http://www.banglajol.info/index.php/JNINB

Original Article

DOI: https://doi.org/10.3329/jninb.v11i1.83474

Journal of National Institute of Neurosciences Bangladesh,
January 2025, Vol. 11, No. 1, pp. 13-18

ISSN (Online) 2518-6612
ISSN (Print) 2410-8030

Etiological Factors of Patients Presented with Cerebral Venous Sinus Thrombosis attended at Referral Neuroscience Hospital in Bangladesh

Md. Merazul Islam Shaikh[1], Md. Zakirul Islam[2], Mohammad Enayet Hussain[3], Abdullah Al Mamun[4], Md Azharul Hoque[5], Atiqur Rahman[6], Dipa Saha[7]

[1]Assistant Professor, Department of Neurophysiology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [2]Associate Professor (Medicine), National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [3]Associate Professor, Department of Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [4]Assistant Professor, Department of Neurophysiology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [5]Former Head and Professor of Clinical Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [6]Assistant Professor (Endocrinology), National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [7]Associate Professor, Pediatric Neurology, Addin Women's Medical College, Dhaka, Bangladesh

Abstract

Background: Cerebral venous sinus thrombosis (CVST) is an uncommon form of stroke with diverse clinical presentation, predisposing factors, brain imaging findings, and outcome. **Objectives:** The objective of the study was to evaluate the risk factors associated with cerebral venous sinus thrombosis and hospital outcome of patients treated conservatively with medical management. Methodology: This prospective observational study was conducted in the inpatient department of neurology at national institute of neurosciences and hospital, Dhaka, Bangladesh over a period of 18 months, from June 2017 to December 2018. Total 50 Patients fulfilling the inclusion & exclusion criteria, were included in this study. All the study patients were evaluated clinically and routine laboratory investigation, specific investigation to confirm the diagnosis of venous sinus thrombosis along with special investigation to find out possible risk factors were done. All patients after diagnosis of venous thrombosis medical treatment with LMWH were given. Results: A total of 50 patients of CVST were included with age more than 18 years. Among them 34 (68%) were females and 16 (32%) were males with average age 28.48 ± 9.55 years in both sexes. Out of 50, 48(96%) patients were presented with symptoms of headache, of total 44(88%) had vomiting and 30(42%) had blurring of vision or double vision, 11 (22%) had Seizures, 12(24%) had altered level of consciousness and limb weakness was observed only 10 (20%) patients. Most common risk factors were Oral contraceptive pill (OCP), which was 25 (78.1%) and puerperium 8(23.1%) among females, infections were 11(22%) and no risk factors were found among 11(22%) of study patients overall. Both superficial and deep venous system were involved. Transverse sinus was most commonly involved and was involved 45 (90%) patients. Mean hospital stay was 12.46 days, most of the patient had significant improvement of symptoms and signs during discharge from hospital after treatment, only 4(8%) patients were died. Conclusion: Cerebral venous sinus thrombosis is a uncommon form of stroke, early diagnosis can be made with high degree of clinical suspicion and available neuroimaging, mortality and morbidity can be reduced by early diagnosis and initiation of treatment. *[Journal of National Institute of Neurosciences Bangladesh, January 2025;11(1):13-18]*

Keywords: Cerebral Venous Sinus Thrombosis; Headache; puerperium; MR Venogram, OCP; Seizure.

Introduction

Cerebral venous sinus thrombosis constitutes a rare cause of stroke; overall incidence is approximately 0.5% to 1.0% cases of all strokes[1]. The venous system contains 70.0% of the cerebral blood volume and is of importance for normal cerebral circulation[2]. The incidence is higher in developing countries. Sometime over diagnosis or under diagnosis happened due to lack of knowledge, clinical exposure and expert radiological opinion for final diagnosis. It usually affects young individuals, caused by a number of prothrombotic states (congenital or acquired) such as deficiencies in anticoagulation-promoting proteins, usage of oral contraceptives, pregnancy, dehydration, trauma,

Correspondence: Dr. Md. Merazul Islam Shaikh, Assistant Professor (Neurophysiology), National Institute of Neurosciences and Hospital, Sher-E-Bangla Nagar, Agargaon, Dhaka-1207, Bangladesh; Email: meraz39rmc@gmail.com; Cell no.: +8801716034806; ORCID: https://orchid.org/0009-0008-1274-1304

inflammatory diseases, infections and many hematological conditions. It is an important cause of stroke especially in the peripartum period and in the young female. In about 30.0% cases no underlying etiology is identified[3].

