore continued surveillance remains mandatory in patients on GH therapy [11].

**Conclusions**

GHD is now well-recognized in many adult patients with TM. This clinical syndrome can be corrected by proper GH replacement. Investigating TM patients within the appropriate clinical context is important to identify those who may be eligible for treatment. Each doctor must base treatment decisions for each patient on the clinician’s independent judgment, knowledge of the patient’s circumstances, and continuing developments in the field to provide maximal safety to the patient. Dynamic tests for investigating GHD should only be performed in patients in whom there is high clinical suspicion and therapy should be limited to those with biochemically proven GHD. The pros and cons of GH treatment must be discussed with each patient, after which GH doses should be individualized and titrated to maximum efficacy with minimal side effects. Prospective studies to monitor potential benefits versus possible side-effects will enable endocrinologist to define recommendations on dosage and the long term effects, particularly on cardiovascular and bone status of GH therapy in adult TM patients.

**REFERENCES**


**SUMMARY**

**GROWTH HORMONE DEFICIENCY IN ADULTS WITH THALASSEMIA: AN OVERVIEW AND THE I-CET RECOMMENDATIONS**


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adult GHD and/or IGF-I deficiency in TM patients varies from 8% to 44% in different Centers. Because GH treatment requires analysis of many factors, including the effect of treatment on cardiac functions, metabolic parameters and psychosocial functioning, along with safety, ethical considerations, financial cost and other burdens of therapy, stringent diagnostic criteria are needed. The Authors report the diagnostic recommendations of the International Study Group of Endocrine Complications in Thalassemia (I-CET) for adult TM patients. The pros and cons of GH treatment must be discussed with each patient, after which GH doses should be individualized and titrated to maximum efficacy with minimal side effects. Prospective studies to monitor potential benefits versus possible side-effects will enable endocrinologists to define recommendations on dosage and the long term effects, particularly on cardiovascular and bone status of GH therapy in adult TM patients.

**Keywords:** Thalassemia major, adults, growth hormone (GH), insulin like growth factor-1 (IGF-1), GH deficiency, IGF-I deficiency, diagnosis, therapy.

**РЕЗЮМЕ**

ДЕФИЦИТ ГОРМОНА РОСТА У БОЛЬНЫХ ТАЛАССЕМИЕЙ: ОБЗОР ЛИТЕРАТУРЫ И РЕКОМЕНДАЦИЙ МЕЖДУНАРОДНОЙ ИССЛЕДОВАТЕЛЬСКОЙ ГРУППЫ ПО ИЗУЧЕНИЮ ЭНДОКРИННЫХ НАРУШЕНИЙ ПРИ ТАЛАССЕМИИ (I-CET)

1Солиман А., 2Де Санктис В., 3Элседфи Х., 4Ясин М., 5Скордис Н., 6Карими М., 7Собги П., 8Раиола Г., 9Эл Холи М.

1Хамадский медицинский центр, департамент педиатрии и радиологии, Доха, Катар; 2Квисисанский госпиталь, амбулаторная клиника детей и подростков, Ферarra, Италия; 3Ан Шамский университет, педиатрический департамент, Каир, Египет; 4Госпиталь Макарис, департамент педиатрии, отделение педиатрической эндокринологии, Никозия, Кипр; 5Хамадский медицинский центр, Алинальский госпиталь, департамент гематологии, Доха, Катар; 6Ширазский университет медицинских наук, Гематологический исследовательский центр, Шираз, Иран; 7Даянандский медицинский колледж, педиатрический департамент, Пуджаб, Индия; 8Госпиталь Пулеше-Чивачио, педиатрический департамент, Катанзаро, Италия

В обзорной статье представлено современное состояние вопроса относительно дефицита гормона роста (ДГР) у взрослых пациентов с больной талассемией (БТ). По данным различных авторов, частота ДГР у взрослых БТ варьирует в пределах от 8 до 44%. При лечении гормоном роста (ГР) требуется анализ многочисленных факторов, включая действие ГР на функцию сердца, метаболические параметры, психо-социальные функции, следует учитывать безопасность лечения, этические соображения, цену и другие трудности терапии. Поэтому необходимы точные диагностические критерии. Авторы представляют диагностические рекомендации Международной исследовательской группы по изучению эндокринных нарушений при талассемии (I-CET) для взрослых пациентов с БТ. Аргументы за и против лечения ГР должны быть обсуждены с каждым пациентом, после чего доза препарата должна быть индивидуализирована и откорректирована для достижения максимальной эффективности при минимуме побочных действий. Проспективные исследования с целью мониторинга потенциальных пользы и вреда (развития побочных эффектов) лечения позволят уточнить рекомендации по дозировке и прогнозированию долгосрочных результатов лечения ГР, в частности, его влияния на состояние кардиоваскулярной системы и костей у взрослых пациентов с БТ.

**Резюме**

Со слов авторов, частота дефицита гормона роста (ДГР) у взрослых пациентов с БТ варьирует в пределах от 8 до 44%. При лечении гормоном роста (ГР) требуется анализ многочисленных факторов, включая действие ГР на функцию сердца, метаболические параметры, психо-социальные функции, следует учитывать безопасность лечения, этические соображения, цену и другие трудности терапии. Поэтому необходимы точные диагностические критерии. Авторы представляют диагностические рекомендации Международной исследовательской группы по изучению эндокринных нарушений при талассемии (I-CET) для взрослых пациентов с БТ. Аргументы за и против лечения ГР должны быть обсуждены с каждым пациентом, после чего доза препарата должна быть индивидуализирована и откорректирована для достижения максимальной эффективности при минимуме побочных действий. Проспективные исследования с целью мониторинга потенциальных пользы и вреда (развития побочных эффектов) лечения позволят уточнить рекомендации по дозировке и прогнозированию долгосрочных результатов лечения ГР, в частности, его влияния на состояние кардиоваскулярной системы и костей у взрослых пациентов с БТ.
HIGH PREVALENCE OF CENTRAL HYPOTHYROIDISM IN ADULT PATIENTS WITH B-TALASSEMAIA MAJOR

1De Sanctis V., 2 Soliman A., 3Candini G., 4Campisi S., 5Anastasi S., 6Yassin M.

