



Clinical Features of Cerebral Venous Sinus Thrombosis

Serebral Venöz Sinüs Trombozunun Klinik Özellikleri

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Abstract

Objective: To investigate the predisposing factors for cerebral venous sinus thrombosis (CVST), presenting patterns of the disease, imaging characteristics, types of treatment, and outcomes of patients.

Materials and Methods: Retrospectively, between April 2011 and September 2016 at Eskisehir Osmangazi Stroke Center, the demographic data, symptoms and findings, neuroimaging and laboratory findings of patients with CVST were collected. Additionally, predisposing factors for the disease, treatment strategies, and the neurologic functions of patients at discharge were examined.

Results: Thirty-one patients with CVST were included in the study, 25 of whom were female. The mean age of the patients was 43.7 years (standard deviation: 16.4; range, 22-78 years). The most common symptom was headache and the most common predisposing factors were pregnancy and puerperium. Also, transverse sinus was the most common thrombosed sinus. In the majority of patients (29/31, 93.6%), anticoagulation was applied and the Modified Rankin Scale score was 2 or below.

Conclusion: In this study, we detailed the characteristics of patients with CVST at our stroke center and contrary to previous knowledge, we showed that the outcomes of patients were good. However, to achieve more accurate conclusions about treatment strategies and outcomes, we need prospective studies with larger cohorts.

Keywords: Venous thrombosis, sinus thrombosis, stroke, stroke subtype

Öz

Amaç: Serebral venöz sinüs trombozunun (SVST) altında yatan nedenleri, hastalığın karşımıza çıkış şekillerini, görüntüleme özelliklerini, tedavi tiplerini ve hastaların akıbetlerini araştırmayı amaçladık.

Gereç ve Yöntem: Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, Nöroloji İnme Merkezi'nde Nisan 2011-Eylül 2016 tarihleri arasında SVST tanısı ile takip ettiğimiz hastaların demografik verileri, başvuru belirti ve bulguları, nörogörüntüleme ve laboratuvar incelemeleri, hastalığın altında yatan nedenleri, tedavi şekillerimiz ve yine hastaların hastaneden çıkarıldıkları sıradaki nörolojik fonksiyonları geriye dönük olarak incelendi.

Bulgular: SVST tanılı 25'i kadın toplam 31 hasta çalışmaya dahil edildi. Hastaların yaş ortalaması 43,7 idi (standart sapma: 16,4 değişim aralığı: 22-78). En sık görülen belirti baş ağrısı olup, en sık alta yatan nedenler gebelik ve lohusalık, en sık tutulan sinüs ise transvers sinüs idi. Hastaların büyük kısmının (29/31, %93,6) antikoagüle edildiği ve taburcu edildikleri sıradaki Modifiye Rankin Skala skorlarınının 2 ya da altında olduğu görüldü.

Sonuç: Bu çalışmada inme merkezimizde takip ettiğimiz SVST tanılı hastaların özelliklerini inceledik ve hastaların akıbetlerinin önceden sanılanın aksine iyi olduğunu gösterdik. Ancak, tedavi şekilleri ve hastalığın akıbeti ile ilgili daha kesin sonuçlara ulaşabilmek için daha geniş kohortlu ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Venöz tromboz, sinüs trombozu, inme, inme alt tipi

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Introduction

Cerebral venous sinus thrombosis (CVST) is a rare type of cerebral vascular disorder that constitutes 0.5-1% of all strokes (1,2). According to data gathered related with hospitalized patients, the incidence of CVST is approximately 2/100,000/years (3,4,5). CVST is often caused by malignancy, infection, pregnancy, puerperium, systemic diseases, dehydration, oral contraceptive (OCs) use, and coagulopathy; however, the etiology is unknown in 30% of patients (6,7,8). CVST frequently affects young adults and females account for 75% of these patients (9). Hormonal factors and OCs use are thought to cause the female dominance in CVST (10,11).

