

Clinical profile, diagnostic challenges, and outcomes in subacute/chronic cerebral sinus venous thrombosis

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Purpose: To report clinical profile, diagnostic challenges, and outcomes in cases of subacute/chronic cerebral sinus venous thrombosis (CSVT) presenting to neuro-ophthalmologists/neurologists. **Methods:** This was a multicentric, retrospective, observational study. Records of patients with neuroimaging proven subacute/chronic CSVT seen from January 1, 2016 to March 31, 2020 were analyzed. Data collected included duration of symptoms, diagnosing physician, ophthalmological vs. focal/generalized neurological symptoms, optic disc examination, perimetry, and neuroimaging findings. Statistical analysis was performed using STATA software. **Results:** Forty-three patients with subacute (30)/chronic (13) CSVT were identified (32 males, 11 females). Median age was 37 (IQR 27–47) years. The presenting complaints were blurred vision 34 (79%), headaches in 25 (58%), vomiting 12 (28%), and diplopia 11 (26%). Eleven patients had associated sixth cranial nerve palsy. All but two patients had either disc edema/optic atrophy; four had unilateral disc edema at presentation. Ophthalmologists and neurologists diagnosed/suspected CSVT correctly in 13/29 (45%) and 11/14 (78.5%) patients, respectively. Most common initial alternate diagnosis was idiopathic intracranial hypertension in 12 (28%). Female gender, age ≤ 36 , unilateral papilledema, not obtaining venogram at initial workup increased chances of initial alternate diagnosis. Median follow-up duration was 21 days. Average visual function remained stable in majority of patients at last follow-up. In total, 47.6% of patients had best-corrected visual acuity $\geq 20/30$ at the final follow-up. **Conclusion:** In our series, subacute or chronic CSVT presented primarily with symptoms of intracranial hypertension. Unilateral papilledema, middle-aged patients, female gender, lack of focal/generalized neurological symptoms created diagnostic dilemma. Visual function remained stable in majority of patients.

Key words: Cerebral sinus venous thrombosis, chronic, diagnostic challenges, outcomes subacute

Cerebral sinus venous thrombosis (CSVT) is an uncommon form of venous thromboembolism that can present with acute focal/generalized neurological symptoms like headache, seizures, altered sensorium, aphasia, diplopia, etc.^[1,2]

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Received: 19-Jan-2021

Revision: 21-Mar-2021

Accepted: 21-Jul-2021

Published: 26-Nov-2021

Access this article online

Website:

www.ijo.in

DOI:

10.4103/ijo.IJO_96_21

Quick Response Code:



However, patients with subacute/chronic CSVT may present predominantly with clinical manifestations of intracranial hypertension (ICH) such as blurred vision, transient visual obscuration, diplopia, and/or papilledema.^[1-4] These patients can be misdiagnosed as idiopathic intracranial hypertension (IIH) or disc edema due to other etiologies.^[5] In addition, magnetic resonance imaging (MRI) can be normal in up to 30% of these patients.^[6]

Uncommonly, these patients can have asymmetric or purely unilateral disc edema, which may raise concern for other causes of optic neuropathies.^[7,8]

Prior literature focuses on the entire spectrum of CSVT; however, subacute/chronic CSVT is not usually described separately. The purpose of the current study is to report the prevalence, demographics, clinical/neuroimaging features, and outcomes of patients with subacute and chronic CSVT. In addition,

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Cite this article as: Sachdeva V, Nalawade R, Kannam M, Kapoor R, Chattannavar G, Kale SB, et al. Clinical profile, diagnostic challenges, and outcomes in subacute/chronic cerebral sinus venous thrombosis. Indian J Ophthalmol 2021;69:3598-606.

we report the possible *challenges associated with establishing a diagnosis of subacute/chronic CSVT.*