Over the course of the past 2-3 decades, hypertransfusion regimens and iron chelation therapy have significantly increased the life expectancy and improved quality of life of patients with thalassaemia major (TM) (22). On the other hand, frequent blood transfusions leading to iron overload and the chronic nature of the disease have contributed to a whole new spectrum of complications in adolescents and young adults suffering from TM [24].

In 1995, our Italian Working Group on Endocrine Complications in TM reported delayed puberty in 47% of females and 51% of males, arrested puberty in 12.6% of females and 15.7% of males, secondary amenorrhea in 25% of adult females, diabetes mellitus in (16.88%), impaired glucose tolerance in (13%), hypothyroidism in (15.9%) and hypoparathyroidism in (6.3%) in a large cohort of thalassemic patients [21]. These complication are mainly attributed to iron overload and chronic liver diseases [4,6,9,21,26].

The commonest form of thyroid dysfunction seen in subjects with TM is primary hypothyroidism due to abnormalities of the thyroid gland which leads to insufficient production of the thyroid hormones [21,26]. Thyroid failure is expected to be more prevalent in older patients (as seen in other endocrine deficits). However, in developing countries it may occur at younger ages as reported by Rindang et al. [25] and Malik et al. [19].

Central hypothyroidism (CH) seems to be an uncommon clinical entity [7,10,16] although the anterior pituitary gland is particularly sensitive to free radical oxidative stresses and MRI shows that even a modest amount of iron deposition within the anterior pituitary can interfere with its function [4]. The diagnosis of CH in TM is not easy because most of the symptoms are nonspecific and frequently are attributed to anaemia or other associated complications [2,12,18].

Therefore, we explored the prevalence of CH in a large group of TM subjects of different ages, followed in our Centres or Outpatient Clinics.

Material and methods. 339 TM patients who were regularly blood transfused to maintain a mean haemoglobin level of 10 g/dl were screened between June 2011 and September 2012. Chelation therapy with desferrioxamine (DFX) or deferiprone was given to all TM patients, from
The minimal detectable levels of FT4 and TSH were 0.2 ng/dL and 0.1 mIU/L, respectively. The inter-assay and intra-assay coefficients of variations of FT4 varied from 5.8% to 6.26%, and from 2.6% to 2.9%, respectively, and those of TSH were from 5.1% to 5.7%, and from 2.2% to 2.9%, respectively.

Characteristics of the studied patients are reported as mean ± standard deviation (SD), median, number and range. Statistical significance of the differences between variables was assessed using the unpaired two-tailed Student’s t test or Wilcoxon test using a software package program. A p value < 0.05 was considered as significant. The analysis of frequency distributions for age and sex were analyzed using chi-square test while the multiple regression analysis was conducted using the multiple linear fitting with least squares method.

**Results and their discussion.** Of the 339 cases of TM, 164 (48.3%) were males and 180 (53%) females, with an age range of 1-48 years (85.2% patients were older than 21 years).

Twenty five were prepubertal (<11 years;13 males), 9 were in peri-pubertal age (between 11 and 16 years; 3 males) and 305 were pubertal (>16 years ; 164 males).

Central hypothyroidism was diagnosed in 26 (7.6%) of patients. Their mean age was 29.9±8.4 years (median 29.1 years). The mean age of TM patients with CH was 30.8±5.8 in males and 28.8±10.9 years (p=NS). The prevalence of CH was 0 % in young patients below 11 years, 22% in peri-pubertal patients and 7.8% in those above 16 years. Twenty two patients (78.5%) were HCV antibody positive and 11 patients (42.3%) HCV –RNA positive

Among the 26 TM patients with CH, 14 (53.8%) were males and 12 (46.1%) were females, with no significant gender difference in the frequency of CH (p=NS). However, the 3 youngest TM patients with CH were females (aged 14, 15 and 18 years, respectively).

Mean FT4 level in TM patients with CH was 0.74±0.08 ng/dL significantly lower when compared to euthyroid TM patients 1.16±0.17 ng/dL and normal controls 1.19±0.17 ng/dL (p<0.01 and p<0.01, respectively).

No specific clinical signs or symptoms of hypothyroidism were reported by the patients.

Serum ferritin levels did not differ significantly between TM patients with CH (1790.7±1872.8 ng/ml) and the euthyroid TM patients (2142.1±2075.2 ng/ml) (p=0.08).
Multiple correlation analysis between FT4, TSH, serum ferritin, serum alanine transferase (ALT) and age, was not significant (F=0.9; p=NS).

Twelve TM patients (46%) with CH had an associated hypogonadotropic hypogonadism (7 males), four (15.3%) had short stature (height < 3rd centile; 1 male), two (12.5%) had insulin dependent diabetes mellitus (1 male and 1 female) and one patient (3.8%) had hypoparathyroidism (1 female).

Nine TM patients (34.6%) with CH were on treatment with L-thyroxine (mean daily dose 40 mcg; range from 12.5 to 75 mcg/ daily).

Central hypothyroidism (CH) has been reported as an uncommon clinical entity in TM patients although the anterior pituitary gland is particularly sensitive to free radicals of oxidative stresses [4,7,13,31]. The presence of CH in TM patients is reported infrequently in the literature, with a prevalence between 2.3% to 8% [10,16].

Clinically, CH in TM is not easy to diagnose because most of the symptoms (fatigue, apathy, weight gain, dry skin, cold intolerance) are non-specific and frequently attributed to anaemia or other associated complications [2,12,18]. The diagnosis of CH is usually made on a biochemical basis (low FT4 associated to inappropriately low or normal TSH) [1,2,12,18].

We performed a cross-sectional analysis using a large database from the clinical records of our TM patients aiming to look at the prevalence of CH in prepubertal (<11 years: 25 patients; 13 males) peri-pubertal (between 11 and 16 years: 9 patients; 3 males), and pubertal TM subjects (>16 years: 305 patients; 164 males).