Occlusion of one or more dural venous sinuses can cause brain edema, increased intracranial pressure, hydrocephalus, cerebral hemorrhage or infarction, and even death (12). The mortality rate in patients with CVST is 5-30% (13,14). Patients with mild CVST are treated with systemic anticoagulants. Local or systemic thrombolysis is recommended in patients with CVST who worsen despite systemic anticoagulation (15,16,17,18). The most appropriate treatment for CVST is not yet clear. Research on the topic is ongoing and new results increase our knowledge. In this study, we aimed to evaluate the demographic features, risk factors, presentations, radiologic features, and outcomes of CVST in patients who were followed up in our clinic.

Materials and Methods

Patients who were hospitalized with CVST in the Stroke Center of Eskişehir Osmangazi Faculty of Medicine, Eskişehir Osmangazi University, between April 2011 and September 2016 were included in the study and were evaluated retrospectively. All medical records are stored electronically in our center. Patients who had CVST findings in cranial magnetic resonance (MR) venography were contacted and their medical records were evaluated. Demographic features, presenting symptoms and findings, underlying factors and related history, neuroimaging findings, factors that could lead to coagulopathy, laboratory investigations including thyroid function tests, performed treatments, and neurologic examinations at discharge were retrospectively gathered from their medical records. With the exception of two patients because of pregnancy, other patients received a verified diagnosis after cranial MR imaging (MRI) combined with cranial MR venography and/or conventional cerebral angiography, brain computed tomography (CT) was performed in all patients. Neuroimaging materials were investigated for the number of thrombosed veins, topography of venous thrombosis, presence of hemorrhage, and brain injury related with congestion. The Modified Rankin Scale (mRS) was calculated for patients at discharge.

The study was approved by the Eskişehir Osmangazi University Faculty of Medicine of Local Ethics Committee (Protocol number/date: 11/09.01.2017).

Statistical Analysis

Categorical variables are shown as frequency distribution and percentage. The chi-square test was used to compare categorical variables. The independent sample t-test was used to compare the mean values of the two groups with normally distributed data. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS

Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for statistical analysis. A p value of <0.05 was considered significant.

Results

Thirty-one patients (25 females, 6 males) with CVST were included in the study. The mean age of the patients was 43.7 years (standard deviation: 16.4; range, 22-78 years). The most frequent presenting symptoms were headache (64.5%) and seizure (35.5%). Nine (29%) patients only presented with headache (Table 1). The laboratory findings, risk factors, and history of the patients revealed an etiology in most patients: pregnancy and puerperium in 8 (35.8%) patients, systemic disease in 7 (22.6%), coagulation disturbance in 4 (12.9%), malignancy in 3 (9.7%), OCs use in 1 (3.2%), trauma in 1 (3.2%), cranial surgery in 1 (3.2%), and infection in 1 (3.2%) patient. Etiology was unknown in 5 (16.1%) patients (Table 2). The mean age of patients with malignancy was higher compared with other patients (p=0.01). Cranial MRI showed hemorrhagic venous infarction in 13 (41.9%) patients,

Table 1. The presenting symptoms of patients with cerebral venous sinus thrombosis

Symptoms	n	%
Headache	20	64.5
Seizure	11	35.5
Motor disturbance	8	25.8
Visual disturbance	6	19.4
Impairment of consciousness	2	6.5
Sensorial disturbance	1	3.2
Speech disturbance	1	3.2

Table 2. The etiologies of patients with cerebral venous sinus thrombosis

Etiology	n
Pregnancy and puerperium	8
Systemic disease	7
Systemic vasculitis	6
Essential thrombocytosis	1
Coagulation disturbance	4
Protein C deficiency	1
Factor V Leiden mutation (homozygous)	2
MTHFR gen mutation (homozygous)	1
Malignancy	3
OCs usage	1
Trauma	1
Infection	1
Postoperative	1
Unknown	5

OC: Oral contraceptives, MTHFR: Methylene tetrahydrofolate reductase

non-hemorrhagic venous infarction in 3 (9.7%), other intracerebral hemorrhages (subarachnoid hemorrhage and parenchymal hemorrhage) in 4 (12.9%), and hemorrhagic venous infarction and other intracerebral hemorrhages together in 2 (6.5%) patients. Cranial MRI was normal in 9 (29%) patients. Transverse sinus was the most frequently thrombosed sinus in MR venography (24/31, 77.4%). In 16 (51.6%) patients, only one sinus was thrombosed; two sinuses were affected in 7 (22.6%) patients, and three or more sinuses were thrombosed in 8 (25.8%) patients (Table 3).

