

# Cerebral Vein and Sinus Thrombosis in Isfahan-Iran: A Changing Profile

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**ABSTRACT: Objectives:** This study was performed to investigate the clinical presentation and predisposing factors for cerebral vein and sinus thrombosis (CVST) in Isfahan, Iran. **Methods:** Data from the records of all patients with CVST referred to the largest tertiary-care hospital of Isfahan during a five-year period (1997 to 2001) were extracted and reviewed. **Results:** The number of cases with CVST diagnosed annually was 6, 9, 11, 14 and 15 patients, respectively. Thirteen men and 42 women were diagnosed to have CVST with the mean age of  $35.1 \pm 3.8$  and  $28.7 \pm 1.3$  years, respectively. Headache was the most frequent complaint (95%) and 63% of patients had focal neurological symptoms, including seizure (58%). Among possible predisposing factors, oral contraceptive pill was the most prevalent one, which was used by 38.1% of affected women for a period of as short as 1-3 months. Anticardiolipin antibodies were detected in 14% of patients. **Conclusions:** It seems that the annual incidence of CVST is increasing in Isfahan, perhaps due to more extensive intake of oral contraceptive pills and usage of more accurate modern diagnostic tools. The use of oral contraceptive pills was the most frequent predisposing factor; infections and postpartum factors were infrequently observed. Despite other reports from the Middle East, Behçet's disease is not a principal risk factor for CVST in Isfahani patients.

**RÉSUMÉ: Thrombose cérébrale veineuse et sinusale à Isfahan, en Iran: un profil en voie de changement.**

**Objectifs :** Le but de cette étude était d'examiner le mode de présentation clinique et les facteurs prédisposants à la thrombose cérébrale veineuse et sinusale (TCVS) à Isfahan, en Iran. **Méthodes :** Nous avons révisé les dossiers de tous les patients atteints de TCVS référés au plus important hôpital de soins tertiaires d'Isfahan sur une période de cinq ans, soit de 1997 à 2001. **Résultats :** Le nombre de cas de TCVS diagnostiqués annuellement était de 6, 9, 11, 14 et 15 respectivement, soit 13 hommes et 42 femmes dont l'âge moyen était de  $32,1 \pm 4,3$  et  $28,2 \pm 3,4$  ans respectivement. La céphalée était le symptôme le plus fréquent, soit chez 95% des patients, et 63% avaient des symptômes neurologiques focaux dont des crises convulsives chez 58%. L'utilisation de contraceptifs oraux était le facteur prédisposant potentiel le plus fréquent, soit chez 39% des femmes atteintes, même avec une utilisation qui pouvait être très courte (1 à 3 mois). Des anticorps anticardiolipine ont été détectés chez 14% des patients. **Conclusions :** L'incidence annuelle de TCVS semble à la hausse à Isfahan, possiblement en relation avec une utilisation plus répandue des contraceptifs oraux et d'outils diagnostiques modernes plus précis. La prise de contraceptifs oraux était le facteur prédisposant le plus fréquent et les infections et le post-partum étaient rares. Contrairement à des données publiées provenant du Moyen Orient, la maladie de Behçet n'est pas un facteur de risque majeur de la TCVS à Isfahan.

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The wide spectrum of clinical presentations associated with cerebral vein and sinus thrombosis (CVST) makes it a diagnostic challenge. The etiology of CVST includes genetically determined procoagulant states, dehydration, Behçet's disease and septic thrombosis.<sup>1-10</sup> While in the western countries hypercoagulable states are the most common etiology of CVST,<sup>9,11-12</sup> peripartum dehydration and septic thrombophlebitis of cranial venous sinuses have been reported as the most prominent predisposing factors of CVST in developing societies.<sup>4,7,13-14</sup> Ethno-geographic differences also seem to influence the distribution of the etiologies. A recent study from

Saudi Arabia revealed Behçet's disease as the most prevalent cause of CVST.<sup>15</sup>

During recent decades, improvements in health care standards and application of modern techniques in Iran have led to earlier

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diagnosis and treatment of infectious diseases and better maternal care during pregnancies.<sup>16,17</sup> Oral contraceptive use has also increased during this period of time.<sup>18-20</sup> With regard to these changes, we investigated the clinical presentation and predisposing factors of CVST in patients referred to the largest tertiary-care hospital (Al-Zahra hospital) in Isfahan, a centrally located city in Iran, over a five-year period from 1997 to 2001.