CH was present in 26 (7.6%) of TM patients; 14 (53.8%) were males and 12 (46.1%) were females. Their mean age was 29.9 years. The prevalence of CH was 6% in patients aged below 21 years and 7.9% in those above 21 years.

This prevalence of CH may be even higher if some of our patients have growth hormone deficiency (GHD). GHD can mask CH in a significant proportion of hypopituitary patients [1]. In a multicenter study we found a severe GHD in 44% of patients with TM [8].

In the general population, the CH prevalence is estimated to be around 1 in 120,000 individuals, and roughly equal in both genders and can arise from a number of pathogenic mechanisms involving the hypothalamus or pituitary [12,18]. Etiology includes all pathologic processes that affect the hypothalamus or pituitary including tumours, trauma, radiation, vascular diseases, infection, lymphocytic hypophysitis, and idiopathic infiltrative diseases; such as hemochromatosis [12,18,20]. Imaging of the brain and the pituitary can help to diagnose the cause.

The precise underlying mechanism of CH in TM patients at present remains not well-known. The mean serum ferritin level was not significantly different between our patients with and without CH, however we cannot exclude iron overload of the hypothalamic-pituitary (central) as an important etiology of CH in our patients because certain tissues, including the pituitary gland, are particularly susceptible to excess iron incorporation when non-transferrin-bound iron (NTBI) is present. This effect is promoted by L-type Ca2+ channels (LTCCs), the front-runners for mediating NTBI transport in iron overload conditions, which are moderately expressed in thyrotrhops [3,14,28]. In addition ferritin is not a sensitive indicator of iron overload in all the tissues.

Tatò et al. [29] studied 14 euthyroid iron-overloaded TM patients (8 females and 6 males, age 15-24 years) with hypogonadotropic hypogonadism. Thyroid-stimulating hormone (TSH), prolactin and free alpha-subunit (FAS) were measured during thyrotropin-releasing hormone (TRH) stimulation test. They observed poor response of FAS to TRH test which they attributed to an involvement of thyrotrhoph cells.

Chronic liver inflammation is a frequent complication in patients with TM, since over 40% of them have positive anti-hepatitis C virus (HCV) antibodies and more than 50% have chronic (persistent or active) hepatitis [5,27]. Hepatitis C infection may be an additional factor in causing hypothalamic-pituitary thyroid axis dysfunction. A central (hypothalamic-pituitary) dysfunction with growth hormone deficiency, secondary to hepatitis C infection, has been reported by Plöckinger et al. [23] in 81% patients with hepatitis C infection before therapy with pegylated interferon-alfa plus either ribavirin or levovirin [4,7,20].

Other alternative explanations for the central etiology of hypothyroidism in addition to different individual sensitivity to iron damage [9], includes increased collagen deposition secondary to increased activity of the iron-dependent protocollagen proline hydroxylase enzyme [15,30] and the hypoxic effect of chronic anemia [6]. The latter cause was excluded in our TM patients who were regularly transfused with packed red blood cells.

In summary, the combination of transfusion and chelation therapy has dramatically extended the life expectancy of these patients, thus transforming TM from a rapidly fatal childhood disease to a chronic life-time illness compatible with longevity. On the other hand, frequent blood transfusions and poor compliance to chelation therapy leads to chronic iron overload that contributed to a whole new spectrum of complications in adolescents and young adults. Central hypothyroidism is not uncommon in young adult TM patients. The diagnosis of CH in TM patients is not clinically noticeable and a normal basal TSH level does not exclude the diagnosis of CH. Because this pattern is
also seen transiently during recovery from severe illness, it the diagnosis should be confirmed on a repeat test when the patient is well.

Clinicians should be alert for the diagnosis of CH through accurate interpretation of thyroid function tests. Brain imaging studies of the hypothalamic-pituitary region could be of help in the investigations of these patients by detecting pituitary iron infiltration (hypointense pattern or heterogeneous intensity) with decreased pituitary volume (Figs. 1, 2).

Fig. 1. T1 appearance of he pituitary gland in a thalassemic patient. Diminished pituitary volume with marked hypointense pattern (Soliman A., personal observation)

Fig. 2. T1 appearance of the pituitary gland in a thalassemic patient. Diminished volume with heterogeneous intensity (Soliman A., personal observation)

Our recommendation is that if the level of FT4 is consistently low, then these patients should start L-thyroxine treatment. Adrenal function shall be investigated before initiating treatment and adrenal insufficiency shall be treated with glucocorticoid replacement before thyroxine therapy to avoid precipitating an adrenal crisis.

Data from the literature have shown that GH deficiency may mask subclinical forms of CH that become biochemically evident only after institution of GH replacement therapy [17]. Replacement therapy for other pituitary hormone deficiencies may require an adjustment of T4 replacement dose. More specifically, females treated with estrogen and males treated with GH may need a higher T4 dose in order to maintain an euthyroid range [2]. All these factors must be taken in consideration in the management of TM patients with CH.

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**SUMMARY**

**HIGH PREVALENCE OF CENTRAL HYPOTHYROIDISM IN ADULT PATIENTS WITH B-TALASSEMA MAJOR**

1. De Sanctis V., 2 Soliman A., 3Candini G., 4Campisi S., 5Anastasi S., 6Yassin M.

2. Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy; 3Department of Pediatrics, Hamad Medical Center (HMC), Doha, Qatar; 4Department of Medical Physics, St.Anna Hospital, Ferrara, Italy; 5Unit for the Diagnosis and Treatment of Thalassaemia, Umberto I Hospital, Siracusa, Italy; 6Department of Thalassaemia, Garibaldi Hospital, Catania, Italy; 7Department of Hematology, Hamad Medical Center (HMC), Doha, Qatar

