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CLINICAL PROFILE AND RADIO-IMAGING FEATURES IN PATIENTS OF CEREBRAL VENOUS THROMBOSIS AT A TERTIARY CARE CENTRE - A CROSS-SECTIONAL STUDY

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Abstract

Background: Cerebral venous sinus thrombosis (CVST), one of the most common cause of stroke in young, is an alarming disease. Owing to the availability of newer imaging techniques and also the increased awareness amongst physicians and neurologists, there is an increase in the diagnosis of CVST. The purpose of this study is to identify the clinical and radiological features prompting towards diagnosis of cerebral~~ortical~~ vein thrombosis in our region.

Methodology- A cross-sectional study was conducted between November 2018 to November 2020 in tertiary care centre at NKP Salve Institute of Medical Science and Lata Mangeshkar Hospital, after institutional ethical committee clearance. Total 40 patients diagnosed with CVST were included in study. Their clinical profile at the time of hospitalization and their radiological features were studied and documented. **Results**- Among 40 subjects, Majority of the patients were in the age group of 26-40 years. Males were commonly affected than females in our study as against other studies. majority of the patients, aetiology was unprovoked thrombosis(77.5%) followed by infection (7.5%) and post-partum status. Higher frequency was seen in those with hyperhomocysteinemia. Most common presenting symptom was headache (72%) followed by paresis (37%), followed by seizures (20%). Multiple cranial nerve palsies (2.5%) were also noticed. Multiple sinuses were involved in our study population (30%) but most common being superior sagittal sinus (75%) followed by right and left transverse sinus.

Conclusions– Our study found that young males are more commonly affected than females. Unprovoked thrombosis was the major etiological factor with higher frequency in those with hyperhomocysteinemia. Headache is the most common presenting complaint. Multiple cranial neuropathies are also common in patients of CVST. High index of clinical suspicion along with MRI and MR venography, which are the most sensitive radio-diagnostic modality, early diagnosis is possible. Hence the prognosis of CVST patients improves significantly by early suspicion, early diagnosis by imaging and early treatment with anticoagulants which is the mainstay of therapy as against other types of strokes.

Keywords- Cerebral venous sinus thrombosis, hyperhomocysteinemia, stroke

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Introduction

Cerebral venous sinus thrombosis (CVST), is an alarming disease. CVST accounts for 0.5 % of all strokes, more common in young. Strokes in the young (<45 years) account for nearly 30% of all cases of stroke in India and CVST accounts for 10-20% of these cases (1). Approximated annual incidence is currently estimated to be 3-4 cases per million people. A prominent female preponderance is seen with almost 75% of cases being females attributed to hormonal factors and oral contraceptive use.

Owing to the availability of newer imaging techniques and also the increased awareness amongst physicians and neurologists, there is an increase in the diagnosis of CVST.

CVST is multifactorial. The use of oral contraceptive (OC) use, females in puerperium or pregnancy states and co-existence of infection, malignancy and prothrombotic conditions are the most frequent risk factors for CVST. Skin infections of the face are the most significant risk factor for thrombosis of the cavernous sinus. (2) Usually, an additional precipitating factor is present in patients with thrombophilia who develop CVST. Inherited prothrombotic tendencies such as factor V Leiden mutations, protein S and C and antithrombin III deficiencies account for up to 10 – 15% of the cases and are an important cause for CVST. Other risk factor includes hyperhomocysteinemia, anaemia, coagulopathy, pregnancy-related, vasculitis and malignancy.In some recent studies male preponderance was noted than females and was also often associated with a higher level of homocysteine (3).