## METHODS

We reviewed the records of all patients with a hospital admission or discharge diagnosis of CVST from 1997 through 2001. Only those patients with a definitive diagnosis of CVST according to angiographic and/or magnetic resonance imaging – MRI and magnetic resonance venography (MRV) – based on accepted definitions,<sup>21-27</sup> were included in the study (for omission of pitfalls e.g. congenital variations in MRV, the presence of visible thrombus was confirmed by MRI and, if needed, follow-up MRI or MRI with contrast enhancement was performed). Patients' demographics, past medical history, current medication usage, physical and neurological complaints, onset of symptoms (acute: <72h / subacute: <1 month / chronic: progressive over months), family history and treatment options were entered into the database. In addition to routine blood chemistry, urine analysis, complete blood count and differential, erythrocyte sedimentation rate, prothrombin time, activated thromboplastin time, antinuclear antibody, evaluation for syphilis (VDRL), antineutrophil cytoplasmic antibody, anti-cardiolipin antibody and lupus anticoagulant were measured. To rule out Behçet's disease and other autoimmune disorders, rheumatological consultation was requested for all patients. If no obvious cause was found for CVST or a thrombotic event was present in his or her past or family history, antithrombin III, protein C and protein S were also measured as the assay became available (from 1999).

## RESULTS

Fifty-five patients were identified with CVST (42 females, 13 males). The number of cases diagnosed annually (from 1997 to 2001) was 6, 9, 11, 14, 15 patients, respectively. The mean of age for all patients was 29.5±1.3 (17-71 years), it was 35.1±3.8 (20-71 years) and 28.7±1.3 (17-51) years for men and women, respectively (P=0.4). Table 1 shows the clinical features of patients during the acute phase (within two weeks of admission). Sudden onset of headache was present in 10.9% (n=6) of patients. The onset of symptoms was acute in 29% (n=16), subacute in 65% (n=36) and progressive over months in 5% (n=3) of patients.

The first two patients (diagnosed in 1997) had abnormal cerebral angiography whereas subsequent patients had diagnostic MRI and MRV.

Venous infarction occurred in 25 patients (45%) including six subjects (10.9%) with hemorrhagic infarction and five patients (9%) with deep cerebral infarction. Partial or complete occlusion of the superior sagittal sinus was observed in 72% of cases (n=40). It was associated with other sinus or venous occlusion in 12 subjects (lateral sinus in six, transverse sinus in two, deep cerebral vein in three patients and jugular vein in one patient) and was isolated in the remaining 28 patients. Isolated lateral

**Table 1: Clinical features of CVST patients in Isfahan-Iran**

Sign/Symptom	No. (%)
Headache	52 (94.5%)
Papilledema	40 (72.7%)
Seizure	32 (58.1%)
Focal sensorimotor symptom	25 (45.4%)
Confusional state	7 (12.7%)
Stupor or coma	6 (10.9%)
Aphasia	4 (7.2%)
Vertigo	4 (7.2%)
Meningeal sign	1 (1.8%)

**Table 2: Predisposing factors of CVST in Isfahan-Iran**

Etiology	Males	Females	Total No. (%)
<b>Hypercoagulable states</b>			
Oral Contraceptives	0	27	27 (64% of women)
Postpartum	0	4	4 (9.5% of women)
Pregnancy	0	3	3 (7.1% of women)
Protein S Deficiency	0	1	1 (1.8%)
Antiphospholipid Antibodies	2	6	8 (14.5%)
<b>Autoimmune disorders</b>			
Lupus	0	2	2 (3.6%)
Rheumatoid Arthritis	0	1	1 (1.8%)
Other Connective Tissue Diseases	1	1	2 (3.6%)
<b>Hematological Disorders</b>			
Polycythemia	1	0	1 (1.8%)
Thrombocytosis	1	0	1 (1.8%)
<b>Others</b>			
Infection	2	2	4 (7.2%)
Malignancy	2	0	2 (3.6%)
Trauma	2	0	2 (3.6%)
Inflammatory Bowel Disease	1	0	1 (1.8%)
<b>Unknown</b>	7	4	11 (20%)

sinus occlusion was reported in 9% (n=5) of patients.