Methods

We retrospectively reviewed records of consecutive patients seen from January 1, 2016 to March 30, 2020, with a final diagnosis of CSVT seen at Neuro-ophthalmology clinics of our three tertiary care centers (and from July 1, 2019 to March 30, 2020 at the fourth tertiary eye care center). CSVT was subclassified as acute, subacute, and chronic, based on the duration of onset of symptoms: acute (<48 h), subacute (48 h to <30 days) and chronic (>30 days).^[2] We included patients with *only subacute/chronic* CSVT diagnosed either first at our institute or diagnosed elsewhere and then referred to us. The diagnosis was based on the radiological evidence of CSVT either on magnetic resonance venography (MRV) or computed tomography venography (CTV) except a couple of patients with conclusive CSVT on computerized tomography (CT)/MRI brain alone. We excluded patients with inconclusive imaging, arterial strokes, intracranial neoplasms, metabolic encephalopathy, and other CNS etiologies. The study was approved by the ethics committee of respective campuses and adhered to the tenets of Declaration of Helsinki.

Data collection

Data collected from electronic medical records included age, gender, body mass index (BMI), presenting complaints, duration of symptoms, diagnosing physician (Ophthalmologist vs. Neurologist/Neurosurgeon), and the initial diagnosis. Additional data collected included visual acuity, pupillary examination, concomitant cranial nerve palsies, automated perimetry findings at the time of presentation and follow-up. We also collected similar data for 72 consecutive patients with established IIH seen (between January 1, 2018 and December 31, 2019) at one of the tertiary eye care centers for comparing their demographic and clinical characteristics with the study patients.

Visual acuity recorded using the electronic Snellen visual acuity charts was converted to logMAR. Two experienced neuroophthalmologists graded the disc edema as per Frisén grading scale^[9] based on fundus photographs.

Automated perimetry done using Humphrey visual field analyzer (Carl Zeiss Meditec, Inc, Jena Germany) at presentation and follow-up visits was analyzed to look for mean deviations and pattern of visual field defects. Visual fields had been performed using 24-2 Swedish Interactive threshold algorithm (SITA)-FAST testing strategy wherever possible. Additionally, automated perimetry was performed using 10-2 SITA-FAST testing strategy if central 10 degrees were depressed. Visual field defects were graded as reported by Bruce *et al.*^[10] on a scale of 1–5; (a) normal, (b) enlargement of the blind spot, (c) nasal or temporal defect, or (d) central depression, (e) diffusely constricted. Data regarding optical coherence tomography (OCT, Cirrus OCT 4.0, Carl Zeiss Meditec, Dublin, USA) of the peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell layer was collected if performed.

In patients with unilateral disc edema, data (grade of disc edema, visual acuity, and visual fields) from the affected eye was used, and in patients with bilateral disc edema, data from the worse eye was used to understand the maximum impact

on the visual function and to avoid confounding effect of using data from both eyes.

Neuroimaging findings recorded included: the type of imaging done, site(s) of and extent of thrombosis, brain parenchymal changes, and if inconclusive, further neuroimaging obtained.

Additionally, data were collected regarding the initial diagnosis (CSVT vs. alternate diagnosis) by the treating physician. Wherever performed, data was collected about thrombotic abnormalities [Protein C, protein S deficiency, factor V Leiden mutation, methyl-tetrahydrofolate reductase (MTHFR) mutation, serum homocysteine levels, anti- β -2-Glycoprotein-1 antibodies, and anti-Cardiolipin antibodies].

Statistical analysis

Statistical analysis was performed using STATA software (STATA version 12.0, STATA corp, Houston, Texas, USA). Shapiro–Wilk test was used to analyze the normality of the data. *P* values < 0.05 were considered significant. Continuous data were summarized using medians and interquartile ranges, while categorical data were summarized using percentages. Fischer exact/Chi-square tests were used for comparing categorical variables and Mann–Whitney *U* test was used to compare continuous data. Binary logistic regression analysis was used to analyze the effect of duration of symptoms, associated cranial nerve palsy, other focal/generalized neurological signs, laterality of disc edema, visual acuity, visual field defect grade, primary physician evaluating the patient, and type of neuroimaging on the initial diagnosis at presentation (CSVT vs. alternate diagnosis).