CVST has a wide spectrum of symptoms, signs and mode of onset. In 50–80% of cases, the onset is subacute (over 48 h, but under 30 days); in a third of the patients the onset is acute (under 48 h), and in 7%, chronic (over 30 days). CVST must always be considered as a differential diagnosis in patients presenting with altered mental status associated with focal neurological deficits. Isolated symptoms such as headache, a single seizure or non-specific behavioural symptoms are also documented to be due to CVST (2,4). Focal neurological features such as hemiparesis and hemisensory disturbance, seizures with status epilepticus, impairment of level of consciousness and papilledema occur in a large number of cases of CVST. Superior sagittal sinus is most commonly involved in CVST followed by lateral sinus thrombosis. More than one sinus can be involved in 30-40% of cases (5,6). CT scan and MRI with MR venogram are the imaging modalities of choice in CVST.

Anticoagulation, control of seizures and management of increased intracranial pressure are the main therapeutic measures implied in clinical practice for the treatment of CVST. Treatment with DOAC (Direct Oral Anticoagulants) is associated with good clinical and radiographic outcomes and favourable safety profile (7).

Due to its wide range of presentation which can be frequently misleading, unpredictable course of the disease and the occasional treatment problems, CVST remains a challenge for the physician. The purpose of this study is to identify the clinical and radiological features prompting towards diagnosis of cortical vein thrombosis.

Methodology

A single centre, hospital-based, cross-sectional study was conducted at NKP Salve Institute of Medical Science and Research Centre and Lata Mangeshkar Hospital, Nagpur over 24 months between November 2018 to November 2020 and patients were enrolled during this period. We included 40 study subjects during the study period. All patients aged ≥ 18 years presenting to our Institute with clinical history like Headache, Seizures, Vomiting, focal neurological deficit, giddiness, altered sensorium, blurring of vision, fever and loss of consciousness with suspicion of CVST and confirming imaging features of cerebral venous thrombosis, were enrolled. However, patients with metabolic encephalopathy and cerebral arterial thrombosis were excluded. Institutional Ethics Committee approval was obtained before the commencement of

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the study. The data were collected after obtaining written informed consent from the patients. Meticulous history was taken, including symptoms suggestive of cerebral venous thrombosis were documented. All Patients with age ≥18 years with clinical features suggestive of CVST were subjected to Neuroimaging and those diagnosed with Cerebral Venous Sinus Thrombosis (CVST) were included in the study population.

Statistical Analysis

The data was processed and analysed using the IBM Statistical Packages for Social Sciences, SPSS software version 22. Shapiro-Wilk test was used to test for normality of the data. Results of continuous measurements was measured as frequency mean and standard deviation. Results of categorical measurements was measured as number (%). Chi-square test was test to measure association between various parameters. Spearman test is used to measure the correlation between Homocysteine and MCV values. P values of less than 0.05 is considered statistically significant.

Results

1. Socio-demographic characteristics –

Our study found that majority of the patients were in the age group of 26-40 years (42.5%). The mean age of the study population was 32.03 ± 13.25 years. majority of the patients were males (75%). Out of 10 female patients, postpartum status was present for 3 patients (30%). Socio demographic data is reflected in table 1.

Table 1: Shows Demographic characteristics of the patients who were diagnosed with Cerebral Venous Sinus Thrombosis (CVST) (n = 40).

Demographic data		Frequency	Percentages
Age	18-25 years	15	37.5
	26-40 year	17	42.5
	>40 years	8	20
	Total	40	100
Gender	Males	30	75
	Females	10	25
Reproductive Status	Postpartum females	3	30
	Non-pregnant females	7	70

Regarding aetiology and Risk factors –

Table 2 illustrates the distribution of study population based on aetiology and age groups. The major aetiology was unprovoked (77.5%); amongst which majority of the subjects were in the age group of 25-40 years. Out of 3 subjects with aetiology of infection, 2 subjects were in the age group of 26-40 years and 1 subject was in the age group of >40 years. All the 3 subjects with aetiology of post-partum origin were in the age group of 18-25 years. There was 1 subject each with aetiology as dehydration in the age group 18-25 years and drug induced in the age group of >40 years and head trauma in the age group of 26-40 years. There was no statistically significant association found.

