Incidence of Cerebral Venous Thrombosis in Iranian Women: A Longitudinal Two-Year Study in Zanjan Province of Iran

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ABSTRACT

BACKGROUND: Cerebral venous thrombosis (CVT) is a disease with high potential of disability and high rates of mortality. It affects females more than males. The estimated annual incidence of CVT is 3 to 4 cases per 1 million, but the incidence rate is much higher in Iran. It particularly increases in Ramadan and Zilhijjah months of the Islamic calendar. We hypothesized that the use of contraceptive components especially during the month of Ramadan is associated with an increase in the risk of CVT in women.

METHODS: A longitudinal descriptive study was conducted from 2010 to 2011 including two consecutive months of Ramadan in Zanjan Province of Iran. The data of 32 female patients with verified CVT, including demographic variables and main CVT risk factors was obtained from hospital records and interview with patients' families.

RESULTS: The annual incidence rate for women in all age groups and child-bearing age was 31.5 and 49 per 1,000,000, respectively. The incidence trends of CVT are increased in concordance with ageing (p-value =0.01). 26 patients (81.25%) reported a history of contraceptive use as a main CVT risk factor. History of OCP administration was 15 times more likely than non-OCP to be vulnerable for CVT (p-value <0.05). More than half of the cases (56.25%) occurred in the month of Ramadan (p-value <0.05).

CONCLUSION: The higher incidence rate of CVT in Zanjan province more than the statistics cited in the literature is related to the higher incidence of CVT in women but not in men. Use of contraceptive components by women in Ramadan, Hajj times or pilgrimage to postpone their menstruation should be considered by healthcare system to control the incorrect use of them among Muslim women.

Keywords: Incidence; Muslim Women; Contraceptive Components; Ramadan; Cerebral Venous Thrombosis

INTRODUCTION

Cerebral venous thrombosis (CVT) is a disease with severe thrombotic manifestations, high potential of disability and high rates of mortality [1]. Its manifestations are variable and include increased intracranial pressure (e.g. headache, nausea, vomiting, diplopia, blurred vision), focal sensory and motor deficits, focal and generalized seizures, behavioral and consciousness disorders and coma [2]. CVT is not a rare disorder as previously thought [3], and is often linked to poor prognosis [4]. Females are more commonly affected than males and the incidence varies by geographical distribution [3, 5]. The important predisposing factors for CVT include thrombotic factors, trauma, malignancy, autoimmune disease, infections, shortage of materials such as folic acid, pyridoxine and cobalamin, pregnancy and use of oral contraceptive pills (OCPs) [1, 6-10]. In literature, the estimated annual incidence of CVT is 3 to 4 cases per 1 million population

[11]; however, the incidence rate is much higher in Iran. It particularly increases in Ramadan and Zilhijjah months of the Islamic calendar [12]. We hypothesized that higher rate of CVT in Iran is related to the higher incidence of CVT in female gender which in turn is due to cultural and religious customs such as the use of OCPs for delaying menstruation to perform religious customs (fasting during Ramadan) and religious travels (e.g. Hajj ceremonies during Zilhijjah).

METHODS AND MATERIALS

Study design: Zanjan province is located at the north west of Iran and has a population of 1 million. Almost 100% of the population is Muslim. Sixty percent of females are in child-bearing age (15-49) [13], of whom 20 percent use OCPs [14]. Zanjan province has only one neurology center where all patients from the province are referred for neurological consultation and treatment.

Data collection procedure: This longitudinal descriptive study was conducted from August 2010 (Ramadan 1431 in Islamic Calendar) to September 2011(Ramadan 1432) including two consecutive months of Ramadan. During this period, we found 33 new cases (one male and 32 females) with definite diagnosis of CVT based on clinical symptoms and confirmed with magnetic resonance venography (MRV), who were referred to the only neurology center of the province. The data on female patients with confirmed CVT, such as demographic variables and main CVT risk factors, were obtained from hospital records and interview with patients' families.

Data treatment: To calculate age-specific incidence rate, the national and provincial census data of 2010 was used as denominators per 1,000,000 populations. To determine CVT incidence trend through age groups, Cochran-Armitage test was used by Winpepi software [15]. The incidence rate of CVT based on a history of OCP administration and Ramadan/non-Ramadan months was compared by incidence rate ratio (IRR).

RESULTS

The mean (±standard deviation) age of CVT patients was 37.6 (±10.21) years and median 38.5 years. The annual incidence rate for women in all age groups and child-bearing age was 31.5 and 49 per 100,000, respectively. The incidence rates of CVT increased with ageing (Table 1, p-value =0.01). Considering contraception products as a main CVT risk factor, 26 patients (81.25%) reported a history of contraceptive components consumption including 24 cases of contraceptive LD, one case of cyproterone compound and one case of depot medroxyprogesterone acetate (DMPA). Subjects with a history of OCP administration were 15 times more likely than non-OCP users to have CVT (p-value <0.05). In comparison of CVT incidence rate in Ramadan with non-Ramadan months, more than half of the cases (56.25%) were reported in Ramadan (p-value <0.05).