Results

Demographics

During the study period, we diagnosed 45 patients with CSVT: two acute and 43- subacute/chronic CSVT [30 subacute and 13 chronic CSVT]. During the same period, we saw 822 and 586 patients with papilledema and IIH, respectively, giving a prevalence of 5.2% (43/822) among all patients with papilledema and 6.8% (43/629) among all patients with IIH or CSVT. Of these, 32 were males and 11 were females. Median age of patients was 37 (interquartile range, IQR: 27–47) years. [Table 1]

Presenting complaints and clinical features

Most common presenting complaints were blurred vision 34 (79%) followed by headache 25 (58%), vomiting 12 (27.9%), and horizontal binocular diplopia 1 (25.6%), Table 1. Eleven patients had sixth cranial nerve palsy (seven bilateral and four unilateral). Six patients (13.9%) reported other focal/generalized neurological symptoms (neck stiffness two, altered sensorium three, seizures one).

All except two patients had disc edema/postpapilledema optic atrophy at presentation [Fig. 1]. At presentation, 4 patients had unilateral disc edema, 13 had frank bilateral disc edema, 18 had atrophic disc edema, and 6 had postpapilledema optic atrophy. The median duration of symptoms in all patients was 30 days (IQR: 15–180) and 160 days (range: 60–180 days) in patients with optic atrophy.

Visual function and OCT findings at presentation

At presentation, median presenting best-corrected visual acuity (BCVA) was 0.3 (IQR: 0–1.7) logMAR [Table 2]. Typically,

Table 1: Demographic and presenting features of patients with CSVT in our series and a comparison group of 72 patients with classical idiopathic intracranial hypertension (IIH) in our institute

Characteristic	CSVT group (n=43)		IIH, * representative group (n=72)		P
	Number	% Or IQR	Count or median	% Or IQR	
Demographic Characteristics					
Women	11	25.6%	67	93%	0.001
Age, (years)	37	27-47	35	28-39	0.01
Built, BMI ^{†‡} >30 kg/m ²	8/27	29.6%	50	69.4%	0.0005
Duration of presenting symptoms (days)	30 (median)	15-180 (IQR)	30 (median)	8.5-150 (IQR)	0.07
Presenting Complaints[§]					
Headache	25	58.1%	43	59.7%	1.0
Vomiting	12	27.9%	9	12.5%	0.048
Other focal/generalized neurological symptoms (confusion, altered sensorium, stroke, limb weakness, seizures, etc.)	6	13.9%%	0	0%	0.002
Blurred vision	34	79.07%	28	38.8%	0.0001
Transient visual obscuration (TVO)	6	13.9%	7	9.4%	0.55
Diplopia	11	25.6%	12	16.7%	0.24
Associated sixth cranial nerve palsy (bilateral 7; 4 unilateral)	11	25.6%	12	16.7%	0.24
History of hypertension	5	9%	4	5.5%	0.29
Unilateral disc edema at presentation	4	9.3%	1	1.35%	0.12

*IIH=idiopathic intracranial hypertension; †BMI=body mass index; ‡BMI recorded only for 27 patients and 8/27 had BMI \geq 30; §Note the total percentage of patients with different complaints adds up to more than 100% because some patients had multiple complaints (headache, blurred vision, TVO in the same patient). Note that in both groups, the majority of the patients had the symptoms of intracranial hypertension (ICH), and in the CSVT group, only six patients had other focal/generalized neurological symptom. Patients with subacute/chronic CSVT were more likely to be men, nonobese, and older in age; had more often blurred vision and other focal/generalized neurological complaints; however, there were no other statistically significant differences in any other characteristics.

25/43 (58.1%) had presenting BCVA greater than or equal to 0.5 logMAR, 7/43 (16.3%) had BCVA 0.5–1.3 logMAR, and 11 (25.5%) had presenting BCVA worse than 1.3 logMAR. Three patients had no light perception vision in the worse eye.

At presentation, formal visual fields were performed/possible in 29 patients, and the average mean deviation was -9.8 dB (IQR: -5.5 to -22.2 dB). The visual field patterns noted were normal (5/29), enlarged blind spot (12/29), nasal/temporal depression (5/29), central field defect (1/29), and advanced field loss (6/29).