The commonest form of thyroid dysfunction seen in subjects with TM is primary hypothyroidism due to abnormalities of the thyroid gland. Central hypothyroidism (CH) has been reported as an uncommon clinical entity in TM patients although the anterior pituitary gland is particularly sensitive to free radical oxidative stresses. Diagnosis is usually made on a biochemical basis showing low circulating concentrations of thyroid hormone associated with an inappropriately low TSH levels. The diagnosis is not clinically obvious and a basal normal TSH level does not exclude the diagnosis of CH. Therefore, it is important that clinicians accurately interpret thyroid function tests. In TM patients, CH prevalence differs at different ages is unknown and it is not easy to diagnose because most of the symptoms of symptoms of CH are non specific and are frequently attributed to anaemia or other associated complications. We performed a cross-sectional analysis on a large database using the clinical records of our TM patients to explore the prevalence of CH in prepubertal (<11 years: 25 patients; 13 males) peripubertal (between 11 and 16 years: 9 patients; 3 males), and pubertal TM subjects (>16 years: 305 patients; 164 males). Central hypothyroidism was present in 26 (7.6%) TM patients. Their mean age was 29.9±8.4 years, 14 (53.8%) were males and 12 (46.1%) were females. The prevalence of CH was 6% in patients with a chronological age below 21 years and 7.9% in those above 21 years. Clinicians should be alert for the diagnosis of CH through accurate interpretation of thyroid function tests. We recommend L-thyroxine therapy if the level of FT4 is consistently low provided that the patient has normal cortisol levels.

**Keywords:** β-thalassemia major, central hypothyroidism, prevalence.
Высокая частота центрального гипотиреоидизма у взрослых пациентов с большой б-тальассемией

1 Де Сантиес В.1, Солиман А.1, Кандинни Г.1, Камписи С., 2 Анастаси С., 3 Яссин М.

Кишинийский госпиталь, амбулаторная клиника детей и подростков, Феррара, Италия; 2 Хамадский медицинский центр, департамент патологии и радиологии, Долах, Катар; 3 Госпиталь св. Анны, департамент медицинской физики, Феррара, Италия; 4 Госпиталь Умберто I, Центр диагностики и лечения талиассемии, Сиракюза, Италия; 5 Госпиталь Гарибальди, департамент талиассемии, Катания, Италия; 6 Хамадский медицинский центр, гематологический департамент, Долах, Катар

Найболее частая форма тиреоидной дисфункции у лиц с большой талиассемией (БТ) — первый гипотиреоидизм развивается вследствие недостатка в щитовидной железе. Центральный гипотиреоидизм (ЦГ) встречается более редко, хотя передний гипофиз особенно чувствителен к свободнорадикальному оксидативному стрессу. Диагноз ЦГ обычно ставится на основании результатов биохимических исследований (в крови отмечается низкое содержание тиреоидного гормона при нормальном уровне кортизола. У больных БТ частота ЦГ различна в различных возрастных группах. Постановка диагноза затруднена, так как симптомы ЦГ в большинстве случаев негативны и часто обусловлены анемией и другими ассоциированными осложнениями. Проведен кросс-секционный анализ большой базы данных (клинические записи о наших больных БТ) с целью определения частоты ЦГ в пребуферент (<11 лет, 25 пациентов, 13 мальчиков), перебуферент (с 11 до 16 лет: 9 пациентов, 3 юношей) и пребуферент (>16 лет, 305 пациентов, 164 мужчин) возрастных периодах. ЦГ был установлен у 26 (7,6%) больных БТ из средний возраст составил 29,9±8,4 лет, 14 (53,8%) были мужского пола, 12 (46,2%) — женского. Частота ЦГ равнялась 6% у больных до 21 года и 7,9% — у больных старше 21 года. Этилисти должны быть наготове в отношении ЦГ и тщательно интерпретировать данные функциональных исследований щитовидной железы. Если уровень свободного тироксина 4 постоянно низок, рекомендуем лечение L-тироксином при условии нормального уровня кортизола.
Thalassemia Expertise Centres (TECs), for the management of thalassemia started operating in developed countries with a high prevalence of thalassemia trait in the 70’s, soon after the implementation of frequent transfusions treatment. Previously the medical and nursing needs of management were manageable, because of lack of any effective therapy and the short survival of patients. Frequent transfusions improved survival, increased considerably the cohort of patients with thalassemia and aggravated the medical and nursing burden of management. To meet the unbearable burden of management, thalassemia expertise centers were established, initially in Children’s Hospitals or in Pediatric Departments of General hospitals in developed countries. Latter, when the cohort of adult patients increased, Adult TEC were organized jointly to Departments of Hematology, Internal Medicine or Transfusion Medicine (Blood Banks).

Evolution and Structure of Thalassemia Expertise Centres

Basic prerequisites for the organization of a TEC are: 1) the precise epidemiological studies to define the magnitude and the burden of thalassemia on health services and 2) the evaluation of the scientific and social activities of the TEC which the existing health system can support and handle.

The implementation of frequent transfusions in the treatment of thalassemia was most effective in ameliorating the clinical features of the disease and in improving survival and quality of life [10]. In parallel medical and nursing burden increased considerably because of frequent admissions and time-consuming transfusion procedure. An example of the extreme differentiation of medical and nursing burden related to implementation of frequent transfusion treatment is illustrated in Fig. 1. It represents the changing pattern of the ratio of annual admissions of patients to the total admissions in the University Department of Pediatrics in the period 1964-1980. In 1964, (the year prior transfusion) there were 115 admissions of thalassemic patients corresponding to 2% of total. Since then a rapid and steady increase of patients’ admissions was observed; in 1980 the total annual admissions of patients rose to 4,760, representing 32% [3].

Fig. 1. Annual admission of patients with thalassemia, in relation to total admissions in the University Department of Pediatrics during the period 1964-1980.
To confront the progressive increase of medical and nursing demands, an independent unit, solely devoted to the treatment of thalassemia, operating on a daily outpatient basis was organized in 1975. For this period, the organization, function, and multidiscipline nature with interconnection to other specialties units of the University Department of Pediatrics and the Children’s hospital, could be considered as prototype of TEC, along with few others operating, in the same period in Italy and later in Cyprus. The Unit fulfilled most of the criteria recently proposed by EUCERD for the designation of Centres of Expertise for rare diseases [1].