Table 1: Incidence rate of CVT based on age groups, OCP consumption and month

	Number of CVT cases	Reference population	Incidence rate (per 100000)	Incidence Rate Ratio (95% CI)
Age group				
15-24	5	109232	4.57	Reference
25-34	9	103131	8.72	1.9 (0.63-5.68)
35-44	7	70244	9.96	2.17 (0.69-6.85)
45-54	11	46339	23.73	5.18 (1.8-14.9)
	X^2 trend:12.44, p-value =0.01			
OCP				
No	7	266775	2.62	Reference
Yes	25	62170 †	40.21	15.32 (6.62-35.43)
Month				
Ramadan	18	657892	2.73*	14.1(7.03-28.43)
Non Ramadan	14	7236812	0.19	Reference

† Number of women (15-54) with a history of OCP consumption in general population
* Incidence rate per person-month

Minimum period of time that a patient had consumed LD included 3 tablets in a day (morning after pill) and the maximum period of time was for a patient with consumption of 12 months LD concomitant with one month of fasting in Ramadan. 17 patients (70.83%) had used LD for less than one month and seven

patients (29.17%) had used it for more than one month. Laboratory findings of the patients were as shown in Table 2.

One of the patients developed Stevens-Johnson syndrome during hospitalization, due to phenytoin administration to control status epilepticus. Three patients died despite anticoagulant therapy. Two of them were referred to our hospital in deep coma with extensive hemorrhagic infarction, and had no risk factors except for one month of LD consumption. The third patient developed diabetic ketoacidosis and died. This patient had used DMPA. Other patients were discharged from the hospital.

Table 2: Laboratory findings of patients

Abnormal Cases	Laboratory Findings
4 (anemia)	CBC
3	FANA
0	ANCA (P and C)
3	Anti ds DNA
0	Pro-C
3	Pro-S
4	Antithrombin
3	APCR
3	Hyperhemocysteniemia
2	APL-Ab
1	ACL-Ab
0	Lupus Anticoagulan
1	β-2 Glycoprotein
0	Prothrombin G20210A Mutation

DISCUSSION

In this study, we found that the incidence rate of CVT is much higher in the Zanjan province of Iran and that the females of child-bearing age who use OCPs had higher risk of developing CVT. We further found that the risk increases with age and increases during the months of fasting (Ramadan) and Hajj (Zilhijjah).

During the 13 lunar months of the study period, we found 32 female patients who presented with CVT to the only neurology referral center in the Zanjan province, consistent with an overall incidence rate of 49 per million childbearing years or 33 per million person-years. This incidence rate is much higher than the reported incidence in literature of 3 to 4 cases per million person-years [16]. The higher incidence rate of CVT in our province is due to the higher incidence of CVT in women but not in men. Several factors may be responsible for the increased incidence seen in women in our study and not in other studies. In our study, the age range of patients was from 21-54 years which is not different than what has been reported in other studies [16, 17]. In our study, 18 female patients (56.25%) were affected in the month of Ramadan, which is significantly higher in comparison with other months (p-value <0.05). Several factors may account for this increased risk. According to the Islamic principles, women are not allowed to fast or enter mosques including the mosques in the holy cities of Mecca or Medina during their menstruation [12]. Driven by a strong desire to fulfill their religious duties, women use OCPs for 30 days until the end of Ramadan to postpone their menstruation, often without consulting a physician. In addition, as fasting includes refraining from drinking or eating anything from pre-dawn to dusk, lack of fluid intake during fasting, sometimes up to 18 hours in summer, results in dehydration. Thus, a combination of dehydration and OCP use may be responsible for the increased risk of CVT seen during the month of Ramadan. Of the 17 patients who had used oral contraceptives in Ramadan, 14 of them had consumed them as a short course in order to fast all the days of Ramadan. During the month of Zilhijjah, women use OCPs so that they can continue to perform their religious rituals during Hajj. Consistent with our findings, Saidee et al. also found an increased risk of CVT during Ramadan in Mashhad in Iran, and suggested that this might be related to the short-term use of OCPs [12].

CONCLUSION

In conclusion, we showed that the incidence of CVT in Zanjan province is much higher than other studies, irrespective of the time of the year or the use of OCPs. This finding highlights the need for further studies with larger sample sizes. Given that the known risk factor with the largest effect in our study was the use of OCPs, women should refrain from OCPs without consulting their physician. Use of contraceptive components in Ramadan, Hajj times or pilgrimage to postpone women's menstruation should be considered by healthcare system to control the incorrect use of them among Muslim women.

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