The difference in presenting BCVA ($P = 0.14$) and visual field mean deviation ($P = 0.31$) was not statistically significant among patients with or without disc pallor [Table 2].

Initial diagnosis

Ophthalmologists and neurologists initially examined 29 and 14 patients, respectively. They correctly diagnosed/suspected CSVT in 13 and 11 patients, respectively. Of these, only 22 were examined by neuroophthalmologists inhouse, while the remaining were initially evaluated by general ophthalmologists and general neurologists elsewhere. The most common alternate diagnosis made at initial presentation was IIH 12 (27.9%), followed by optic neuritis and NAAION in two each (7%) and infiltrative optic neuropathy, malignant hypertension with bilateral NAAION in one each (2.3%).

Neuroimaging performed and abnormalities

Initial neuroimaging comprising MRI brain with MRV was performed in 31/43 (72%) patients. However, all except two patients underwent MRV/CTV during subsequent evaluation by us. The two patients who did not undergo MRV had signs of frank CSVT on CT/MRI brain. Further, the second patient was advised MRI brain with contrast and MRV but had

chronic renal failure and did not undergo further imaging. Interestingly, 15/43 (35%) patients underwent neuroimaging multiple times, and in four patients, diagnosis of CSVT could only be suspected on MRV brain without contrast and be established only by MRV with contrast.

Excluding the two patients who did not undergo MRV, 27/41 (65.8%) patients had multiple sinus involvement. Transverse sinus was most commonly affected in 35 (85%) followed by sigmoid sinus in 26 (65%) cases [Figs. 2 and 3]. Only two patients had venous infarcts, and none had abscess, thrombophlebitis, tumors, or other causes of secondary CSVT.

Treatment

All patients were managed in consultation with a neurologist. The patients were treated with acetazolamide and oral anticoagulants (acenocoumarol as per their standard of care) with monitoring of prothrombin time and international normalized ratio. In addition, low-molecular-weight heparin and oral anticonvulsants were needed in three and nine patients, respectively, who had subacute presentation. *None of the patients with chronic CSVT received unfractionated heparin/warfarin/other anticoagulants.* The dose of acetazolamide was adjusted according to the severity of disc edema and visual field defects. The median duration of treatment with acetazolamide and acenocoumarol was 8 (range: 6–12) and 6 (IQR: 3–12) months, respectively. Median time for resolution of disc edema was 7 (IQR: 2.5–11) months.

Systemic comorbidities/thrombotic profile

Thrombotic profile evaluation had been performed in all patients with chronic CSVT prior to starting anticoagulants and in patients with associated seizures/altered sensorium