The clinical presentations are extremely variable and nonspecific, making the diagnostic difficulties. Symptoms are usually related to the area of sinus involved. Patient commonly presented with headache, vomiting, visual loss, focal or generalized seizures, focal neurologic deficits, confusion, altered consciousness and coma[4,5.] Most common findings are papilledema and focal neurological signs-including focal seizures[6,7]. A high degree of clinical suspicion in the setting of common presenting symptoms and signs that helps in early diagnosis. Mortality rate ranges from 5.5-30%[7] which depends upon time of presentation initiation of management, Ferro et al. showed a mortality rate of 4.3% at the acute phase and 8.3 % at 16 months follow-up[8].Transtentorial herniation due to a unilateral focal mass effect or to diffuse edema and multiple parenchymal lesions were independent predictors of death.

The new and modern means of investigation mostly development of neuroimaging helps in early diagnosis. MRI with MRV is the single most sensitive diagnostic technique[9,10,11,12,13]. Along with this various other laboratory investigation are necessary for establishing a diagnosis of CVST. Outcome depends upon several factors, with bilateral lesions, outcomes were unfavorable (50.0% of modified Rankin score (mRS) 4 or 5; or 42.0% to die) compared to 11.0% in unilateral lesions. Coma[14], mental disturbance of deep CVST thrombosis, right intracerebral hemorrhage and posterior fossa lesion[2] were also associated with poor outcome. The objective of the study was to evaluate the risk factors associated with cerebral venous sinus thrombosis and hospital outcome of patients treated conservatively with medical management.

Methodology

Study Settings and Population: This cross-sectional study was conducted from June, 2017 to November, 2018 in the Department of Clinical Neurology at the National Institute of Neurosciences and Hospital, Dhaka, Bangladesh. A total 50 patients were selected according to the selection criteria and after confirmation by laboratory and Neuroimaging test. Details of the study that included nature, purposes & procedure of the study, type of investigations & their risk, definite treatment and their side effects and management were well briefed to the patient and their attendant.

Study Procedure: Written consent was taken from patient or their legal attendant. Details history and meticulous examination were performed to collect the data according to the variable of interest. All necessary investigations were done at an optimum time. All the confirmed cases of CVST were investigated with complete blood count, renal function tests, liver function tests, prothrombin time, activated partial thrombin time, antinuclear antibodies, antiphospholipid antibodies, procoagulant states like protein C, protein S, antithrombin III and serum homocystine with aim to detect underlying etiology. Patients were treated as per available guidelines. Data recorded during discharge from hospital were disability according to modified Rankin Scale (mRS), death. Outcome was dichotomized as good (mRS score 0-2) and poor (mRS >2) in the study. D-dimer levels measured before the initiation of anticoagulant treatment. D-dimer was categorized as positive (>0.5 mg/L and negative(<0.5mg/L).

Statistical Analysis: Statistical analysis was performed by Windows based software named as Statistical Package for Social Science (SPSS), versions 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous data were expressed as mean, standard deviation, minimum and maximum. Categorical data were summarized in terms of frequency counts and percentages. Chi-square test was used for comparison of categorical variables and Student t test was applied for continuous variables. Every efforts were made to obtain missing data. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

Ethical Consideration: All procedures of the present study were carried out in accordance with the principles for human investigations (i.e., Helsinki Declaration 2013) and also with the ethical guidelines of the Institutional research ethics. Formal ethics approval was granted by the local ethics committee (Ref: IRB/NINS/19, 07.03.2017). Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and were analyzed using the coding system.

Results

A total of 50 patients (34 females and 16 males) were included in this study. Baseline analysis were performed. Average hospital stay was 12.46 ± 3.81

days. The mean age was 28.48± 9.55 years with a range from 18 to 65 years. Majorities were in the age group 21-40 years. most of the study patients were female 34(68%) & were house wife 29(55.8%). BMI range of the study population was 25-29.9 kg/m2 (Table 1).