The flow-chart of the structure of the Thalassemia Unit of the University Department of Pediatrics in Aghia Sophia Children Hospital (Fig. 2) consists of: 1) the Out-patient Clinic, where patients are followed regularly for all health problems, including psychological and social. The clinic is also involved in genetic counseling and in programming and monitoring treatment. 2) The Day-Treatment Clinic involved in the clinical and laboratory evaluation of patients, the administration and monitoring of transfusions and chelation and the implementation of appropriate treatment for the complications related to the disease or of the treatment. 3) The special Laboratory and Research Unit, which runs specific and advanced procedures used in diagnosis, follow and monitoring of treatment. A major activity of the Unit focuses on basic and clinical research on thalassemia, hemoglobinopathies and other common and rare anemias. The TEC collaborates closely with the hospital Blood Bank, the hospital General laboratory and the General and Sub-specialties Units of the University Department of Pediatrics.

Another main objective of the TEC joined to research is education and training of heath professionals on thalassemia.

The original structure and activities of the Unit were gradually modified supplemented and upgraded following the international evolution and advances in the management and prevention of thalassemia. More precisely, in the 80’s when a good proportion of patients reached adulthood, the permanent medical staff was enriched with adult specialists jointly with collaboration and adult specialties departments of endocrinology, cardiology and others. Thus the Unit was modified to a combined pediatric and Adult TEC capable to cover children, adolescents and adults.

Other additional activities were and are: 1) the active participation, in the implementation of national prevention program which started in 1980 covering: genetic counseling, screening for detection of couple at risk, prenatal and preimplantation diagnosis using advanced molecular techniques. 2) Implementation of cure treatment by bone marrow transplantation which started in 1995 in collaboration with the Bone Marrow Transplantation Unit of our Hospital. 3) Collaboration with the High Risk Pregnancy Unit of the University Maternity Hospital. 4) Collaboration with MRI centre specialized in evaluation of iron content of liver, heart and endocrine glands.
The structure and activities of Thalassemia Unit cover the proposed criteria of European Commission of Health for reference centres for rare diseases [1]. In Greece, parallel to the combined TEC, a number of purely Pediatric and Adult Units operate, covering basically the treatment of patients following national and international recommendations, while the prevention program is coordinated by the National Prevention Center. In other developed countries with a high prevalence of thalassemia, TEC have similar structure.

In developed countries where thalassemia is considered a very rare anemia for the native population, thalassemia patients are referred for diagnosis and management either to Expertise Centres for rare anemias or to pediatric or adult hematology departments or units. Special units for the management of hemoglobinopathies has been established in developed countries hosting large immigrant communities with high prevalence of hemoglobinopathies.

In European Union, a pilot program of Rare Disease Reference network (RD ERNS) for congenital anemias (ENERCA) is operating since 2002 [1]. Thalassemia and hemoglobinopathies are covered by the network of rare anemias as the prevalence of hemoglobinopathies I, for the whole European Union population, considered low. At this time the European Union of Experts for Rare diseases (EUCERD) is working to define criteria for the designation of Centres of Expertise for rare diseases, that have to operate on a multidiscipline basis. The structure of the TEC described, fulfilled, from its initial form, the prerequisite of the multidiscipline function [1].

**Expectations of patients and their families**

Older patients with longstanding follow and treatment in Athens University TEC, are in general satisfied from the continued improvement of the efficacy of treatment that results in significant amelioration of clinical symptoms, and improvement of survival, quality of life and social adaptation [4].

They do expect that in the near future, conventional treatment will be more efficient and more easily applicable, (especially chelation) and the risks for severe complications from the endocrine glands and the heart will be further minimized. They also expect that complete cure with bone marrow transplantation will be extended to an increasing proportion of patients, using HLA compatible non relative donors, or a compatible sibling in case of artificial fertilization combined with appropriate preimplantation genetic diagnosis.

Last but not least, they wish the studies on gene replacement therapy to move more rapidly and successful clinical trials start soon.

**Perspectives for Thalassemia Expertise Centres**

The evaluation of the efficacy of longitudinal implementation of national programs of prevention and treatment in developed countries with high prevalence of thalassemia trait, demonstrated the valuable contribution of TECs in the management of thalassemia, the change in epidemiology and the age distribution of the cohort of patients.

Published data from Italy, Greece and Cyprus showed impressive and similar results on improvement of survival and quality of life [2,6,8].

Most interesting observations of the longitudinal evaluation of prevention and treatment programs is the change of the prevalence of patients with thalassemia major as well as the age distribution of thalassemia population.

![Fig. 3. Changes in annual input, total number and age distribution in patients with thalassemia treated in the Thalassemia Unit of the University Department of Pediatrics at “Aghia Sophia” Childrens Hospital during the period 1965-2010 n=total number of patients (n): number of new patients during intervals](image-url)
Publication on a recent registry of hemoglobinopathies in Greece [9] and another on the efficacy of the prevention program [7] demonstrated:
1. A very low prevalence of thalassemia (3.2 patients per 10,000 population) compared to the expected (7.7 patients per 10,000), if only conventional treatment was implemented.
2. A dramatic change of the age distribution of patients with thalassemia to older ages. In 2010 of the whole cohort of 3,241 patients only 3.8% were below the age of 10 years while the mean age was 36 years. Characteristic are the longitudinal changes of age distribution of patients followed in our unit from 1965-2010 (Fig. 3). The figure illustrates how a short survival fatal disease of childhood turned to a chronic disease of adolescence and adulthood, after conventional treatment and how a predominant monogenic disease of childhood after successful implementation of prevention turned to a very rare disease of childhood [5].

These data combined with amelioration of the impact on health services indicate that countries with successful implementation thalassemia programs through TECs have to reconsider the activities of these centres.