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Table 2 Distribution of CVST patients based on aetiology

Aetiology		Age Group				Chi-Square	P
		18-25 Years	26-40 Years	>40 Years	Total		
Unprovoked	N	11	14	6	31	13.915	0.18 NS
	%	27.5%	35.0%	15.0%	77.5%		
Infection	N	0	2	1	3		
	%	0.0%	5.0%	2.5%	7.5%		
Post-Partum	N	3	0	0	3		
	%	7.5%	0.0%	0.0%	7.5%		
Dehydration	N	1	0	0	1		
	%	2.5%	0.0%	0.0%	2.5%		
Drug Induced	N	0	0	1	1		
	%	0.0%	0.0%	2.5%	2.5%		
Head Truama	N	0	1	0	1		
	%	0.0%	2.5%	0.0%	2.5%		
Total	N	15	17	8	40		
	%	37.5%	42.5%	20.0%	100.0%		

Chi-square test;*Statistically significant; p<0.05;NS-not-significant

Serum Homocysteine was normal (5-15µmol/L) in 2 patients. It was mildly elevated(15-25µmol/L) in majority of the patients (55.0%). and Severe and significantly elevated (50-500µmol/L) in 1 subject. Homocysteine was intermediately elevated (25-50µmol/L) in 37.5% of the patients. The mean Homocysteine level was 31.83 ± 12.77 as shown in figure no. 1

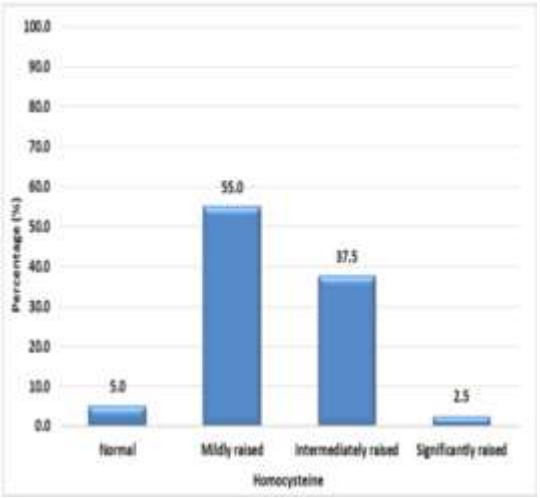

Figure no. 1 –Distribution of patients as per Homocysteine levels

Presenting signs and Symptoms

Most of the patients presented with Headache (72.5%) followed by paresis (37.5%). 22.5% presented with projectile vomiting with headache, 20.0% presented with convulsions, 20.0% presented with altered Sensorium 7.5% presented with non-projectile vomiting, 10.0% presented with fever. Figure no. 2 illustrates the distribution of study population based on presenting symptoms.

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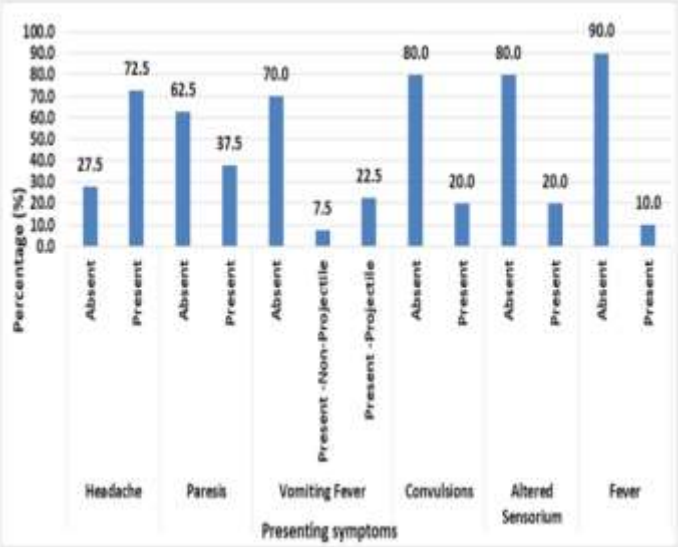

Figure no. 2: Distribution of study population based on presenting symptoms

On examination, 90.0% of the patients were conscious and normal speech was present in 80% of the patients. Impaired visual acuity was seen in 22.5% of the patients. Cranial nerve palsies were noted in 20% with multiple nerve involvement in 2.5% of the patients, Papilledema was present in 17.5% and there was 1 subject with gaze paresis as illustrated in Figure 3.