Most of the patients were anticoagulated (29/31, 93.6%). In 22 patients who were anticoagulated, low-molecular-weight heparin (LMWH) was used (1 mg/kg subcutaneous, once every 12 hours),

unfractionated heparin (UFH) was used (800-1400 U/hour, at a dose to keep aPTT 1.5-2.5 times the normal level) in 7 patients. In 10 patients, oral anticoagulant treatment was used following LMWH or UFH. Endovascular treatment was performed in a patient who was resistant to anticoagulation. Antiplatelet treatment was used in one patient using OCs, and one patient with unknown cause who presented with only headache and had only one thrombosed sinus. In addition to these treatments, antiepileptic drugs for seizures and mannitol to decrease intracranial pressure were used, and decompression surgery and extraventricular drainage were performed in one patient each.

The neurologic status of the patients at discharge was evaluated using the mRS; the mean mRS score was 0.48. Eighty-four percent of patients (26/31) fully recovered, mRS was ≤ 2 in 93.6% of patients (29/31). Outcomes were worse in patients with hemorrhagic venous infarction + other intracerebral hemorrhages compared with the other patients ($p=0.042$). There was no relationship between other demographic and clinical features and outcomes of the patients ($p>0.05$).

One of the patients included in the study is presented below.

Case: A woman aged 22 years was admitted to the emergency department with headache, which she had had for 3 days, and sudden deterioration of consciousness. She was confused in the neurologic examination. She had given birth 10 days previously. "Dens cord" sign was found in the superior sagittal sinus, transverse sinus, and sinus rectus in cranial CT (Figure 1). The superior sagittal sinus, sinus rectus, right transverse sinus, right sigmoid sinus, and right jugular vein could not be visualized in MR venography. The patient was hospitalized in the intensive care unit (ICU) and UHF and anti-edema treatment were initiated. She had a generalized tonic clonic seizure and anti-epileptic treatment was initiated. During her stay in the ICU, her state of consciousness worsened and she was intubated. There was no new hemorrhage or infarction in follow-up cranial CT. Cerebral angiography was performed for endovascular treatment. Following a right common carotid injection, the superior sagittal sinus, bilateral transverse sinuses, and sinus rectus could not be seen in venous phase. The left transverse sinus and superior sagittal sinus were reached via the left jugular vein. Recombinant tissue plasminogen activator

Table 3. The imaging findings of patients with cerebral venous sinus thrombosis		
Imaging findings	n	%
Intracerebral lesions		
Normal	9	29
Hemorrhagic venous infarction	13	41.9
Non-hemorrhagic venous infarction	3	9.7
Other intracerebral hemorrhages	4	12.9
Hemorrhagic venous infarction + other intracerebral hemorrhages	2	6.5
Thrombosis of one sinus		
Transverse sinus	9	29
Superior sagittal sinus	6	19.4
Inferior sagittal sinus	1	3.2
Thrombosis of two sinuses		
Superior sagittal + transverse sinuses	3	9.7
Transverse + sigmoid sinuses	4	12.9
Thrombosis of three or more sinuses		
Superior sagittal + transverse + sigmoid sinuses	3	9.7
Superior sagittal + transverse + rectus + sigmoid sinuses	5	16.1

