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ORIGINAL ARTICLE

Evaluation of cerebral venous thrombosis secondary to oral contraceptive use in adolescents

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Abstract Our goal was to evaluate the clinical patterns, additional risk factors, treatment and outcome of cerebral venous thrombosis (CVT) related to adolescent oral contraceptive pill (OCP) usage. We evaluated 22 patients with CVT related to OCPs admitted to Firat and Dicle University Hospitals from January 2008 to January 2013. We assessed the clinical features, risk factors, imaging results and prognosis. Magnetic resonance imaging (MRI) and magnetic resonance were the preferred procedures for the diagnosis of CVT. MRI revealed parenchymal lesions in 11 (50 %) patients, and the remaining patients had normal MRIs. The sinuses most frequently affected by thrombosis were the superior sagittal sinus and the transverse sinus. The additional risk factors identified for CVT were antiphospholipid syndrome, protein C deficiency, protein C and S deficiency, factor V Leiden associated with heterozygous antithrombin III deficiency, methylenetetrahydrofolate reductase and prothrombin gene mutations. CVT may be overlooked in adolescents because it is more common among middle-aged and elderly adults. CVT should be suspected in the presence of neurological symptoms in adolescents, especially in those using OCPs.

Keywords Adolescents · Cerebral venous thrombosis · Oral contraceptives

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Introduction

Cerebral venous thrombosis (CVT) is a relatively rare disease that usually occurs with cerebral infarcts, which may lead to seizures, other neurological symptoms, or death. It is a potentially life-threatening disease, accounting for approximately 0.5 % of stroke cases [1]. The estimated annual incidence of CVT in the general population is three to four cases per million. It can affect all age groups, but it has a tendency to affect younger individuals, specifically women of childbearing age [2]. The risk of CVT is increased by factors that cause a hypercoagulable state or venous stasis, such as surgery, trauma, prolonged immobilisation, pregnancy, postpartum state and hormonal changes in young adult women [3–6].

Oral contraceptive pills (OCPs) are the most common modern method of contraception, followed by female sterilisation, in the world. They are also used to treat other medical conditions, such as polycystic ovary syndrome (PCOS), endometriosis, amenorrhea, menstrual cramps, adenomyosis, excessive menstrual bleeding, menstruation-related anaemia and dysmenorrhea. Menstrual-related disorders and irregular menses are particularly common during adolescence, with 70–91 % of female adolescents reporting painful periods and 25 % experiencing menstrual disturbances [7–9]. Oral contraceptives are frequently used in the treatment of the aforementioned diseases.

The majority of adolescents use OCPs for non-contraceptive reasons, most commonly menstrual pain (54 %), menstrual regulation (33 %) and acne (30 %) [10]. A strong association between CVT and oral contraceptive use has been established in case–control studies [3, 6]. This study aimed to describe the additional risk factors, clinical and neuroimaging features and outcomes of CVT secondary to OCP use in adolescents.

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Methods

Using the International Classification of Diseases (ICD 10) [11], we retrospectively studied the medical records of 37 adolescents with CVT admitted to Firat and Dicle University Hospitals from January 2008 to January 2013. Diagnosis was confirmed by computed tomography (CT)/CT venography or magnetic resonance imaging (MRI)/magnetic resonance venography (MRV).

We required complete blood count, coagulation profile, blood biochemistry, prothrombin time, activated partial thromboplastin time, D-dimer and human immunodeficiency virus test from all the patients. We have also determined the hypercoagulable state (protein C, protein S, antithrombin III, factor V Leiden, total homocysteine levels, prothrombin gene mutation, anticardiolipin antibodies and antinuclear antibodies) of each patient. DNA analysis for mutation in factor V Leiden, prothrombin genes, methylenetetrahydrofolate reductase (MTHFR), 4G/5G PAI-1, F II 20210 A and FV R506Q was evaluated.

A neurologist performed a complete neurologic examination, including the evaluation of mental status, sensory modalities, motor function, cranial nerves and ophthalmoscopy. We evaluated the following information: clinical presentation, risk factors, OCP types, dosage and usage time, location of the thrombus, treatment and outcome. The purpose of OCP use was determined, and each patient was evaluated by an obstetrician.

