

ORAL CONTRACEPTIVE PILLS CONSUMPTION AND CEREBRAL VENOUS THROMBOSIS

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Abstract

BACKGROUND: Causes of cerebral venous thrombosis (CVT) vary around the world. Oral contraceptive pills (OCP) are among the most frequent causes of cerebral venous thrombosis.

METHODS: Consecutive patients admitted with cerebral venous thrombosis in Ghaem hospital, Mashhad during 2005-2008 were prospectively investigated. Diagnosis of cerebral venous thrombosis was made by corresponding results of MRI, and MRV or conventional angiography. All of the patients had a complete medical history, physical examination and underwent a standard battery of diagnostic investigations by stroke neurologists.

RESULTS: Sixty two patients (51 females, 11 males) with mean age of 32.3, ranged 18-62 years were admitted with cerebral venous thrombosis. Oral contraceptive pills consumption was found as risk factor in 56.8% of females with cerebral venous thrombosis. These females had used LD and HD types of oral contraceptive pills in 97% and 3% respectively. 41% of females with cerebral venous thrombosis; (21/51) were on short term oral contraceptive pills consumption. In this latter group of females, Ramadan and Hadj religious months were the reason of using short term oral contraceptive pills in 86% and 5% respectively.

CONCLUSION: Short term oral contraceptive pills consumption is the most common cause of cerebral venous thrombosis in Iranian women. Programs for public awareness should be conducted for reducing use of these pills in short term periods during Ramadan and Hadj months.

Keywords: Cerebral venous thrombosis (CVT), Etiology, Oral Contraceptive Pills (OCP).

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Introduction

For a long time, cerebral venous thrombosis (CVT) was considered a rare disease confirmed by autopsy and associated with poor prognosis. In recent decades, the outlook for CVT has been dramatically improved by the use of Magnetic Resonance Imaging (MRI) and MR Venography leading to earlier diagnosis¹.

Numerous conditions, both intracranial and extracranial, have been implicated to cause CVT. When the thrombosis arises without an obvious cause, an extensive and early workup is necessary because the underlying disease may require special treatment.¹ Even after full investigations, in 20-25 percent of cases, the cause remains uncertain.² A diagnosis of idiopathic CVT should be made with caution, because other features of an underlying disease may only become evident on follow-up and after repeated investigations.¹ Distribution of etiology of CVT varies around the world, e.g. Behcet disease accounted for about 25% of all CVT in

Saudi Arabia.³ Puerperium remains a frequent cause of CVT, particularly in developing countries, which have more frequent prenatal infections and dehydration.⁴ Among drugs associated with the occurrence of CVT, oral contraceptive pills (OCP) are by far the most common.¹ This etiologic study investigates the causes of CVT in the east of Iran.

Materials and Methods

Consecutive patients with definite diagnosis of CVT, admitted in Ghaem hospital, Mashhad during 2005-2008 enrolled in a prospective observational study. Diagnosis of CVT was made by stroke neurologists. Confirmation of CVT is by corresponding both MRI and MRV. Thrombosis should be observed in T₁ and T₂ sequences of MRI with loss of signal void in the corresponding T₂ sequence of the related sinus.⁵ Detection of cut-off point or filling defect in the related sinus in MRV is necessary for confirmation of CVT

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diagnosis by MRI technology.^{5,6} Patients who were highly suspicious to CVT and had no MRI and MRV clues of CVT, underwent conventional angiography for detection of sinus filling defect.^{5,6} Detailed history of OCP consumption, its duration and type of OCP based on the estradiol component, were taken.⁷ Short-term OCP consumption defined as using OCP in recent 3 months.⁷ Postpartum period defined as 3 months after delivery.^{7,8} All of the patients underwent a standard battery of diagnostic investigation to determine cause of CVT.⁸ The research was approved by ethics committee of Ghaem hospital. A signed informed consent was obtained from the patients or their first degree relatives.

Results

Sixty two patients (51 females, 11 males) with mean age of 32.3, ranged 18-62 years were admitted with CVT. Table 1 represents etiologies of CVT in our patients. Multiple causes were found in 29% of the patients. OCP consumption was found as risk factor in 56.8% of females (29/51) with CVT. This group of females had used LD (35 µg ethynil estradiol and 0.3 µg norgestosterone) and HD (50 µg ethynil estradiol and 0.5 µg norgestosterone) types of OCP in 97% and 3% respectively. Short term (less than 3 months) OCP consumption was found in 41.2% of females (21/51). Short term consumption was found in 72.4% of females with CVT who had taken OCP (21/29); 95.2% of this latter group used LD (20/29 LD and 1/29 HD respectively). Among females on short term OCP, Ramadan and Hadj religious months were the reason for using short term OCP in 85.7% (18/21) and 4.8% (1/21) respectively. Distribution of CVT in Ramadan was significantly higher than other months in the females ($\chi^2 = 14.7$, $P = 0.001$). 63.6% of our males with CVT had uncertain etiology despite complete diagnostic investigations.