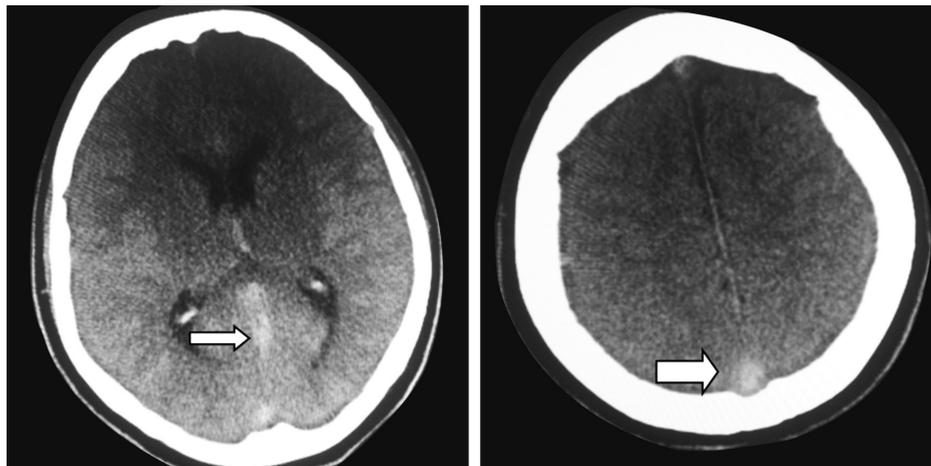


Figure 1. "Dens cord" sign in sinus rectus (thin arrow) and superior sagittal sinus (thick arrow)

was given through a microcatheter. Continuous aspiration was then performed using a “penumbra” device. Recanalization of the superior sagittal sinus was observed. Aspiration was repeated in the right jugular vein. Thiopental infusion was administered for 24 hours and then stopped by decreasing the dose in ICU. Forty-eight hours after the procedure, the patient’s level of consciousness improved and she was extubated. Thrombophilia panel and vasculitis tests were normal. Warfarin was initiated following UFH, which was administered 24 hours after endovascular treatment. In follow-up MR venography, flow signal was seen despite some irregularities in the superior sagittal sinus, right transverse sinus, right sigmoid sinus, right jugular vein, left sigmoid sinus, and left jugular vein, which was interpreted as the former thrombosis. The mRS score was 0 at discharge and warfarin treatment was planned to continue for 1 year.

Discussion

CVST is more frequent in young adults compared with arterial stroke. The mean age of patients was 43.7 years (standard deviation: 16.4; range, 22-78 years) in our study (17,19). Similar to other studies, female dominance with a rate of 80.6% was revealed in our study (2,9).

Headache is the most frequent symptom. It could be the only symptom or the front runner of other symptoms (20,21). Headache is caused by an increase in intracranial pressure due to impairment of venous drainage (22) and it was the most frequent symptom with a rate of 64.5% in our study. Visual disturbance was the most accompanying symptom in our study and it was thought to be related with increased intracranial pressure because the patients with headache also had papilledema. Seizure and motor disturbance were the most frequent symptoms after headache, respectively. Seizures were found in 50% of patients with motor disturbances and motor disturbances improved after seizures were controlled. Thus, motor disturbances were thought to be secondary to seizures.

The transverse sinus (77.4%) and superior sagittal sinus (58.1%) were the most frequently thrombosed sinuses in our study, similar to other studies (17,23). In 48.4% of our patients, two or more sinuses were thrombosed, but a combination of local infection and thrombosis of the transverse and sigmoid sinuses, which has been reported in other studies, was not found in our study ($p > 0.05$) (23).

The frequency of intracerebral hemorrhage (including hemorrhagic infarction) in patients with CVST was reported as 30-40% in other studies (17,18). There was no lesion in cranial imaging in 29% of patients. Intracerebral hemorrhages were found in 61.3% of patients (19/31), most of which (48.4%, 15/31) was venous hemorrhagic infarction. The intracerebral hemorrhage rate was higher compared with other studies. We found no relationship between etiologies and imaging findings. A cranial CT without contrast was performed in all our patients except two. Hemorrhagic infarction in cranial CT which does not fit with arterial territory and “Dens cord” sign suggesting a thrombosed vein, implies CVST (21,24,25). We found at least one of these CVST suggesting findings in 58.1% (18/29) of patients in our study.

Female dominance in CVST is thought to be related with pregnancy, puerperium, and OCs use (10,11). Pregnancy and

puerperium were the most frequent etiologies in our patients (25.8%, 8/31). In a recently published systematic analysis, this rate was found as 28.1%, which was similar to our finding (26). In the same analysis, the rate of OCs use was 38.4%, which was higher than our rate (3.2%). Women in developed countries use two times more OCs than women in developing countries (27). Our low rate of OCs use as an etiology in CVST could be caused by geographic/cultural differences. The second most frequent etiology in our study was systemic diseases, including systemic vasculitis in most patients (6/7). In a study with a large cohort, coagulation disturbance was detected in 22% of patients as an etiology in CVST (17). Coagulation disturbance was found as an etiology in CVST in 13% (4/31) of our patients, including 2 patients with a homozygous FV Leiden mutation, 1 patient with a homozygous methylenetetrahydrofolate reductase gene mutation, and 1 patient with protein C deficiency. Malignancy was detected in 9.7% (3/31) of our patients. The mean age of patients with malignancy was 66.3 years, which was higher compared with those without malignancy. The occurrence of malignancy in advanced age is expected.