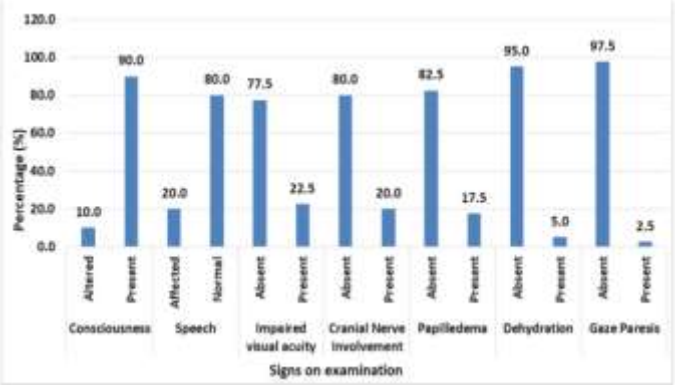

Figure 3: Distribution based on clinical presentations

Out of 8 patients with Cranial Nerve involvement, there were 2 patients with CN(cranial nerve) II involved, 4 patients with CN VII involvement and 1 subject with CN XII involvement. There was 1 subject with involvement of CNI, CNVI, CNVII, CNVIII, CVIX and CNX involvement each while 2.5% patients had multiple CN palsy as reflected in figure 4

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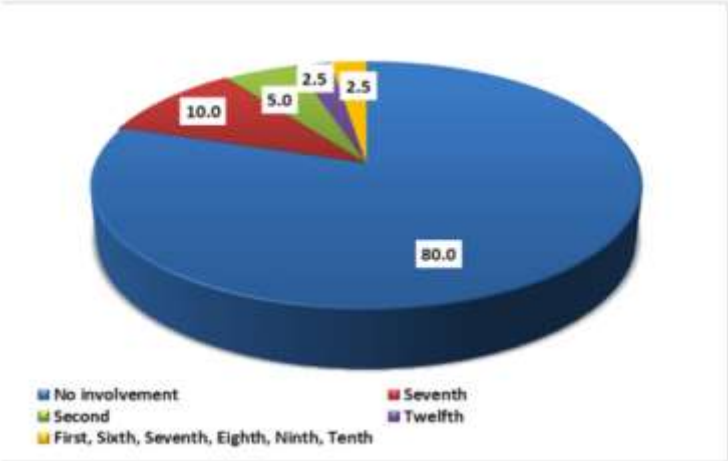

Figure 4: Shows Cranial nerve involvement in CVST subjects

Distribution of study population based on findings of CT scan of brain

Empty delta sign was seen in 17.5% of the cases followed by Cord sign (15.0%) and Haemorrhagic infarcts (7.5%). There were 2 patients where Dense triangle sign and non-haemorrhagic infarcts were seen. In 1 subject Right mastoiditis with cholestoma and Sub arachnoid haemorrhage was seen as shown in table no. 3

Table 3: distribution of study population based on findings of CT scan of brain

Findings of CT scan brain	Number	Percentage
1.Empty delta sign1	7	17.5
2.Cord sign	6	15.0
3.Hemorrhagic infarct	3	7.5
4.Dense Triangle sign	2	5.0
5.Non-hemorrhagic infarct	2	5.0
6.Right mastoiditis with chloesteatoma	1	2.5
7.Subarchnoid hemorrhage	1	2.5

2. Distribution of study population based on Sinuses involved in thrombosis

Concerning the finding on the imaging about venous sinus involvement, majority of the patients had superior sagittal sinus involvement (75.0%) followed by right transverse sinus (40.0%) and left transverse sinus (37.5%) as shown in figure no.-5. More than 1 (multiple) sinus involvement was evident in 30% patients. Multiple sinus involvement is also reflected in table 4.