Exclusion criteria included pregnancy, puerperium, severe heart failure, valvular heart disease, malignant hypertension, Cushing syndrome, central nervous system vasculitis, congenital vascular disease, trauma, dissection, thyroid and kidney dysfunctions, liver failure and local and systemic infections.

Results

Thirty-seven adolescent patients were diagnosed with CVT. Twenty-two (59 %) patients had OCP-related CVT, and the remaining 15 patients had other etiologic factors. Median age was 15.50 (13–18) years. Average duration of symptoms in patients was 33.72 days. Average oral contraceptive usage time was 125.45 days. The follow-up period ranged from 5 to 24 months (mean 16 months). The patients' 3-month follow-up of clinical findings is summarised in Table 1. Two of the patients did not come back for reevaluation.

Frequently observed symptoms and signs were headache (95.5 %), papilledema (50 %), vomiting (22.5 %), focal motor deficit (13.5 %), seizure (13.5 %), altered consciousness (4.5 %) and cranial nerve involvement (4.5 %) (Table 2).

Seventeen of our patients had used cyproterone acetate/ethinyl estradiol, and five patients had used drospirenone/ethinyl estradiol. Twelve patients had hirsutism, five had menstrual irregularity and ten had PCOS.

We obtained the MRI and MRV scans of all patients. MRI revealed parenchymal lesions in 11 (50 %) patients, and the remaining patients had normal MRI. In the MRV, we found involvement of the superior sagittal sinus in 36 % of patients, transverse sinus in 36 %, sigmoid sinus in 31.5 % and straight sinus in 4.5 %. About 9 % of cases involved multiple sinuses (Table 3).

The additional etiologic factors of CVT are shown in Table 1. Antiphospholipid syndrome secondary to systemic lupus erythematosus was diagnosed in one patient. Inherited thrombophilia was identified in two patients. Protein C deficiency was identified in one patient, and protein C and S deficiency was found in two patients. Factor V Leiden associated with heterozygous antithrombin III deficiency was identified in one patient. Mutations in the MTHFR gene were found in one patient. Prothrombin gene mutation was discovered in one patient (Table 1).

We followed the international normalised ratio (INR) of patients on warfarin and adopted the target INR of 2–3. Prothrombin time and INR were used to monitor the effectiveness of warfarin to achieve the target INR of 2–3. One patient with observed allergy and three patients with menorrhagia were not administered with warfarin. Enoxaparine was given to these patients. The patients who had an underlying hypercoagulable state were advised to continue anticoagulation indefinitely, and those with no identifiable risk factors were treated for a period of 6 months. Sixteen patients were completely recovered, and six were partially recovered with some neurological deficit.

Discussion

Cerebral venous thrombosis during adolescence is rare. This study is the first to evaluate CVT related to OCPs in adolescents. Headache is the predominant symptom of CVT in most studies [12]. In our study, 95.5 % of patients presented with headache. Headache presented in a subacute or chronic manner, suggesting a clinical picture consistent with intracranial hypertension. Headache associated with papilledema was observed in 50 % patients, which is greater than the figure reported by Kajtazi et al. [13] (36.3 %). Other associated symptoms were vomiting, seizures, focal motor deficit and altered level of consciousness. According to the International Study on Cerebral Vein and Dural Sinus Thrombosis, seizure occurs in 39 % of patients [14]. Focal motor deficits are the presenting feature in 13.5 % of patients. The deficits include hemiparesis, monoparesis and paraparesis [15].

