



**CASE REPORT**

Medicine Science 2017;6(3):576-8

## Cerebral venous thrombosis occurring during oxymetholone therapy

Gokce Pinar Reis<sup>1</sup>, Aysenur Bahadir<sup>2</sup>, Erol Erduran<sup>3</sup>, Tulay Kamasak, Ilker Eyuboglu<sup>4</sup>

<sup>1</sup> Erzurum Education and Research Hospital, Department of Pediatric Hematology and Oncology, Erzurum, Turkey

<sup>2</sup> Karadeniz Technical University School of Medicine, Department of Pediatric Hematology and Oncology, Trabzon, Turkey

<sup>3</sup> Karadeniz Technical University School of Medicine, Department of Pediatric Neurology, Trabzon, Turkey

<sup>4</sup> Karadeniz Technical University School of Medicine, Department of Radiology and Radiodiagnostic, Trabzon, Turkey

Received 18 November 2017; Accepted 29 March 2017

Available online 12.04.2017 with doi: 10.5455/medscience.2017.06.8618

### Abstract

Oxymetholone, an androgen analogue, is widely used in the treatment of Fanconi Aplastic Anemia (FAA). Androgen is known to cause cerebral venous thrombosis (CVT). A 9-year-old girl under monitoring with a diagnosis of FAA presented to our hospital with severe headache. She had been receiving oxymetholone therapy for 1 year. Neurological examination was normal. Superior sagittal sinus thrombosis was detected at magnetic resonance imaging (MRI) of the brain. The thrombosis was thought to be oxymetholone-related, and oxymetholone therapy was discontinued. The patient was started on enoxoparin therapy and the symptoms resolved. Control images 4 months later were normal. We think that the risk of venous thrombosis must be considered with administering oxymetholone therapy in patients with FAA.

**Keywords:** Cerebral venous thrombosis, oxymetholone, FAA

### Introduction

Cerebral venous sinus thrombosis is much rarer than arterial stroke and is generally seen in young people [1]. The exact incidence is uncertain [2]. Pregnancy, use of oral contraceptives, coagulopathies, intracranial infections, cranial tumors, penetrating head trauma, lumbar puncture, malignancy, dehydration, inflammatory bowel disease, connective tissue diseases, Behcet's disease, sarcoidosis, nephrotic syndrome, parenteral infusions and various drugs are implicated in the etiology [3,4]. The superior sagittal sinus is most commonly affected [3,5]. Clinically, thrombosis depends on the site and the speed of development. The most common symptom is headache. Other symptoms include seizure, hemiparesis, isolated intracranial hypertension, aphasia and hemianopsia [3,6]. Oral antithrombotic drugs, low molecular weight heparin or a combination thereof are used in treatment [7].

Oxymetholone (synthetic androgen) is widely used in the treatment of FAA to stimulate hematopoiesis. The mechanism involves increasing production of erythropoietin and stimulation of erythroid progenitors [8]. Hepatomegaly, cholestatic jaundice, elevation in hepatic enzymes, peliosis hepatis, hepatocellular adenoma and

carcinoma may be seen with long-term use [9,10]. Thrombosis is very rarely reported [10].

We describe a case of FAA using oxymetholone and developing cerebral venous thrombosis.