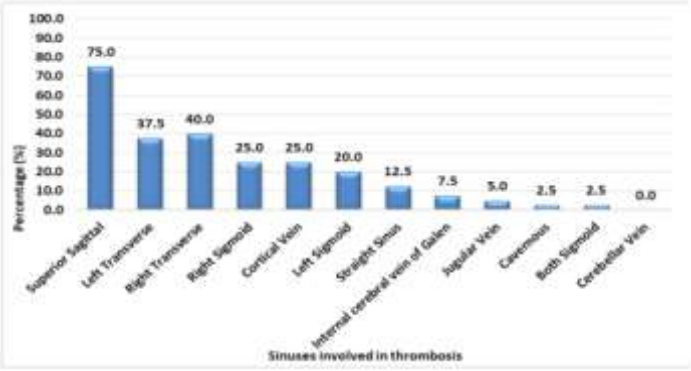

Figure no. 5- Distribution of study population based on Sinuses involved in thrombosis.

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Table 4 – Combination of multiple sinuses involvement

Sinuses involved thrombosis	Number	Percentage(%)
1. Superior sagittal sinus	5	12.5
2. Superior sagittal sinus, right transverse sinus, right sigmoid sinus	5	12.5
3. Superior sagittal sinus, right transverse sinus	3	7.5
4. Superior sagittal sinus, left transverse sinus, left sigmoid sinus	3	7.5
5. Left Transverse sinus	3	7.5
6. Superior sagittal sinus, right transverse sinus, left transverse sinus, cortical veins	2	5.0
7. Superior sagittal sinus, left transverse sinus	2	5.0
8. Superior sagittal sinus, left transverse sinus	2	5.0
9. Superior sagittal sinus, right transverse sinus, right sigmoid sinus, cortical veins	2	5.0
10. Straight sinus	1	2.5
11. Superior sagittal sinus, left transverse sinus, left Sigmoid sinus, Cortical veins, Jugular veins	1	2.5
12. Superior sagittal sinus, right transverse sinus, left transverse sinus, straight sinus, internal cerebral vein of galen, cortical veins	1	2.5
13. Cortical veins, Cavernoius sinus		
14. Superior sagittal sinus, left transverse sinus, left sigmoid sinus, straight sinus, internal cerebral vein of galen	1	2.5
15. Left Transverse sinus, left sigmoid sinus	1	2.5
16. Internal Cerebral vein of Galen	1	2.5
17. Right Transverse sinus, right Sigmoid sinus	1	2.5
18. Left Sigmoid sinus, Jugular veins	1	2.5
19. Superior sagittal sinus, left transverse sinus, left sigmoid sinus, cortical veins	1	2.5
20. Superior sagittal sinus, Both sigmoid sinus	1	2.5
21. Cortical veins	1	2.5
22. Superior sagittal sinus, Cortical veins	1	2.5

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Distribution of patients as per MCV values on RBC indices

MCV was normal in majority of the patients (52.5%). MCV was decreased in 14 patients and increased in 5 patients. The mean MCV level was 85.98 ± 14.70 shown in table 5.

Table 5 - Distribution of patients as per MCV values

MCV values	No. of cases	Percentages
Normal –80-100fl	21	52.5
Decreased <80fl	14	35.0
Increased >100fl	5	12.5
Total	40	100

Discussion

In contrast to arterial stroke, cerebral venous sinus thrombosis often occurs in young individuals. A high index of suspicion by the treating physician is crucial in diagnosing CVST due to its varying symptoms and presentations which often makes it a diagnostic challenge. Significant improvement in the detection rates of CVT is now possible as modern imaging techniques are available. If coupled with appropriate lab investigations like pro-coagulant workup the etiological enigma to a great extent is solved. We compared our experience of CVST, highlighting its manifold clinical presentations, varied predisposing factors, and Neuro-imaging with other studies.