The predisposing factors for CVST are shown in Table 2. The most frequent risk factor was the oral contraceptive pill (OCP), which was taken by 59.3% (16 out of 27) of female users for a period of as short as one to three months and for longer than three months in 40.7% of cases (11 out of 27).

High dose (norgestrel 0.5 mg + ethinyl estradiol 0.05 mg) and low dose (norgestrel 0.3 mg + ethinyl estradiol 0.03 mg) estrogen contraceptive pills were taken by four and 22 of the women in this series, respectively and one patient was using cyproterone compound (cyproterone acetate 2 mg + ethinyl estradiol 0.05 mg).

## DISCUSSION

Our investigation shows an increase in the diagnosis of CVST annually. This is probably attributed to the increasing availability of modern noninvasive diagnostic techniques such as MRI and MRV in recent years and increased usage of OCPs for family planning in Iran.<sup>18-20</sup>

Symptoms and signs in this series were similar to other studies,<sup>1,2,11,12,15,28</sup> but we observed a higher prevalence of sudden-onset headache (10.9%) compared to previous reports.<sup>29</sup>

Although infection was considered as a main cause for CVST in previous studies,<sup>2,30</sup> it has been found in only 8% of cases in recently performed series.<sup>11,12</sup> Similarly, only 7% of our patients had an infectious cause for CVST. This is in accordance with the results of another study in the Middle East region,<sup>15</sup> and may be the result of recent improvements of health and infectious care standards in Iran.<sup>16-17</sup>

No definitive case of Behçet's disease was detected in our patients, although other autoimmune disorders, (systemic lupus erythematosus, rheumatoid arthritis), were detected in 9% as predisposing factors. It has also been reported in 16%<sup>2</sup> and 25%<sup>15</sup> of CVST cases in similar studies. Our findings are in contrast to higher prevalence of this disorder in the Middle East region.<sup>31</sup> In Arab patients in Israel, Kuwait and Saudi Arabia<sup>32-34</sup> neuro-Behçet's was reported in 16% to 44% of patients but in Iran and Iraq<sup>35,36</sup> less than 6% of patients with Behçet's disease had neurological manifestations. These regional differences may probably be due to ethnic as well as geographical factors.

In recent years, OCP intake, various types of coagulopathies and coexistence of these risk factors are frequently reported in patients with CVST.<sup>37-42</sup> In our study, 64% of women had been on OCPs. Although the search for thrombophilia was not systematically and completely performed in the present study, a case of protein S deficiency was found among our most recently diagnosed patients. However, because of multidisciplinary management of CVST, it is necessary to perform a complete screening of various types of coagulopathies and thrombophilia even in patients with a definitive identified risk factor.

In the series reported by Bloemenkamp et al,<sup>43</sup> a considerable number of patients with deep vein thrombosis (DVT), who had a history of short-term OCP intake (less than one year), also had a prothrombotic defect. In the majority of our female patients who were taking OCP (59.2%), the period of drug usage was short (one to three months), so it is possible that the presence of prothrombotic defects in this group of women is more likely. Although our results show that hypercoagulable states and autoimmune disorders were more prevalent risk factors in women as compared to men (in whom trauma and malignancy were more commonly detected), these data could not be supported by statistical analysis due to sample size limitations.

Elevated homocystein level, in recent studies after 2001,<sup>44-48</sup> has been shown to be a common cause of CVST, and this also has not been investigated in this study.

In 20% of our patients, no definitive predisposing factor was found. However, even in other recent reports,<sup>11,12</sup> no clear cause was observed in 20% to 30% of patients.

This study has its own special limitations including retrospective design, which might have led to bias. Another limitation of the present study is incomplete etiologic workup,

which may be due to the retrospective design and unavailability of some diagnostic tests at the time of CVST diagnosis.

In conclusion, the incidence of CVST is increasing annually in Isfahan, Iran, perhaps due to availability of more accurate diagnostic techniques and greater OCP usage. Infections are not major causes of CVST, perhaps because of improved national health services. Unlike other studies in the Middle East region, Behçet's disease was not a frequent predisposing factor for CVST in Iran.

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