Table 1: Demographic Profile among the Study Cases (n=50)

Variable	Values
Mean Age ±SD Years	28.48 ± 9.55
Gender (M:F)	
• Male	16
• Female	34
• M:F	1:2.1
BMI (Kg/m^2)	
• Less than 24.9	7
• 25 to 29.9	40
• 30 to 39.9	3
Occupation	
• Housewife	29
• Student	11
• Service	8
• Business	2
Educational status	
• Illiterate	5
• Primary	8
• Secondary	18
• Higher Secondary	10
• Graduate	11.5
• Post-Graduate	3
Monthly income	
• <10000	11
• 10000-20000	17
• 200000-30000	15
• >30000	7

Among all the identified risk factors, OCP was found to be the most common which was, 25 (78.1%) of the study participant. Infection was the second most common one, which was 11(22%). Of the other identified risk factors, puerperium, pregnancy & dehydration were found as 8 (23.1%), 3 (8.8%) and 1 (2.0%) respectively (Table 2).

Among other etiological factors protein C, protein S, antithrombin III deficiency and ANA were positive as 03, 04, 01 and 02 cases respectively. Hyper-homocystinemia was found among 7 cases. No identifiable etiological factors were found among 11(22.0 %) of study patients. Headache and vomiting were the most common presenting symptoms, present in 48 (96.0%) and 44 (88.0%) cases respectively. Papillo-edema was the most common neurological sign, seen in 34 (78.0%) patients with majority had bilateral involvement. Blurring of vision and double vision were found as 15 (30.0 %) and 9 (18.0 %) respectively. About 11(22.0%) of patients had had generalized seizure, 12(24.0%) with altered level of consciousness and 10(20.0%) of patient had had limb weakness at the time of diagnosis in the form of hemiparesis, monoparesis or quadriparesis (Table 3).

Table 2: Underlying etiological Factors of CVST among the Study Cases (N=50)

Etiological Factors	Frequency	Percent
OCP ingestion (34)	25	78.1
Pregnancy (34)	3	8.8
Puerperium (34)	8	23.3
Dehydration	1	2.0
Infection	11	22.0
Protein C∗	3	8.8
Protein S∗	4	9.1
Anti-thrombin III∗	1	2.0
ANA	2	3.8
pANCA	0	0.0
cANCA	0	0.0
Homocysteine∗	7	19.6
Anti-phospholipid antibody∗	0	0.0
Others	11	22.0

∗not done in all participant; OCP= oral contraceptive pill, pANCA= perinuclear anti-neutrophil cytoplasmic antibodies, cANCA= cytoplasmic antineutrophil cytoplasmic antibody.

Table 3: Clinical Profiles of the Study Cases (N=50)

Clinical features	Frequency	Percent
Headache	48	96.0
Vomiting	44	88.0
Double vision	9	18.0
Blurring vision	15	30.0
Generalized seizure	11	22.0
Altered consciousness	12	24.0
Limb weakness		
• Monoparesis	1	2.0
• Hemiparesis	8	16.0
• Quadriparesis	1	2.0
Fundoscopic findings	34	78.0

Cranial nerves are frequently involved in CVST which was 35 (70.0%) of the study participant. Among them optic nerve involvement was 22(44.0%), 6th cranial nerve was 16 (16.0%) both unilateral and bilateral, other cranial nerves involvement were 3(6.0%). Altered level of higher psychic function was found to had 12(24.0) of

cases (Table 4).

Table 4: Cranial Nerves Involvement Among the Study Cases (N=50)

Variables	Frequency	Percent
Altered higher psychic function	12	24.0
Cranial nerve involvement		
• Optic nerve	22	44.0
• Unilateral III nerve	2	4.0
• VI nerve palsy		
o Unilateral	8	16.0
o Bilateral	8	16.0
Other cranial nerve palsy	3	6.0

Brain imaging was done in all patients. Transverse sinus was the most commonly involved in 45(90.0%) of cases. Next was the superior sagittal sinus which was found to be involved in 39(78.0%) of cases. Involvement of the other sinuses in-accordance of their frequency are Sigmoid sinus, Straight sinus, Inferior sagittal sinus, vein of Gallen and Cavernous sinus (Figure I).