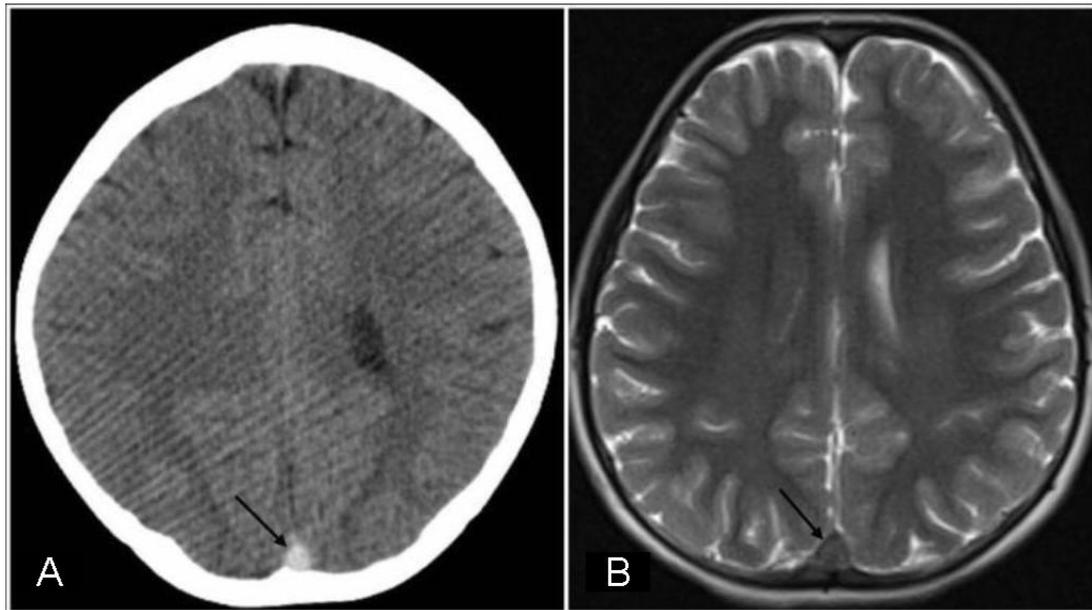
### Case

A 9-year-old girl presented to our clinic with severe headache. The patient had been monitored with a diagnosis of FAA for the previous year and had been receiving oxymetholone for 6 months. System examinations were normal, and no phenotypic findings specific to FAA were determined. The diepoxybutane test was positive, however. Full blood count values were Hb: 10.3 g/dl, MCV: 99.8, RDW: 23.3, white cell count 3500/mm<sup>3</sup> and thrombocyte number 106,000/mm<sup>3</sup>. There was no pathology in blood biochemistry and coagulation parameters. Superior sagittal sinus thrombosis was determined at CT of the brain and MR (Figure 1 A, B). There was no history of thrombosis in the family and the patient was using no drug other than oxymetholone. Oxymetholone was discontinued due to the probable thrombotic effect of androgens, and the patient was started on enoxoparin therapy at 1 mg/kg twice daily. Factors VIII and IX, antithrombin III, protein C and S, and Factor V V Leiden mutation were investigated to exclude other etiological causes, and were all normal. MTHFR 677 C>T polymorphism was heterozygous mutant. The patient's homocysteine level resolved at 44.6 umol/l. Elevated hypersegmented neutrophils and macrocytes were

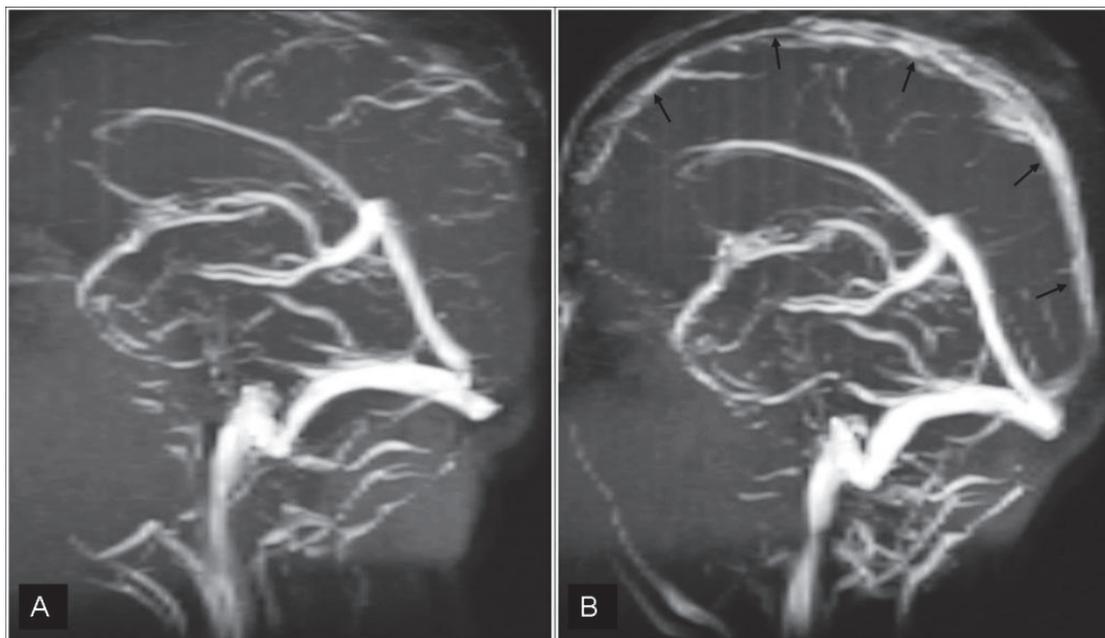
\*Corresponding Author: Gokce Pinar Reis, Erzurum Education and Research Hospital, Department of Pediatric Hematology and Oncology, Erzurum, Turkey  
E-mail: [dr.gpr1979@gmail.com](mailto:dr.gpr1979@gmail.com)