1. **Sociodemographic data** -

We conducted a study on 40 patients over 2 years. The patients of CVST evaluated were in the second and third decade of their age. In our study, the mean age of the patients was 32.03 years (SD13.25) similar to earlier studies from India by Dhadke VN *et al.* (8), Nagaraja *et al.* (9), and Narayan D *et al.* (10). The majority of the patients were in the age group of 26-40 years (42.5%). Our present study also showed a similar finding comparable with Indian studies conducted by Bhat SJ *et al.* (11) and Rajendran A. *et al.* (12).

In the early times, the Indian scenario reported a higher proportion of women affected from CVST than men, except a series of 110 angiographically proven CVST by Parikh *et al.* (13), which had a male dominance. Nagaraja D *et al.* (14) conducted a large hospital-based case series of 317 patients recruited over 8 years had only 15 male patients. Gender-specific risk factors like the use of oral contraceptives and the influence of other factors such as pregnancy, puerperium, and hormone replacement therapy were the possible attribution for the gender bias. In contrary to earlier findings, the present case series from India do not show this trend of female dominance. Narayan *et al.* (10) studied 428 patients of CVST from a tertiary care hospital of Hyderabad, which had a larger proportion of males than females. Pai *et al.* (15) conducted a prospective study which recruited 612 consecutive patients of CVST from various hospitals of Mumbai had a male to female ratio of 3:2. In our study, we too had a male predominance in patients with the male: female ratio of 3:1 and it was consistent with the recent trends in India.

In earlier Indian case studies of CVST had a very high proportion of puerperal CVST but in recent times, a change in this trend has been noted. The NIVSR cohort study and the study by Pai *et al.* (15) reported a small percentage of patients (9.8% and 8% respectively) in the postpartum or pregnant state. The timely and prompt obstetric care could be the possible reason. Our study group consisted of 10 females. The postpartum CVST group consisted of 3 women only(30%) and the non-postpartum group consisted of 7 women (70%) and this data is consistent with the findings of recent studies.

2. Aetiology and Risk factors –

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The pro-thrombotic state is identified as the most common cause for unprovoked CVST in published literature throughout the world and its prevalence ranges from 34% in the International Study on Cerebral Venous Thrombosis (ISCVT) (16) cohort to 12-18% in Indian studies (15). In our study, unprovoked thrombosis was the most common etiological factor in young male patients. Financial constraints didn't allow us to do a complete panel in patients and the prothrombotic state of the patients couldn't be evaluated.

Aaron *et al.* (17) in their study of 41 patients reported that 34% had hyperhomocysteinemia. Similarly in our study, 40% of the population had hyperhomocysteinemia. Pillai *et al.* (18) in their study with CVST, tested for homocysteine levels and had increased levels in 11 out of 15. Rajput *et al.* (19) in their case report of CVST found that acquired hyperhomocysteinemia, presumably due to nutritional deficiencies, and was treated with LMWH, followed by warfarin, vitamin B12, vitamin B6, and folic acid, and recovered successfully. These findings are comparable with our results. Several mechanism are responsible for prothrombotic state and endothelial dysfunction in hyperhomocysteinemia.

Although infective causes of CVST were frequently reported in the earlier series, they account for a very small percentage of patients in recent studies. The availability of potent broad-spectrum antibiotics could be the reason for this change (10,15). In our study infection was present in only 7.5% of our patients.