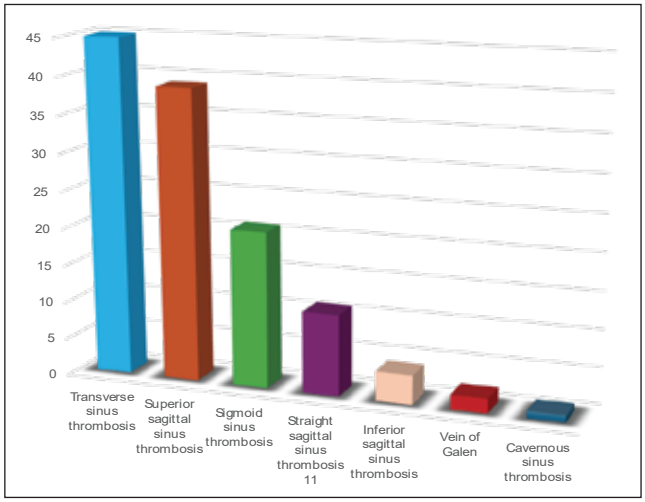

Figure I: Bar diagram showing commonly involved sinuses with their frequency

Majority of study patient had two sinus involvement 25 (50%), next was three sinus involvement 11 (22%), lastly was single and four sinus involvement it was 6 (12%) in both cases (Table 5).

Table 5: No of Venous Sinuses Involved in Study Cases (N=50)

No of Sinus Involved	Frequency	Percent
01	6	12.0
02	25	62.0
03	11	84.0
04	6	96.0
05	2	100.0
Total	**50**	**100.0**

Discussion

CVST is reported to be more common in developing countries, and has been linked to pregnancy, OCP ingestion, dehydration, and infections. Early diagnosis and management is now possible with the help of advanced neuroimaging and laboratory facilities. This study aims to describe the demoghraphic & etiological factors and clinical presentation, type and number of venous sinuses involved. CVST represents 0.5%-1% of all strokes. Regarding demographic data this study shows 34 (68.0%) of them are female. The mean age of male was 28.18 ± 8.89 (min = 19, max = 45) and the mean age of female was 29.76 ± 9.35 (min = 18, max = 50). Most of the patients were between 20 and 40 years old, Jalili et al[16] showed most of the study patient age range was between 25 and 35 and maximum age was72 years.

This study is not consistent with the age group affected possibly due to small sample size and low average life span of our country and early age at marriage and use of OCP may be the cause of at early presentation. However, Patil et al[15] shows 78.0% cases of patients were younger than 50 years, which is consistent with this study. Jalili et al[16] shows majority of the CVST patients were female 85.5%,[16] findings of this study is also similar to that. In this study clinical presentations are headache 48(96.0%), vomiting 44(88.0%), visual complaints 24(48.0%) and 11(22.0%) have seizure at presentation which are similar to other study, Patil et al15 and Yadav et al[17]. Gunes et al[18] state that papilledema has the most frequent physical sign, in this study among neurological signs papilledema is 34(68.0%) which is consistent with the previous study and majority have bilateral papilledema which is also consistent with that study[18]. This study shows females who are using OCP, 25 (78.0%) out of 34 develop cerebral venous sinus thrombosis which is consistent with the findings of Jalili et al[16], where OCP was found as a etiological factors in about 66.03% cases. This study shows females are also developed CVST more during puerperium 8 (23.0%) and pregnancy 3 (8.8%) among all female cases.

In this study homocystine was done only 25 patients among them 7(14.0%) patients homocystine was elevated, which does not match with other study, which show 24.0% have elevated homocystine level[15], this is possibly due to small sample size. In the present study, 20(40.0%) of cases are anaemic which is higher 26.7% of the cases in other study[16], than other studies possibly due to nutritional deficiency, multiparity and

other factors. Present study shows no identifiable etiological factors for cerebral venous sinus thrombosis among 11(22.0%) cases which is higher than previous study which was only 8.0% cases[17]. This may be due to small sample size and financial constrain for doing some costly investigations.