observed at peripheral blood smear. We provisionally attributed the high homocysteine level to Vitamin B12 deficiency. Blood folic acid level was 5.75 ng/ml (3.1-19.9) and B 12 level 207 ng/dl (182-866). Concealed Vitamin B12 deficiency was suspected and the patient was given Vitamin B12 support. Symptoms improved after discontinuation of oxymetholone and replacement by enoxoparin therapy, and the patient was discharged and invited for subsequent check-ups at our clinic. No

symptoms were observed at follow-ups. The patient received regular Vitamin BV12 therapy for 2 months. A control homocysteine level of 6 umol/l was determined. The thrombosis was seen to have contracted at MR Venography of the brain (Figure 2 B). Enoxoparin was reduced to 1 mg/kg per day. Enoxoparin therapy was continued at this dosage for 1 month and then discontinued.



**Figure 1.** Unenhanced Brain CT (A) reveals superior sagittal sinus thrombosis with high attenuation (arrow). Axial T2-weighted MR image (B) demonstrates hypointense thrombus (arrow) within the superior sagittal sinus.



**Figure 2.** 2D Time-of-Flight (TOF) MR Venography (A, B) demonstrates absent flow in the superior sagittal sinus consistent with thrombus. (A, arrow). After the specific therapy, complete recanalisation is seen (B, arrows).

## Discussion

Thrombosis is less common in the pediatric age group compared to adults. The incidence of thrombosis has increased with increasing survival rates in diseases such as premature birth, heart diseases and cancer that create a disposition to thrombosis [11]. Thrombosis in children is most commonly seen in the newborn and adolescent periods. Low protein C, protein S, antithrombin III and heparin cofactor levels, decreased fibrinolytic capacity and increased factor VIII levels, hyperhomocysteinemia and factor V Leiden mutation are causes of congenital thrombophilia [12]. We also investigated the causes in our patient and identified elevated homocysteine levels. Hyperhomocysteinemia may have acquired or genetic causes. Acquired causes result from deficiencies of folate, Vitamin B 12 or Vitamin B 6 in the diet, while genetic causes result from mutations in the methionine synthase or methylenetetrahydrofolate reductase (MTHFR) genes. High plasma homocysteine levels are characterized by both venous and arterial thromboses. Particular attention is being directed to MTHFR C677T polymorphism. Heterozygous MTHFR C677T polymorphism was determined in our patient. While heterozygous mutant development of MTHFR C677T polymorphism by itself is not that significant, if it is supported by hyperhomocysteinemia this is thought to be important in terms of thrombosis [13,14]. Since homocysteine levels were high in our patient, heterozygous MTHFR C677T positivity was regarded as significant.