At least for Greece and following the continuous trend of reduction of the number of patients, a subsequent reduction of the number of TEC seems logical. Based on the changes of the age distribution, a modification of the activities of Pediatric TECs which follow children and adolescents is indicated. For these ages the present prevalence of thalassemia major is extremely low and comparable to other chronic disease of adolescence and adulthood, after conventional treatment and how a predominant monogenic disease of childhood after successful implementation of prevention turned to a very rare disease of childhood [5]. It is hoped that the experience gained from the longitudinal implementation of prevention and management programs for thalassemia in developed countries combined with continued advances in biotechnology, will facilitate developed and under development countries to organize the most efficient Thalassemia and hemoglobinopathies Expertise Centres to control these diseases.

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SUMMARY

ATHENS UNIVERSITY THALASSEMIA EXPERTISE UNIT: EVOLUTION, STRUCTURE, PERSPECTIVES AND PATIENTS’ EXPECTATIONS

1Kattamis C., 2Sofocleous Chr., 1Ladis V., 1Kattamis A.

1Thalassemia Unit, First Department of Pediatrics, Athens University, “Aghia Sofia” Childrens’ Hospital, Athens; 2Laboratory of Medical Genetics, Athens University, “Aghia Sofia” Childrens’ Hospital, Athens

Thalassemia Expertise Centres (TECs), were first organized in developed countries with high thalassemia prevalence in
the 70’s to meet the increasing demands of the implementation of frequent transfusions in the treatment of thalassemia, and to consequently adopt, the rapid advances in the management of the disease.

Recent evaluation of longitudinal implementation of the national programs for prevention and treatment, demonstrated their efficacy for patients and public health. The beneficial effects focused on clinical symptoms amelioration, reduction of incidence and severity of complications and considerable improvement in survival, quality of life and social adaptation. National programs led to the modification of the most common genetic, fatal pediatric disease with short survival, to a chronic long-lived disease for adults and a very rare disease for children. In the few developed countries new perspectives for pediatric TECs need to be considered.

Keywords: thalassemia, Expertise centres, evolution, structure and perspectives.

РЕЗЮМЕ

ЦЕНТР ЭКСПЕРТИЗЫ ТАЛАССЕМИИ АФИНСКОГО УНИВЕРСИТЕТА: ЭВОЛЮЦИЯ, СТРУКТУРА, ПЕРСПЕКТИВЫ И ОЖИДАНИЯ ПАЦИЕНТОВ

1Каттамис Ц., 2Софоклеис Хр., 1Ладис В.,
1Каттамис А.

1Афинский университет, Первый педиатрический департамент, Центр талассемии, Лаборатория медицинской генетики; Детский госпиталь «Айя-София», Афины; 2Афинский университет, Лаборатория медицинской генетики; Детский госпиталь «Айя-София», Афины, Греция

Центры экспертизы талассемии (ЦЭТ) впервые были организованы в развитых странах с высокой частотой талассемии в 70-е годы XX века. С целью ответа на возросшие потребности внедрения частых переливаний крови в лечение талассемии и, следовательно, адаптации новейших успехов менеджмента этого заболевания. Недавняя оценка лонгитудинальной имплементации национальных программ для превенции и лечения, показало их эффективность для пациентов и общественного здравоохранения. Благотворные эффекты заключались в уменьшении интенсивности клинических проявлений, частоты и тяжести осложнений, значительное улучшение выживаемости, качества жизни и социальной адаптации. Национальные программы привели к модификации наиболее частых генетических фатальных педиатрических заболеваний с короткой продолжительностью жизни в хронические долготекущие заболевания взрослых. Следует обсудить новые перспективы ЦЭТ в некоторых развитых странах.

Keywords: thalassemia, Expertise centres, evolution, structure and perspectives.
HEALTH ISSUES IN ADOLESCENTS’ INTERNET USE - BENEFITS AND RISKS

Hardoff D.

Israel Center for Medical Simulation, Chaim Sheba Medical Center, Tel Hashomer And Adolescent Medicine Services of the Clalit Health Services, Israel

The media represent one of the most powerful influences on child and adolescent development and health [38]. The Internet has turned during the past decade into a major information resource in various domains of life and a communication venue among adolescents who seek health information via the net. Both “old” media (television, movies, and magazines) and “new” media (the Internet and social networking sites, video/computer games, cell phones) can have an impact on virtually every health concern that practitioners and parents have about young people [37]. Adolescents are avid Internet users; data have suggested that more than 90% of teens have access to the Internet and most teens report daily use of the Internet [27]. Adolescents far outnumber adults in their use of e-communication technologies, such as instant messaging and social network sites [42]. The increasing availability of computers in homes, as well as wireless Internet access, means that adolescents today can go online anywhere, at any time [36]. It has been estimated that 55% of Internet-using adolescents use online social networking Web sites [24] and 28% get health information via online sources [21]. Digital media have become an important source of information, and sometimes misinformation, about health problems [14]. The media are not the leading cause of any major health problem, but they do contribute significantly to a variety of adolescent health problems: aggressive behavior, sexual activity, drug use, obesity, sleep disorders, eating disorders, depression, suicide and self harm [8, 12, 30, 36]. Unmonitored Internet use may place adolescents at a significant risk, such as cyberbullying, unwanted exposure to pornography, and potential revealing personal information to sexual predators [32].

This paper focuses on 3 major health issues in adolescents’ Internet use: Body image and eating behaviors; sexuality and reproductive health behaviors; and self harm and suicidal behavior. Finally, this paper demonstrates Internet venues where reliable health information is provided to young people by health professionals highlighting also some difficulties in the provision of such information.