Table 1 Demographic characteristics of patients with CVT

Patient no/age	Duration of symptoms (days)	OC type and usage time	Reason of OC	Additional risk factor(s)	Clinical outcome (3-month follow-up)
1/15	125	CE, 200 days	Hirsutism		Normal
2/14	5	CE, 21 days	Hirsutism	Protein C and S deficiency	Normal
3/16	120	CE, 15 days	Polycystic ovary syndrome		Normal
4/17	15	DE, 55 days	Polycystic ovary syndrome	Obesity	Normal
5/18	3	DE, 45 days	Polycystic ovary syndrome	Factor V Leiden and antithrombin III deficiency	Focal motor deficit
6/15	3	CE, 180 days	Hirsutism		Seizure
7/18	130	CE, 365 days	Hirsutism		Normal[a]
8/18	2	CE, 65 days	Hirsutism, menstrual dysfunction	SLE, antiphospholipid antibodies	Focal motor deficits
9/17	21	CE, 100 days	Hirsutism, menstrual dysfunction		Normal[a]
10/15	12	CE, 65 days	Hirsutism, menstrual dysfunction		Normal
11/15	2	CE, 30 days	Hirsutism, menstrual dysfunction	MTHFR C677 T mutation	Sensory symptoms
12/15	15	CE, 50 days	Hirsutism		Normal
13/16	1	CE, 25 days	Menstrual dysfunction	Protein C and S deficiency	Cranial nerve involvement, Seizure, focal motor deficits
14/14	1	CE, 22 days	Menstrual dysfunction		Seizure
15/14	1	CE, 84 days	Menstrual dysfunction	Obesity	Normal
16/14	1	DE, 42 days	Hirsutism		Normal
17/16	35	DE, 102 days	Hirsutism, menstrual dysfunction	Smoking	Normal
18/18	10	CE, 94 days	Polycystic ovary syndrome	Prothrombin gene mutation	Normal
19/13	5	CE, 120 days	Polycystic ovary syndrome	Protein C deficiency, obesity	Normal
20/17	100	CE, 380 days	Menstrual dysfunction		Normal
21/16	35	CE, 420 days	Hirsutism		Normal
22/15	100	DE, 280 days	Menstrual dysfunction		Normal

CE cyproterone acetate/ethinyl estradiol, *DE* drospirenone/ethinyl estradiol, *SLE* systemic lupus erythematosus

[a] Clinical outcome of patients after hospital discharge

MRI/MRV is the best method for the diagnosis and follow-up of CVT. However, MRI may still be normal in some cases [16]. In our study, 11 patients had normal MRI. In evaluating the MRV, the most frequently involved sinuses were the superior sagittal sinus and the transverse sinus. Thrombosis of the superior sagittal sinus and then of the transverse sinus are the most predictive of developing headache, which is the most commonly occurring symptom [17]. Non-haemorrhagic infarcts, parenchymal oedema with venous infarction and haemorrhagic transformation can occur in 10–50 % of cases [18]. These findings were observed in 50 % of our patients. A decreased chance of parenchymal damage could occur with a slower rate of occlusion. This condition is caused by the increased time available for collaterals to form; consequently, no change in the CT of the brain occurs [18]. The same situation could also apply to our patients who had normal MRIs, prolonging the establishment of the CVT diagnosis. Similarly, an increased chance of haemorrhagic transformation could occur with the rapid development of venous thrombus; this finding was observed in four of our patients [18].

The overall absolute risk of venous thrombosis per year for every 100,000 males who use combined oral contraceptives is approximately 60 and that for non-users is 30

Table 2 Clinical symptoms and signs of patients with CVT

Symptoms and signs	*N* (%)
Headache	21 (94.5)
Papilledema	11 (50)
Vomiting	5 (22.5)
Focal motor deficit	3 (13.5)
Seizures	3 (13.5)
Altered consciousness	1 (4.5)
Cranial nerve involvement	1 (4.5)

Table 3 MRI and MRV findings of patients with CVT

MRI	*N* (%)
Normal	11 (50)
Haemorrhagic infarcts	4 (18)
Nonhaemorrhagic infarcts	7 (31.5)
MRV	
Thrombosed superior sagittal sinus	8 (36)
Thrombosed transverse sinus	8 (36)
Thrombosed sigmoid sinus	7 (31.5)
Thrombosed straight sinus	1 (4.5)
Multiple sinuses	2 (9)

MRI magnetic resonance imaging, *MRV* magnetic resonance venography

[19]. OCPs have been considered a contributing factor to the development of CVT, and their usage has been reported in 54–71 % of CVT patients [20]. The risk of thromboembolism varies with different types of birth control pills. Comparing combined oral contraceptives containing levonorgestrel with the same dose of oestrogen and duration of use, the rate of deep venous thrombosis for combined oral contraceptives with norethisterone is 0.98, norgestimate is 1.19, desogestrel is 1.82, gestodene is 1.86, drospirenone 1.64 and cyproterone is 1.88 [19]. Our patients used OCPs containing drospirenone and cyproterone because of the anti-androgenic effects of these drugs.