Androgens have previously been reported to lead to SVT. Oxymetholone is a synthetic androgen analogue widely used in the treatment of FAA. Oxymetholone stimulates hematopoiesis in bone marrow. It causes an increase in numbers of young and immature thrombocytes and an increase in thrombocyte adhesion capacity. This results in hypercoagulation [9]. Androgen has not been reported to have direct effects on the arterial wall; however, several studies have shown that oral contraceptives increase the risk of cerebral venous thrombosis and coronary artery disease [15,16]. More cases are needed in order to definitively establish the cerebral venous thrombosis-inducing effect of oxymetholone.

We think that the fact that androgens may lead to thrombosis must be considered before starting oxymetholone therapy and that care should be taken during it. Oxymetholone use should be planned on a profit and loss basis, especially with patients with other risk factors, as well. Our patient had elevated homocysteine, which we attribute to Vitamin B 12 during cerebral venous thrombosis. We think that the elevation in homocysteine, which resolved after treatment, further increased the hypercoagulability of oxymetholone and facilitated the development of thrombosis.

We consider that wider case series are needed before deciding whether or not screening for thrombophilia should be performed before starting oxymetholone therapy. However, we think that in cases with a family history of stroke it would be more appropriate for oxymetholone therapy to be started after thrombophilia tests.

## References

- 1- Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of Cerebral Vein and Dural Sinus Thrombosis. Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke*. 2004;35(3):664-70.
- 2- Masuhr F, Mehraein S, Einhaupl K. Cerebral venous and sinus thrombosis. *J Neurol*. 2004;251(1):11-23.
- 3- Allroggen H, Abbott RJ. Cerebral venous sinus thrombosis. *Postgrad Med J*. 2000;76(891):12-5.
- 4- Ferro JM, Canhão P, Bousser MG, Barinagarrementeria F. Cerebral vein and dural sinus thrombosis in elderly patients. *Stroke*. 2005;36(9):1927-32.
- 5- Damak M, Crassard I, Wolff V, Bousser MG. Isolated lateral sinus thrombosis: a series of 62 patients. *Stroke*. 2009;40(2):476-81.
- 6- Renowden S. Cerebral venous sinus thrombosis. *Eur Radiol*. 2004;14(2):215-26.
- 7- Nagaraja D, Sarma GR. Treatment of cerebral sinus/venous thrombosis. *Neurol India*. 2002;50(2):114-6.
- 8- Zhang QS, Benedetti E, Deater M, Schubert K, Major A, Pelz C, Impey S, Marquez-Loza L, Rathbun RK, Kato S, Bagby GC, Grompe M. Oxymetholone therapy of fanconi anemia suppresses osteopontin transcription and induces hematopoietic stem cell cycling. *Stem Cell Reports*. 2015;4(1):90-102.
- 9- Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol*. 2004;77(3):257-67.
- 10- Chu K, Kang DW, Kim DE, Roh JK. Cerebral venous thrombosis associated with tentorial subdural hematoma during oxymetholone therapy. *J. Neurol Sci*. 2001;185(1):27-30.
- 11- Egeberg O. Inherited antithrombin deficiency causing thrombophilia. *Thromb Diath Haemorrh*. 1965;13:516-30
- 12- Nowak-Göttl U, Kosch A, Schlegel N, Salem M, Manco-Johnson M. Thromboembolism in children. *Curr Opin Hematol*. 2002;9(5):448-53.
- 13- den Heijer M, Koster T, Blom HJ, Bos GM, Briet E, Reitsma PH, Vandenbroucke JP, Rosendaal FR. Hyperhomocysteinemia as a risk factor for deep vein thrombosis. *N Engl J Med*. 1996;334(12):759-62.
- 14- Ray JG. Meta-analysis of Hyperhomocysteinemia as a risk factor for thromboembolic disease. *Arc Intern Med*. 1998;158(19):2101-6.
- 15- Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. *JAMA, J Am Med Assoc*. 1998;280(7):605-13.
- 16- Lidgaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism. A case-control study. *Contraception*. 1998;57(5):291-301.