Recent guidelines recommended anticoagulation (LMWH or UFH) in CVST, even if there is accompanying intracerebral hemorrhage or hemorrhagic transformation (21). We evaluated the treatment of our patients only in the acute period and found that 90.3% of all patients and all of the patients with a systemic disease or a coagulation disturbance were anticoagulated. ‘The International Study on Cerebral Vein and Dural Sinus Thrombosis’ compared patients who were anticoagulated with LMWH and UFH and found that outcomes of patients who were anticoagulated with UFH were better (28). We administered LMWH in 76% and UFH in 24% of the patients and found no difference between them in terms of outcomes. Age > 37 years, male sex, coma, seizure, intracranial hemorrhage on admission, thrombosis of the deep cerebral venous system, accompanying hematologic disorder, central nervous system infection, and malignancy were related with unfavorable treatment outcomes in a previous study (17). We found that only a combination of hemorrhagic venous infarction with intracerebral hemorrhage was related with unfavorable outcomes, and we found no relationship between other demographic and clinic data and outcomes.

Study Limitations

Our study has some limitations. We had a small number of patients, which presents a limited representation of the general population. Patients were retrospectively evaluated using their medical recordings, which prevented us from evaluating some of the patients’ long-term treatments and outcomes. A prospective study would reveal more precise data.

Conclusion

As a result, we analyzed risk factors, presenting symptoms and findings, imaging findings, treatments, and outcomes of patients with CVST in detail at our stroke center. Outcomes were favorable (mRS ≤ 2) in 93.6% of patients, which could be related with increased awareness about CVST and the changes in treatment strategies. Also, we found that hemorrhagic or non-hemorrhagic infarction had no effect on outcomes, and the relationship between

OCs use and CVST was weaker compared with other studies. Prospective studies with larger numbers of patients are needed to evaluate predictors of outcomes in CVST.

Ethics

Ethics Committee Approval: The study was approved by the Eskisehir Osmangazi University of Local Ethics Committee (Protocol number: 11/09.01.2017).

Informed Consent: Consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.S.E., A.Ö.Ö., Concept: E.S.E., A.Ö.Ö., Design: E.S.E., A.Ö.Ö., Data Collection or Processing: E.S.E., Analysis or Interpretation: E.S.E., A.Ö.Ö., Literature Search: E.S.E., Writing: E.S.E.