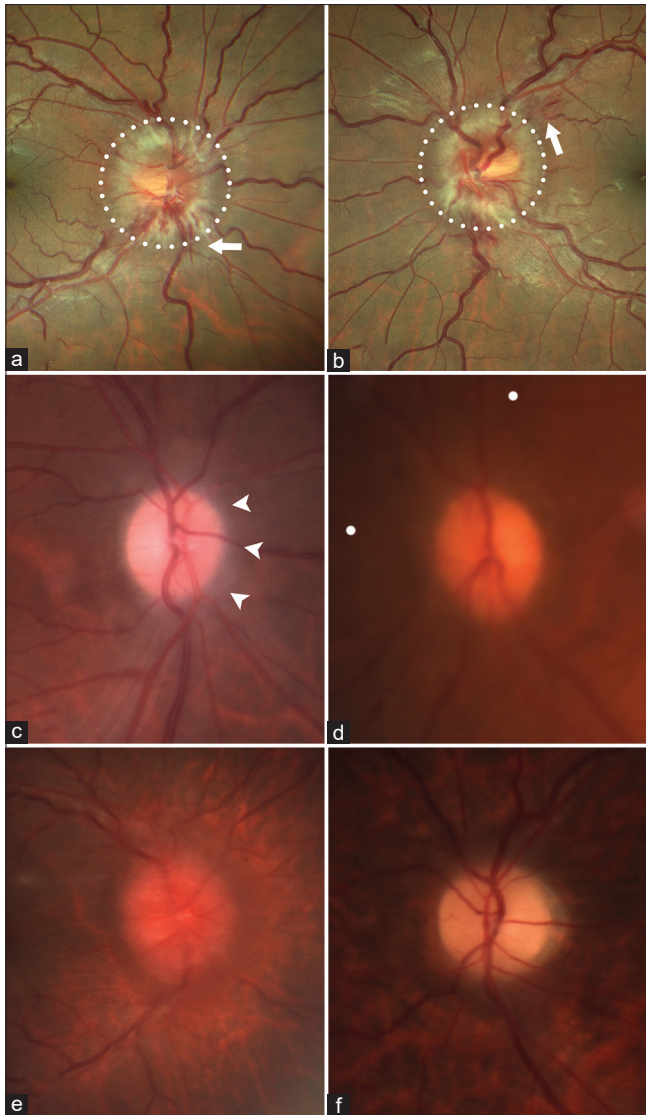


Figure 1: (a–f). Composite fundus photograph showing the various fundus abnormalities observed in our series. Majority of the patients had bilateral frank disc edema and peripapillary RNFL edema (dotted white circle), peripapillary hemorrhages (white arrow), (a, b), or postpapilledema optic atrophy (note the presence of peripapillary RPE changes white arrows, (c, d)). Panels (e, f) show a patient with frank disc edema in the right eye and secondary (compressive) optic atrophy in the left eye

after 6 weeks of initial episode in consultation with treating neurologist. Only 12 patients completed evaluation for prothrombotic abnormalities due to financial constraints. Among them, prothrombotic abnormalities were found in nine patients and four patients had multiple abnormalities [E-Supplement Table 1]. Most common prothrombotic abnormality was hyperhomocysteinemia (six patients, median serum homocysteine: 33.7, range: 22.8–41.5 $\mu\text{mol/L}$). None of the female patients had recent pregnancy or history of using oral contraceptive pills.

Visual acuity and visual outcomes

Median duration of follow-up for all patients was 21 (IQR: 1–257) days. Typically, 54% patients did not complete even

1-month follow-up; however, in the remaining patients, median follow-up duration was 278 days (IQR: 85–432 days).

At the last follow-up, with available data for 21 patients, the median BCVA was 20/40 (0.3, IQR: 0–1.4 LogMAR), Table 2.

Thirteen patients underwent automated perimetry in follow-up. In these patients, average mean deviation (at last follow-up) was -5.2 dB (IQR: -2.7 to -16.7 dB) and 2 (14.2%) had residual central/advanced visual field defects.

The average improvement in BCVA ($P = 0.37$) and visual field mean deviation ($P = 0.45$) were not statistically significant different in eyes with and without disc pallor [Table 2].

Diagnostic challenges

As noted above, initial diagnosis of subacute/chronic CSVT was in only 24/43 patients. We analyzed factors that could have affected the initial thought process leading to alternate diagnosis:

1. Patient demographics: In females with bilateral disc edema and BMI >30, most frequent initial alternate diagnosis was IIH. However, a comparison of clinical and demographic characteristics of 72 patients with IIH [Table 1] showed that patients with CSVT were more likely to be middle-aged men, nonobese, and more likely to have other focal/generalized neurological symptoms and blurred vision than patients with IIH.

2. Laterality of disc edema: All patients with unilateral disc edema at presentation were initially thought to have an alternate diagnosis: NAAION (2), infiltrative optic neuropathy (1), and optic neuritis (1) in these patients [Table 3]. Further, of the remaining 39 patients with bilateral disc edema/atrophy, an initial diagnosis of CSVT was not considered in 15 (38%) patients.

3. Alternate diagnosis by specialty and initial imaging: Ophthalmologists and neurologists correctly diagnosed/suspected CSVT in 13/29 and 11/14 patients, respectively ($P = 0.05$). The most common alternate diagnosis of IIH was considered by neurologists in 3/14 and by ophthalmologists in 9/29 patients ($P = 1.0$).