OCPs have long been known to cause an increased risk of venous thromboembolism, especially in carriers of common inherited thromboembolic defects. Factor V Leiden, prothrombin factor G20210A polymorphism, MTHFR (C677T) mutation and 4G/5G polymorphism of the PAI-1 gene account for the majority of thromboembolic events in association with oral contraceptive use. The risk is further increased by first usage, the use of preparations containing third-generation progestins, thrombophilia due to antithrombin, protein C and S deficiency, homozygous factor V (Leiden) and combined defects [21]. An increase in levels of procoagulant factors, such as factors VII, X, XII and XIII, associated with oestrogen use and a reduction in anticoagulant factors, including protein S and antithrombin, can occur [22]. We detected inherited thromboembolic defects in six of our patients. These patients had used OCPs for a short period unlike other patients.

Oral contraceptives are commonly used for reasons other than contraception. For instance, they are used in the treatment of PCOS. Hirsutism and acne are common and distressing symptoms in adolescents. These symptoms are frequently associated with PCOS, which may also cause disturbances in the menstrual cycle. The combination of anti-androgen cyproterone acetate and ethinyl estradiol has been effective in the management of symptoms for both hyperandrogenism and regulation of the menstrual cycle. However, its long-term use has been discouraged because of the concern for increased risk of venous thromboembolism [22]. In our study, 11 patients had used OCPs for the treatment of hirsutism. Four of these patients had other risk factors for thrombosis. Seven patients were also long-term OCP users.

PCOS is a common endocrine disorder associated with multiple comorbidities, such as diabetes, dyslipidemia, hypertension and metabolic syndrome, all of which predispose women with PCOS to early thrombosis [23]. Okoroh et al. [23] concluded that the prevalence of venous thromboembolism was higher among women with PCOS than in women without PCOS, and that oral contraceptive use might be a protective factor against venous thromboembolism. They indicated that oral contraceptives suppress the elevated levels of the luteinising hormone among women with PCOS and consequently the ovarian androgen production. Therefore, this reduction in androgens likely improves the impaired fibrinolysis present among women with PCOS. In our study, five of our patients had PCOS, but four of them had other contributing risk factors for thrombosis. These findings are required to be investigated with other thrombophilia factors in venous thrombosis in adolescents with PCOS, especially in those using OCPs.

The treatment of CVT requires therapeutic anticoagulation. Treatment with low-molecular-weight heparin in the acute phase followed by oral anticoagulant has been proven safe and effective in the prevention of disease progression [24]. Warfarin should be used in the chronic phase. Adolescent females on warfarin commonly suffer from menorrhagia [25]. We chose low-molecular-weight heparin and warfarin in our management of CVT. We observed menorrhagia in two patients who had used warfarin and changed therapy accordingly. We determined which patients had menorrhagia during the policlinic controls.

Twelve (54.5 %) patients were not diagnosed within the first 7 days and five (22.7 %) of these patients were diagnosed with CVT about 3 months after the first symptom onset. Headache associated with pain was described as sharp, dull, aching, or throbbing. These patients were

misdiagnosed with migraine, chronic tension-type headache or idiopathic intracranial hypertension in other clinics. In particular, adolescents who presented with headaches and normal neurological examinations were overlooked. Therefore, adolescents who use OCPs should have a thorough examination when they have neurological symptoms because of the risk that they may have venous thrombosis.

The limitations of the study are its retrospective nature and the assessment of clinical improvements of the patients in the first 3 months. The clinical improvements should be evaluated in the prospective studies.

Our findings indicate that adolescents who take OCPs to treat hirsutism, menstrual dysfunction, or PCOS may also have some risk factors for thrombosis, such as hereditary coagulopathy. The coexistence of these diseases and OCP use can increase the risk for CVT. Commonly used OCPs containing drospirenone and cyproterone may increase the risk of thrombosis. Adolescents who take OCPs should be evaluated for additional risk factors. Signs and symptoms are confused with other diseases in this age group, and they could make the diagnosis of CVT difficult. Detailed imaging, especially MRV, should be performed in these patients.

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