CLINICAL PROFILE –

Clinically CVST may present as symptoms due to (a) Those related to raised intracranial pressure due to diminished venous drainage; and (b) those due to focal brain injury from venous ischemia/infarction or haemorrhagic incidents. Headache is the most common and most of the times, the first symptom of CVST. Headache may have different nature and characteristics viz. acute, sub-acute, chronic or may even have a thunderclap-like presentation. Stretching of nerve fibres in the walls of the occluded sinus and local inflammation is the postulated theory of headache and is suggested by the evidence of contrast enhancement of the sinus wall surrounding the clot. In our study headache was seen as the initial and most common symptom (72.5%) which closely resembles the NIVSR cohort (88.3%) (10).

Seizures are frequent in CVST as compared to arterial stroke with occurrences in 35-50% of all patients and even higher incidence in postpartum CVST (76%) (16). Kalita *et al.* (22) evaluated the frequency and the predicting factors responsible for seizures in patients with CVST. In their study, 42 patients out of 90 presented with seizures, of whom 10 had status epilepticus. In our study seizure was seen in 20% which closely resembles the above study. None of our patients had status epilepticus.

All other cranial nerves have been described to be involved except for the olfactory nerve. Pai *et al.* (15) reported 7.3% of patients having cranial nerve palsies in their hospital-based study. Bousser *et al.* (20) reported 3 cases with affected cranial nerves: a patient with a left III cranial nerve palsy, another one with multiple cranial nerve palsies (V –X) and the third with a right VI nerve palsy. In our study, cranial nerves involvement was seen in 20% of the patients. Amongst them, the facial nerve (VII) was the most commonly (50%) affected nerve followed by the optic nerve (25%). There was only one patient with thrombosis in the cavernous sinus with presented with multiple cranial nerve involvement (First, Sixth, Seventh, Eighth, Ninth, Tenth). In the NIVSR cohort, a stroke-like presentation was present in 28.5% of patients, similarly in our study stroke-like presentation was present in 37.5% of patients (10).

INVESTIGATIONS

Our study confirms the facts that isolated single sinus involvement was less common than multiple sinuses involvement. Superior sagittal sinus was noted to be the most common sinus

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involved (75%) followed by transverse sinus. Our observations were similar to the international study on cerebral vein and dural sinus thrombosis, where they reported superior sagittal sinus (62%) & transverse sinus (42%) as the most common sinuses involved (16). In about one-third of cases, the CT Brain directly demonstrates the signs of CVST, such as (a) The cord sign, usually seen on head CT with contrast, where the visualization of the hyperdense thrombosed cortical vein is appreciated; (b) the dense triangle sign, viewed on non-contrast head CT, by appreciating the presence of a fresh thrombus in the posterior part of the sagittal sinus; and, (c) the most frequent direct sign is the "empty triangle" or delta sign, seen as non-filling of the confluence of sinuses after contrast injection. In the NIVSR cohort, only 11.2% of patients demonstrated an empty delta sign (10). Our study showed a similar trend where the empty delta sign was found in 17.5% of our patients.The Indian guidelines for stroke management suggest that patients suspected of stroke due to CVST should be investigated by MRI/MRV/CTV only if the CVST is not diagnosed by a primary CT scan (In a suspicious case, the diagnosis should be confirmed by more sensitive imaging techniques such as an MRI and MRV) The conventional MR sequences show flow voids in the patent dural sinuses. A negative plain CT or MRI does not rule out the possibility of a CVST and it is recommended to perform a venographic study (either CTV or MRV) in strongly suspected CVST if the plain CT or MRI is negative. (8).

In the present study, low molecular weight heparin(LMWH) in all patients was started until an adequate level of anticoagulation was achieved along with oral anticoagulants and then changed to warfarin alone after a few days once INR between 2 and 3 was achieved.

Conclusion

Our study found that young males are more commonly affected than females in patients with CVST. Unprovoked thrombosis was the major etiological factor with higher risk in those with hyperhomocysteinemia. Headache is the most common presenting complaint. Multiple cranial neuropathies are also common in CVST. MRI with MR venography being the most sensitive diagnostic modality early diagnosis can be made. Prognosis of CVST improves by early suspicion, diagnosis of CVST by imaging and starting early treatment with anticoagulants.

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