In this study 46 (92.0%) cases are with high D-dimer level which is nearly consistent with other study, 87.0%, Pfefferkorn et al[19]. Neuro-imaging is the cornerstone in the diagnosis of cerebral venous sinus thrombosis. Imaging modalities of choice in CVST are CT scan and MRI with MR venogram. CT scan may be normal in 15.0% to 30.0% cases but MRI with MRV is almost 100.0% diagnostic[17], in this study only 28(56.0%) have CT brain abnormality and 100.0% of patient have MRV abnormality which is consistent with previous study. MRV findings of the study patients shows most commonly involved sinus is transvers sinus 45(90.0%), superior sagittal sinus is 39 (78.0 %), sigmoid sinus involvement is 21(42.0 %) and straight sinus involvement is 11 (22.0%). Others studies also have similar result[18,20]. In this study multiple sinus involvement are 36 (72.0%) cases and single sinus involvement is only 12.0 %, whereas other studies show involvement of multiple sinuses were 66.7% cases[18] which is similar to the present study.

Prediction of risk of developing venous thrombosis among OCP user were risk of superior sagittal sinus thrombosis P value was (P= 0.047) which was statistically significant this also similar to other study done outside Bangladesh[18,20]. All patients are treated with standard protocol for CVST. All patients were treated with low molecular weight heparin (LMWH). 92.0% stabilized and later improved. Heparin was then switched to oral anticoagulants; this study result is similar to other study[19]. Average hospital stay is 12.46±3.81days. Significant improvement of symptoms occurs at discharge. Cases with superior sagittal sinus and transverse sinus involvement bear poor outcome than other sinuses involvement. In this study, average mRS score at admission is more than 3 among 34 (68.0%) of the study cases, however during discharge average mRS score is less than 1 in 45 (90.0%) of cases. Only 4(8.0%) patients died. Yadav et al[17] shows 84.0% patients were discharged with partial and/or total recovery from illness, which is similar to this study result. In this study mortality is 4 (8.0%) which is similar to other study[17].

There are some limitations, this is a single Centre study which may not represent the whole population. Moreover, due to resource and financial limitations, genetic prothrombotic factors and uncommon hematological conditions were not possible to evaluate in all study patients which might influence study results. Lack of long term follow up, small sample size and multiple confounding variables could affect the study result.

Conclusion

Cerebral venous sinus thrombosis is an uncommon form of stroke. Most of the female patients of cerebral venous sinus thrombosis using OCP, infection also important etiological factors for CVST. Majority of patients are presenting with features of raised ICP and multiple cranial nerves are involved. Neuroimaging plays a crucial role for diagnosis; transvers venous sinus is most commonly involved. Early diagnosis and judicious treatment reduce morbidity and mortality of the disease.

Acknowledgements
None

Conflict of interest: Authors declared no conflict of interest.

Financial Disclosure
This research project was not funded by any organization.

Contribution to authors: Shaikh MMI, Islam MZ, Hussain ME conceived and designed the study, analyzed the data, interpreted the results, and wrote up the draft manuscript. Hussain ME, Mamun AA, Hoque MA involved in the manuscript review and editing. Mamun AA, Hoque MA, Rahman A conceived and manuscript writing. All authors read and approved the final manuscript.

Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Ethical approval for the study was obtained from the Institutional Review Board. As this was a prospective study the written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

How to cite this article: SShaikh MMI, Islam MZ, Hussain ME, Mamun AA, Hoque MA, Rahman A. Etiological Factors of Patients Presented with Cerebral Venous Sinus Thrombosis attended at Referral Neuroscience Hospital in Bangladesh. J Natl Inst Neurosci Bangladesh, 2025;11(1):13-18

ORCID:
Md. Merazul Islam Shaikh: https://orchid.org/0009-0008-1274-1304
Md. Zakirul Islam: https://orchid.org/0009-0002-9772-7152
Mohammad Enayet Hussain: https://orchid.org/0000-0002-0379-1923
Abdullah Al Mamun: https://orchid.org/0009-0005-8267-1848
Md Azharul Hoque: https://orcid.org/0000-0002-0370-4543
Atiqur Rahman: https://orchid.org/0000-0002-4077-5295
Dipa Saha: https://orcid.org/0000-0002-6338-6858