Body image and eating disorders
The media are saturated with images promoting thinness, and links between disordered eating behaviors and exposure to thin-ideal images have been identified in both cross-sectional and longitudinal research [25,41]. Indeed, studies have concluded that thin-ideal internalization can trigger eating disorder symptoms [40], thus highlighting the vulnerability individuals high in thin-ideal internalization might have to media exposure [2]. Although there are insufficient data to state that the media cause eating disorders, media exposure can certainly be considered as a significant risk factor [16,20,25], and may even contribute to the development of eating disorders [36]. Google search of pro-eating disorder Web sites revealed about 7,280,000 results within 0.30 seconds. On the Internet there are now over 100 pro-eating disorders websites that not only encourage disordered eating but offer specific advice on purging, restricting caloric intake, and exercising excessively (e.g. pro-Ana and pro-Mia) [9]. These websites are popular among youth who wish to be thinner, because they offer spaces, where one can find support as well as express one’s feelings and thoughts around the disturbing eating lifestyle. Participants describe blogging as a cathartic experience and perceive the social support they receive from other members of the pro-Ana community as a benefit. The main motive for joining the online community is to be provided with both advice regarding weight loss and support and many pro-anorexic websites members equate thinness with happiness and are satisfied with their membership [33]. Pro-Ana and pro-Mia are social and harmful movement on the Web. They may have undesired and negative effects in adolescents because they contribute to the encouragement of disruptive eating behaviors or to the maintenance and aggravation of already existing eating disordered behavior. They also present graphic materials and photographs to encourage, support, and motivate site users to continue their efforts with anorexia and bulimia [9,13,46].

Sexuality and reproductive health
The Internet has become a widely used resource for sexual health information, especially among adolescents. The appeal lies in the ease and anonymity with which online seekers can obtain advice and reassurance, particularly regarding sensitive sexuality topics [22,23]. Media play an important role in providing sexual information to adolescents [8,12] and in shaping their beliefs about how males and females behave in romantic relationships [11]. Indeed, the increased use of the Internet by teens has dramatically increased exposure to x-rated materials, with more than 50% of teens indicating incidental exposure to sexual materials [44].

Longitudinal correlation studies that allow cause-and-effect conclusions to be drawn show an impact of sexual content in the media on adolescents’ sexual behavior [36].

A Google search for “teen-pornography” revealed about 38,200,000 results within 0.28 seconds. Nationwide US studies found that by age 18,93% of males and 62 % of
females reported seeing pornography [34], and that nearly half of the Internet users had been exposed to on-line pornography in the previous year [43]. A longitudinal study of more than 1500 10 to 15 year olds found a nearly six fold increase in the odds of self-reported sexually aggressive behavior with exposure to violent x-rated material over time [31].

Although all of this sounds alarming and concerning, both “old” and “new” media can be a powerful source of positive sexual information as well. New technology is also exploding with possibilities, such as text-messaging safe sex information and information of testing for sexually transmitted infections as well as using computer video games to increase knowledge and attitudes favoring avoiding teen pregnancy. Online media education about social networking sites has been shown to reduce displays of risky sexual behaviors [36].

**Suicide and self-harm**

One of the major concerns in the current debates around suicide as applied to the media in general and the Internet in particular, is related to the role that the computer-generated systems, services and devices play in suicide stimulation. The potential influence of the Internet on its suicide-sensitive users was especially relevant as regards the influence exerted upon young people. Studies have linked media coverage and portrayals of suicide with an increase in actual suicides, a type of “suicide contagion” that affects teens far more than adults [36]. Cybersuicide is a term used in reference to suicide on the Internet, and it is associated with websites that lure vulnerable members of society and empower them with various methods and approaches to deliberate self-harm [7]. The Internet as a means of communication may encourage suicidal behavior by depicting ways by which suicide may be committed. Moreover, some internet websites may discourage people from seeking help, condone suicide, and forbid entry to anyone offering to discourage users from committing suicide. However, the internet may be a resource to help a potentially suicidal person get help, and can be used to identify those at risk for suicide, communicate with them, and potentially prevent suicide. If used appropriately, the internet is a powerful communication tool that can be used to benefit suicidal patients [1]. Interviews with suicide and self-harm websites users revealed that participants perceived these sites as sources of empathy and understanding, and as a way of coping with social and psychological distress, thus giving users access to important, socially valued identities, such as being understood, belonging to a community and coping with their problems [3].

The behaviors of non-suicidal self-injury (NSSI) and deliberate self-harm (DSH) are prevalent among adolescents, and an increase of NSSI and DSH rates in recent years has been postulated [28]. Many youth who self-injure go online to connect with others who self-injure and view others’ NSSI experiences and share their own through text and videos platforms. These exposures can introduce young people to risks, such as NSSI reinforcement, through the sharing of stories and strategies, as well as risks for triggering of NSSI urges and hiding them from parents and friends. Some pro self harm sites also offer information that promotes eating disorders. Sites with pro self injury and pro self harm agendas target vulnerable people, but their reach extends far beyond the self injurers themselves. When a person suffers irreparable physical or mental damage as a result of following the advice on these sites, the harm extends outward in a concentric fashion affecting parents, siblings, extended family, friends, and even strangers. Therefore, intervention in this area should encourage substitution of healthier online activities for the activities that may currently foster harm [26].

Major publicity now surrounds suicides precipitated by Internet bullying and harassment [4,6,15,45]. Cyberbullying has been shown to possess different ramifications from traditional school-yard bullying [39]. This modern mode of bullying performed using electronic forms of contact (e.g., SMS, MMS, Facebook, YouTube), has been considered as being worse than traditional bullying in its consequences for the victims. This difference was mainly attributed to the increased potential for a large audience, the anonymity of the bullying perpetrators, the lower levels of direct feedback, and the lower levels of supervision [35].

**Internet venues for reliable health information provided to young people**

Despite the evidence of potential harm, there is also evidence that media can be beneficial for youth [19]. New media technologies give youth the opportunity to create their own expressions of individuality, whether through social networks like Facebook or file-sharing sites like YouTube [10]. New media also allow adolescents to experience community communication in a time of life when they often feel unmoored, by increasing empathy and acceptance of diversity through modeling of pro-social behaviors. For example the site “It Gets Better Project”, which was created after a series of suicides by youth who had been bullied over their sexuality, gives lesbian, gay, bisexual, and transgender (LGBT) youth the space to tell their stories and to hear the encouragement of LGBT adults who have successfully navigated the turbulent teen years [36]. The site “Recover Your Life” helps people who suffer from self harm, as well as people with other issues such as eating disorders, mental health problems, and abuse. However, the benefits of socializing on-line are not equal for every child or adolescent, and the positive Internet effect holds only when adolescents also talk directly with their friends and family [5].