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References

- Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. *Lancet Neurol* 2007;6:162-170.
- Einhäupl K, Stam J, Bousser MG, De Bruijn SF, Ferro JM, Martinelli I, Masuhr F; European Federation of Neurological Societies. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. *Eur J Neurol* 2010;17:1229-1235.
- Ferro JM, Correlá M, Pontes C, Baptista MV, Pita F; Cerebral Venous Thrombosis Portuguese Collaborative Study Group (Venoport). Cerebral vein and dural sinus thrombosis in Portugal 1980-1998. *Cerebro Dis* 2001;11:177-182.
- Mak W, Mok KY, Tsoi TH, Cheung RT, Ho SL, Chang CM. Cerebral venous thrombosis in Hong Kong. *Cerebro Dis* 2001;11:282-283.
- Janghorbani M, Zare M, Saadatnia M, Mousavi SA, Mojarrad M, Asgari E. Cerebral vein and dural sinus thrombosis in adults in Isfahan, Iran: Frequency and seasonal variation. *Acta Neurol Scand* 2008;117:117-121.
- Bousser MG, Chiras J, Borjes J, Castaigne P. Cerebral venous thrombosis-a review of 38 cases. *Stroke* 1985;16:199-213.
- Bousser MG. [Cerebral venous thrombosis. Report of 76 cases]. *J Mal Vasc* 1991;16:249-254.
- de Bruijn SF, de Haan RJ, Stam J. Clinical features and prognostic factors of cerebral venous sinus thrombosis in a prospective series of 59 patients. For The Cerebral Venous Sinus Thrombosis Study Group. *J Neurol Neurosurg Psychiatry* 2001;70:105-108.
- Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005;352:1791-1798.
- Coutinho JM, Ferro JM, Canhao P, Barinagarrementeria F, Cantu C, Bousser MG, Stam J. Cerebral venous and sinus thrombosis in women. *Stroke* 2009;40:2356-2361.
- Dentali F, Crowther M and Ageno W. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. *Blood* 2006;107:2766-2773.
- Tsai FY, Higashida RT, Matovich V, Alfieri K. Acute thrombosis of the intracranial dural sinus: direct thrombolytic treatment. *AJNR Am J Neuroradiol* 1992;13:1137-1141.
- Sebire G, Tabarki B, Saunders DE, Leroy I, Liesner R, Saint-Martin C, Husson B, Williams AN, Wade A, Kirkham FJ. Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. *Brain* 2005;128:477-489.
- Schwarz S, Daffertshofer M, Schwarz T, Georgiadis D, Baumgartner RW, Hennerici M, Groden C. Current controversies in the diagnosis and management of cerebral venous and dural sinus thrombosis. *Nervenarzt* 2003;74:639-653.
- Wasay M, Bakshi R, Kojan S, Bobustuc G, Dubey N, Unwin DH. Nonrandomized comparison of local urokinase thrombolysis versus systemic heparin anticoagulation for superior sagittal sinus thrombosis. *Stroke* 2001;32:2310-2317.
- Ferro JM. Causes, predictors of death, and antithrombotic treatment in cerebral venous thrombosis. *Clin Adv Hematol Oncol* 2006;4:732-733.
- Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F; ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004;35:664-670.
- Ferro JM, Crassard I, Coutinho JM, Canhão P, Barinagarrementeria F, Cucchiara B, Derex L, Lichy C, Masjuan J, Massaro A, Matamala G, Poli S, Saadatnia M, Stolz E, Viana-Baptista M, Stam J, Bousser MG; Second International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT 2) Investigators. Decompressive surgery in cerebrovenous thrombosis: a multicenter registry and a systematic review of individual patient data. *Stroke* 2011;42:2825-2831.
- Ferro JM, Canhao P, Bousser MG, Stam J, Barinagarrementeria F; ISCVT Investigators. Cerebral vein and dural sinus thrombosis in elderly patients. *Stroke* 2005;36:1927-1932.
- Dodick D. Thunderclap headache. *Headache* 2002;42:309-315.
- Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY; American Heart Association Stroke Council and the Council on Epidemiology and Prevention. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:1158-1192.
- Wang JW, Li JP, Song YL, Tan K, Wang Y, Li T, Guo P, Li X, Wang Y, Zhao QH. Clinical characteristics of cerebral venous sinus thrombosis. *Neurosciences (Riyadh)* 2015;20:292-295.
- Damak M, Crassard I, Wolff V, Bousser MG. Isolated lateral sinus thrombosis a series of 62 patients. *Stroke* 2009;40:476-481.
- Agrawal K, Burger K, Rothrock JF. Cerebral Sinus Thrombosis. *Headache* 2016;56:1380-1389.
- Leach JL, Fortuna RB, Jones BV, Gaskill-Shiple MF. Imaging of cerebral venous thrombosis: current techniques, spectrum of findings, and diagnostic pitfalls. *Radiographics* 2006;26(Suppl 1):19-41.
- Zuurbier SM, Saskia Middeldorp S, Stam J and Coutinho JM. Sex differences in cerebral venous thrombosis: A systematic analysis of a shift over time. *Int J Stroke* 2016;11:164-170.
- World contraceptive use 2011. United Nations, department of economic and social affairs, population division. http://www.un.org/esa/population/publications/contraceptive2011/wallchart_front.pdf (2011, accessed 1 July 2015).
- Coutinho JM, Ferro JM, Canhao P, Barinagarrementeria F, Bousser MG, Stam J; ISCVT Investigators. Unfractionated or low molecular weight heparin for the treatment of cerebral venous thrombosis. *Stroke* 2010;41:2575-2580.