Physicians obtaining MRI and MRV in initial evaluation correctly diagnosed CSVT in 21 patients. However, the choice of imaging was dictated by the initial diagnosis. For instance, referring ophthalmologists initially obtained MRI brain with contrast in three patients with an initial diagnosis of IIH, NAAION, and malignant hypertension. Similarly, in three out of four patients with unilateral disc edema, where initial suspicion was an optic neuropathy, initial investigation was MRI brain with contrast and MRV brain was obtained later after initial hypothesis failed [Table 3].

Logistic regression analysis suggested that the female gender, age ≤ 36 , absence of other focal/generalized neurological symptoms, not obtaining MRV/CTV, and unilateral disc edema predicted the chances of initial alternate diagnosis. However, on analyzing the effect of individual factors, unilateral disc edema and not obtaining MRV/CTV at initial work-up were the only significant factors associated with an initial diagnosis other than CSVT ($P = 0.03$), e-supplement Table 2.

Table 2: Distribution of the average visual acuity and visual field mean deviation at presentation and last follow-up for patients in the current study

Characteristic (for worse eye)	All patients median (IQR), n	With disc pallor median (IQR), n	Without disc pallor median (IQR), n	P
Average presenting BCVA (logMAR, n=43)	0.3 (0-1.7), 43	1.43 (0.3-2.0), 22	0.1 (0-0.3), 21	0.14
Average visual field mean deviation (MD) at presentation (dB, n=29)	9.8 (-5.5 to -22.2), 29	-24.7 (-7.4 to -32.08), 17	-8.7 (-5.5 to -10.38), 12	0.31
Average final BCVA (logMAR, n=43)	0.3 (0-1.4), 21	0.4 (0-1.47), 9	0.05 (0-0.34), 12	0.30
Average visual field mean deviation (MD) in at final visit (dB, n=29)	5.2 (-2.7-16.7), 13	0 (-1.71-2.5), 4	0.94 (-1.29-4.52), 9	0.37
Average improvement in BCVA (logMAR, n=20)	0.03 (IQR: 0-0.10), 21	0 (-0.01-0.20), 9	0.07 (0-0.1), 12	0.37
Average improvement in visual field mean deviation (n=13)	0 (-1.29-4.52), 13	0 (-1.7-2.5), 4	0.94 (-1.3-4.52), 9	0.45

All data was calculated for the involved eye in unilateral cases and worse eye in case of bilateral disc edema/optic atrophy. BCVA=best-corrected visual acuity, MD=mean deviation, and IQR=interquartile range. As seen in the above table, average BCVA and visual field mean deviation tended to be worse for patients with disc pallor, but this difference did not reach statistical significance.

Table 3: Summary of clinical details and evaluation of patients with unilateral disc edema at initial presentation

Clinical presentation	Initial diagnosis at presentation	Possible hypothesis and initial work up	Reason for reevaluation as CSVT	Investigations confirming diagnosis of CSVT
48-year-old, nonobese woman, incidentally, found unilateral disc edema in the right eye ^[8] *	Incipient Non-NAAION [†]	Work up to rule out disc drusen, Normal visual function; MRI brain with contrast-normal.	Persistent disc edema at 18- month follow-up; middle aged woman, non -obese, old MRI showing subtle signs of elevated ICP	MRI brain and orbits with contrast and MRV brain which showed signs of elevated ICP, and suspected chronic thrombus in both transverse sinuses, confirmed on MRV with contrast
36-year-old man: unilateral disc edema, blurred vision, headache, and optic atrophy in the fellow eye; due to prior compressive optic neuropathy	Atypical optic neuritis	MRI brain and orbits with contrast; serology testing for neuromyelitis optica and MOG-optic neuritis [‡]	No features of acute inflammatory optic neuritis on MRI; MRI showing subtle signs of elevated ICP	MRV brain suspicious of chronic thrombus and confirmed on MRV brain with contrast
39-year-old, obese woman, acute blurred vision in the left eye, Unilateral disc edema, profound vision loss in the left eye, multiple retinal hemorrhages	Infiltrative optic neuropathy	MRI brain and orbits with contrast: thickening and enhancement of the affected optic nerve. Hemogram, peripheral smear, CSF analysis, bone marrow biopsy which were all normal or negative	Negative work-up for infiltrative optic neuropathy; development of subtle disc edema in fellow eye after 5 days; review of old MRI signs of elevated ICP	MRV brain- suspicious of subacute thrombus, MRV brain with contrast- onfirmed thrombus
42-year-old woman, gradual vision loss in the right eye of 20 days duration, diffuse field defect	NAAION [†]	Referral to our institute	Development of bilateral disc edema by time of presentation; massive disc edema, associated tinnitus, and headaches	MRI brain and MRV brain