Discussion

In developed countries, the role of OCP is more important.^{1,9} 82.2 % of our CVT were seen in females and OCP was the causing factor in 56.8% of them. OCP consumption constituted 43% of CVT etiologies and found in 51% of females with CVT in Tabriz, north western Iran.¹⁰ In a French study on 134 CVT patients, OCP was the only etiologic factor in 10% of the cases, however OCP usage was also associated with other conditions such as systemic lupus erythematosus (SLE) or Behcet disease in another 10%.¹¹ The detection of congenital thrombophilia should be systematic in CVT since it potentiates the risk of venous thrombosis associated with other conditions, including OCP or puerperium.^{9,12} The use of OCP in carriers of thrombophilic abnormality extensively increases the risk of CVT (Ods Ratio: 149).¹³ De Bruijn et al reported a 30-fold increased risk of CVT in women with a combination of thrombophilic abnormalities and use of OCP compared with women without either risk factor.¹⁴ Increased levels of coagulation factors 7, 8, 10, fibrinogen and prothrombin has been found in women using OCP, these findings are more common in women on OCP containing desogestrol.¹⁵ LD is the usual type of OCP in Iranian drug market. Short term LD-OCP has an extremely important role in development of CVT in Iranian women. Since menstrual period prohibits Muslim women from entering the holy places during Hadj customs and disallows their fasting in Ramadan, they use short term OCP for a month in order to postpone menstruation and performing religious duties. At the other side, dehydration during fasting in Ramadan facilitates development of CVT in females on OCP. This concept highlights the need for public awareness of this important complication of OCP in Muslim women especially during Ramadan month.

Table 1. Etiologies of cerebral venous thrombosis in 62 Iranian patients

Etiology	Females (n = 51) (%)	Males (n = 11) (%)	Both genders (n = 62) (%)
Oral Copntraceptives	29-56.8	–	29-46.8
Dehydration	17-33.3	1-9.1	18-29
Hypercoagulable state	7-13.7	2-18.2	9-13.8
Postpartum	2-3.9	–	2-3.2
Pregnancy	3-5.9	–	3-4.8
Other Medications	2-3.9	–	2-3.2
Otitis	1-1.9	1-9.1	2-3.2
Meningioma	1-1.9	–	1-1.6
Lupus Erythematosus	1-1.9	–	1-1.6
Multiple	18-35.3	–	18-29
Uncertain	8-15.7	7-63.6	15-24.2

References

1. Mas JL, Meder JF. Cerebral venous thrombosis. In: Ginsberg MD, Bogousslavsky J, editors. Cerebrovascular disease: pathophysiology, diagnosis, and management. vol 2. New York: Blackwell Science; 1998. p. 1496-7.
2. Bousser MG, Russell RR. Volume 3 of major problems in neurology cerebral venous thrombosis. 1st ed. Philadelphia: W.B. Saunders; 1997.
3. Daif A, Awada A, al Rajeh S, Abduljabbar M, al Tahan AR, Obeid T, et al. Cerebral venous thrombosis in adults. a study of 40 cases from Saudi Arabia . Stroke 1995; 26(7): 1193-5.
4. Cantu C, Barinagarrementeria F. Cerebral venous thrombosis associated with pregnancy and puerperium; review of 67 cases. Stroke 1993; 24(12): 1880-4.
5. Biller J, Love BB. Ischemic cerebrovascular disease. In: Bradely NG, Daroff RB, Fenichel GM, Jankovic J, editors. Neurology in clinical practice. Philadelphia: Butterworth-Heinemann; 2007. p. 1245.
6. Ferro JM, Canhao 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.
7. Ghandehari K, Izadi Z. The Khorasan stroke registry: results of a five-year hospital-based study. Cerebrovasc Dis 2007; 23(2-3): 132-9.
8. Warlow C, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG. Stroke: a practical guide to management. 2nd ed. London: Wiley-Blackwell; 2001.
9. Bousser MG, Barnett HJM. Cerebral venous thrombosis. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, editors. Stroke: pathophysiology, diagnosis & management. Philadelphia: Churchill Livingstone; 1998. p. 627-8.
10. Pashapoor A, Arami MA, Valaei A. Cerebral venous thrombosis in adults: a clinical study of 64 Iranian cases. The Internet Journal of Neurology 2007; 7(1): 295.
11. Ameri A, Bousser MG. Cerebral venous thrombosis. Neurol Clin 1992; 10(1): 87-111.
12. Buchanan DS, Brazinsky JH. Dural sinus and cerebral venous thrombosis. incidence in young women receiving oral contraceptives. Arch Neurol 1970; 22(5): 440-4.
13. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med 1998; 338(25): 1793-7.
14. De Bruijn SF, Stam J, Koopman MM, Van den-broucke JP. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in [correction of who are] carriers of hereditary prothrombotic conditions. the cerebral venous sinus thrombosis study group. BMJ 1998; 316(7131): 589-92.
15. Agnelli G, Verso M. Epidemiology of cerebral vein and sinus thrombosis. Front Neurol Neurosci 2008; 23: 16-22.