In order to address the vast amount of uncontrolled and sometimes dangerous health information messages on the Internet, specific health websites have been developed,
where reliable health professionals respond on line to health related questions raised anonymously by adolescents [18,29]. The advantage of these websites is that the on-line communication is between the young person and the health professional, and is free of any non-professional intervention. Other health websites that function as “forums” allow non-professionals to respond to the discussed issues, and thus enabling larger online audiences the chance to receive reliable health information.

An Israeli survey of a representative sample of contacts to a teen-health-forum (“The body during adolescence”) run by 6 adolescent medicine pediatricians was performed in 2009. Among 412 adolescents’ contacts (51% females), 44% of the questions were related to sexuality issues and 17% were related to self image and body composition. [17]. This Internet health forum enables adolescents and parents to ask questions and raise doubts and anxieties regarding various health issues without the fear of being exposed and of expressing their concerns face-to-face with a healthcare provider. Sensitive issues regarding sexuality and self-image that frequently are not raised during clinical encounters are expressed and receive professional responses in the forum. Notwithstanding the significance of a rapid professional contribution, physicians responding to contacts in Internet venues need to recognize the barriers related to their communication with persons whom they have not met and for whom follow up is impossible. When a youngster expresses acute distress, the responding health professional may feel helpless in suggesting medical or psychosocial advice, not knowing the patient and without the possibility to directly examine the patient. Delivering bad news in an Internet health forum is also problematic and may be detrimental to the young person on line. Telemedicine requires adherence to ethical issues including refraining from criticism of other physicians, who may have been involved in the health care of the individual on line. These barriers may be the reason for the high referral rate to clinical medical consultation in the teen-health-forum survey that reached 40% [17]. Health professionals who see adolescents at their clinics need to understand that spending some time with their adolescent patients discussing media use, may be as important as discussing school difficulty, aggressiveness, disordered eating, or poor sleep patterns [37].

In summary, the Internet of the 21st century is affordable, convenient and anonymous and may provide unique potential health education. However, health professionals need to recognize the hazards of adolescents Internet use, and to address potential Internet abuse when encountering adolescents in clinical settings.

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SUMMARY

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Hardoff D.

Israel Center for Medical Simulation, Chaim Sheba Medical Center, Tel Hashomer And Adolescent Medicine Services of the Clalit Health Services, Israel

The Internet has turned during the past decade into a major information resource in various domains of life
and a communication venue among adolescents who seek health information via the net. The increasing availability of computers in homes, as well as wireless Internet access, means that adolescents today can go online anywhere, at any time. The media are not the leading cause of any major health problem, but they do contribute significantly to a variety of adolescent health problems, including aggressive behavior, sexual activity, drug use, obesity, sleep disorders, eating disorders, depression, suicide and self harm. This paper focuses on 3 major health issues in adolescents’ Internet use: Body image and eating behaviors; sexual activity and reproductive health behaviors; and self harm and suicidal behavior. This paper also demonstrates Internet venues where reliable health information is provided to young people by health professionals. Health professionals need to recognize the hazards of adolescents Internet use, and to address potential Internet abuse when encountering adolescents in clinical settings.

Keywords: adolescents, health, internet, benefits, risks.

РЕЗЮМЕ

ВОПРОСЫ ЗДРАВООХРАНЕНИЯ ПРИ ИСПОЛЬЗОВАНИИ ИНТЕРНЕТА ПОДРОСКАМИ – ВЫГОДЫ И РИСКИ

Харлоф Д.

Израильский центр медицинской симуляции, Медицинский центр Хаим Шеба, Тель-Хашомер; Медицинское обслуживание подростков Службы медицинских услуг «Каллит»

В последнюю декаду интернет превратился в главный информационный ресурс в различных областях жизни и коммуникационное средство для подростков, ищущих информацию о здоровье в сети. Растущая доступность компьютеров дома, а также доступа к беспроводному интернету означают, что сегодня подростки могут войти в сеть всюду и в любое время. Средства массовой информации не являются ведущей причиной основных медицинских проблем, тем не менее, они вносят значительный вклад в развитие различных проблем, касающихся здоровья подростков, включая агрессивное поведение, сексуальную активность, применение наркотиков, ожирение, нарушение сна и питания, депрессию, суицид, самоповреждение. В статье фокусируется внимание на 3 основных медицинских проблемах, возникающих при использовании подростками интернета: образ тела и пищевое поведение; сексуальное и действующее на репродуктивное здоровье поведение; самовредительное и суицидальное поведение. В статье также указаны интернет ресурсы, в которых соответствующая информация о здоровье предоставляется молодым людям профессионалами здравоохранения. Профессионалы здравоохранения должны распознавать опасности использования интернета подростками и учитывать их в клинической деятельности.

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ярлоф д. израильский центр медициновой симуляций, медициновский центр хаим шеха, тель-хашомер; медицинское обслуживание подростков службы медицинских услуг. в последнюю декаду интернет превратился в главный информационный ресурс в различных областях жизни и коммуникационное средство для подростков, ищущих информацию о здоровье в сети. растущая доступность компьютеров дома, а также доступа к беспроводному интернету означают, что сегодня подростки могут войти в сеть всюду и в любое время. средства массовой информации не являются ведущей причиной основных медицинских проблем, тем не менее, они вносят значительный вклад в развитие различных проблем, касающихся здоровья подростков, включая агрессивное поведение, сексуальную активность, применение наркотиков, ожирение, нарушение сна и питания, депрессию, суицид, самоповреждение. в статье фокусируется внимание на 3 основных медицинских проблемах, возникающих при использовании подростками интернета: образ тела и пищевое поведение; сексуальное и действующее на репродуктивное здоровье поведение; самовредительное и суицидальное поведение. в статье также указаны интернет ресурсы, в которых соответствующая информация о здоровье предоставляется молодым людям профессионалами здравоохранения. профессионалы здравоохранения должны распознавать опасности использования интернета подростками и учитывать их в клинической деятельности.