Article Info
Received on: 7 September 2024
Accepted on: 24 November 2024
Published on: 1 January 2025

References

1. Saposnik G, Barinagarrementeria F, Brown Jr RD, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158-92.
2. 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.
3. Tsai FY, Wang AM, Matovich VB, Lavin M, Berberian B, Simonson TM, et al. MR staging of acute dural sinus thrombosis: correlation with venous pressure measurements and implications for treatment and prognosis. American Journal of Neuroradiology. 1995;16(5):1021-9.
4. Ferro JM, Canhao P. Complications of cerebral vein and sinus thrombosis. Front Neurol Neurosci 2008:23:161-7.
5. Imtiaz KE, Rajpara S, Majeed T. Cerebral venous sinus thrombosis: a diagnosis not to be missed. British Journal of Hospital Medicine (2005). 2010;71(9):528-9.
6. Einhäupl K, Stam J, Bousser MG, De Bruijn SF, Ferro JM, Martinelli I, et al. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. European journal of neurology. 2010;17(10):1229-35.
7. Caprio F, Bernstein RA. Duration of anticoagulation after cerebral venous sinus thrombosis. Neurocritical care. 2012;16(2):335-42.
8. Schaller B, Graf R. Cerebral venous infarction: the pathophysiological concept. Cerebrovascular diseases. 2004;18(3):179-88.
9. Guenther G, Arauz A. Cerebral venous thrombosis: a diagnostic and treatment update. Neurología (English Edition). 2011;26(8):488-98.
10. Saposnik G, Barinagarrementeria F, Brown Jr RD, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158-92.
11. Rizzo L, Crasto SG, Rudà R, Gallo G, Tola E, Garabello D, et al. Cerebral venous thrombosis: role of CT, MRI and MRA in the emergency setting. La radiologia medica. 2010;115(2):313-25.
12. Linn J, Pfefferkorn T, Ivanicova K, Müller-Schunk S, Hartz S, Wiesmann M, et al. Noncontrast CT in deep cerebral venous thrombosis and sinus thrombosis: comparison of its diagnostic value for both entities. American journal of neuroradiology. 2009;30(4):728-35.
13. Liang L, Korogi Y, Sugahara T, Onomichi M, Shigematsu Y, Yang D, et al. Evaluation of the intracranial dural sinuses with a 3D contrast-enhanced MP-RAGE sequence: prospective comparison with 2D-TOF MR venography and digital subtraction angiography. American Journal of Neuroradiology. 2001;22(3):481-92.
14. Saadatnia M, Fatehi F, Basiri K, Mousavi SA, Mehr GK. Cerebral venous sinus thrombosis risk factors. International Journal of Stroke. 2009;4(2):111-23.
15. Patil VC, Choraria K, Desai N, Agrawal S. Clinical profile and outcome of cerebral venous sinus thrombosis at tertiary care center. Journal of neurosciences in rural practice. 2014;5(3):218.
16. Jalili M, Ghourchian S, Shahidi GA, Rohani M, Rezvani M, Zamani B. A study of factors associated with cerebral venous thrombosis. Neurological Sciences. 2013;34(3):321-6.
17. Yadav K, Dabla S, Sharma B, Yadav P, Kumar S, Juneja H. A study of clinical profile, risk factors and outcome in patients of cerebral venous sinus thrombosis. Headache. 2016;22:73-3.
18. Gunes HN, Cokal BG, Guler SK, Yoldas TK, Malkan UY, Demircan CS, et al. Clinical associations, biological risk factors and outcomes of cerebral venous sinus thrombosis. Journal of International Medical Research. 2016;44(6):1454-61.
19. Pfefferkorn T, Crassard I, Linn J, Dichgans M, Boukobza M, Bousser MG. Clinical features, course and outcome in deep cerebral venous system thrombosis: an analysis of 32 cases. Journal of neurology. 2009;256(11):1839-45.
20. Khealani BA, Wasay M, Saadah M, Sultana E, Mustafa S, Khan FS, et al. Cerebral venous thrombosis: a descriptive multicenter study of patients in Pakistan and Middle East. Stroke. 2008;39(10):2707-11.