*This case is previously published, and summary of findings published with permission from the Journal.^[8] [†]NAAION=Nonarteritic anterior ischemic optic neuropathy, [‡]MOG=Myelin oligodendrocyte Glycoprotein.

Discussion

In our study, we report clinical characteristics, diagnostic challenges, and outcomes of patients diagnosed as subacute/chronic CSVT, while majority of the existing literature focuses on acute CSVT.^[1,4,11,12] Our study shows a high preponderance of subacute/chronic CSVT (95% cases) as compared to prior literature (range: 62.4–85.2%).^[1,12-14] This could be attributed to patients with acute CSVT presenting initially to neurologists/emergency departments.

Our study suggests that *one in 20 patients with papilledema* might have subacute/chronic CSVT and should be investigated appropriately. Similarly, nearly 7% (one out of 14 patients) with presumed IIH (CSVT and IIH) could be CSVT. This is slightly less compared to 9.4% as reported previously, possibly due to relatively stable patients presenting with visual complaints, headache, and/or papilledema in our series.^[14]

e-supplement Table 3 compares in detail demographics and clinical characteristics of patients in our series with

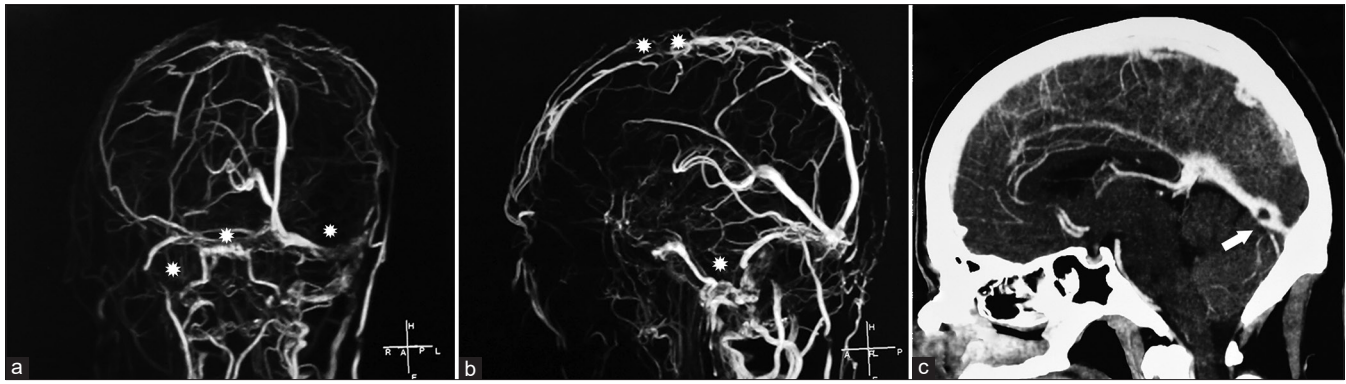


Figure 2: Composite photograph of the magnetic resonance venogram (MRV) showing various sites of irregular filling defects suggestive of thrombosis in the transverse sinuses, sigmoid sinus, superior sagittal sinus and inferior sagittal sinus. (labelled as white asterisk/arrows) observed in different patients in our study

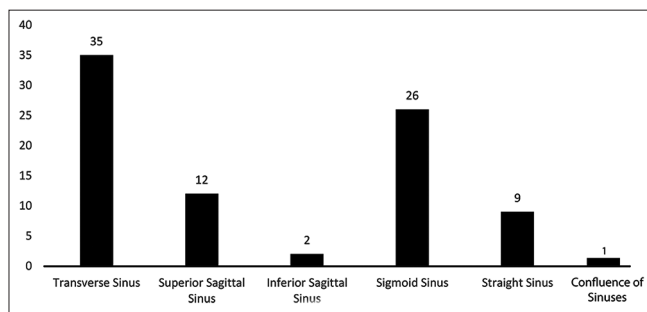


Figure 3: Bar graph showing the distribution of various sites of thrombosis in patients in our series. The figure shows that transverse sinus thrombosis was the most commonly affected followed by sigmoid sinus. Note: Many patients had thrombosis of multiple cerebral venous sinuses

important published literature.^[1,4,11-13,15,16] We describe in brief important observations in our study as compared to prior literature.

In our study, nearly three-fourths of the patients were middle-aged males. This is in contrast to existing literature reporting high prevalence in women and puerperium. Only Nithyanandam *et al.*^[15] reported slightly greater prevalence of CSVT in men in their series. This possibly also explains why NAAION was considered as the differential diagnosis in middle-aged men. This is similar to prior reports.^[17,18]

There are four reported patterns of CSVT.^[2,19] They can be focal syndrome, isolated ICH, diffuse subacute encephalopathy, and cavernous sinus syndrome. As noted in Table 1, majority of our patients presented with headache, diplopia, or blurred vision as presenting complaints or were referred for evaluation of papilledema, suggestive of pattern of intracranial hypertension. This could have contributed to initial diagnosis of IIH. Prevalence of frank papilledema/atrophic disc edema (81.4%) in our series was similar to the prior reported literature (32–86%),^[1,2,4,11-13,20] possibly explaining why majority of the patients first presented to ophthalmologists.

In our series, headache was less frequent compared to prior literature [80–93%, e-supplement Table 3].^[1,4,11-13,15,16] This might be due to infrequent presentation with stroke, seizures, and focal/generalized neurological symptoms in our series.

Only few prior studies have analyzed differences in patients with IIH and CSVT.^[4] We found that male gender, BMI <30, age >36, blurred vision, and associated focal/generalized neurological complaints were more likely predictive of subacute/chronic CSVT versus IIH [Table 1]. These differences are important because IIH is an important differential diagnosis among women of childbearing age.^[20,21]

To our surprise four patients had unilateral disc edema at presentation and posed a diagnostic dilemma [described in detail in Table 3]. Though seldom reported in CSVT,^[7,8] prior literature does suggest that a few patients with intracranial pathologies or intracranial hypertension may present with asymmetric or unilateral disc edema and could possibly be due to anatomical differences between the lamina cribrosa or optic canal.^[22-24]

Majority of patients had multiple sites of thrombosis, and the transverse sinus was the most common site. Cerebral sinus thrombosis involving multiple sinuses is frequently reported, but the distribution might vary.^[1,2,4,11-13] In the International Study on Cerebral Vein and Dural Sinus Thrombosis, sagittal sinus was more frequently involved (62%), followed by transverse sinuses (left: 44.7%, right: 41.2%) and straight sinus (18%).^[1]

Prothrombotic abnormalities could be assessed only in 12 patients due to financial constraints. Of these, three quarters had prothrombotic abnormalities. Hyperhomocysteinemia alone or with MTHFR gene mutation was the most common abnormality. One patient also had a history of ulcerative colitis, which is also reported to be an association.^[25]

Similar to prior reports,^[1,15] 4/9 (44%) patients had multiple prothrombotic risk factors. Therefore, comprehensive evaluation of thrombotic risk factors is recommended in consultation with neurologist/hematologists. In patients with acute CSVT, it should be performed after at least 6 weeks of initial episode, and 2–4 weeks of initial anticoagulation if given.^[26] However, in patients with subacute/chronic CSVT, it might be performed at the time of diagnosis itself prior to starting anticoagulants.^[27]

Our study suggests that establishing a diagnosis of subacute/chronic CSVT can be challenging. Initial diagnosis of CSVT was suspected in only two-third (58%) patients by the treating physician. Neurologists suspected CSVT more often than

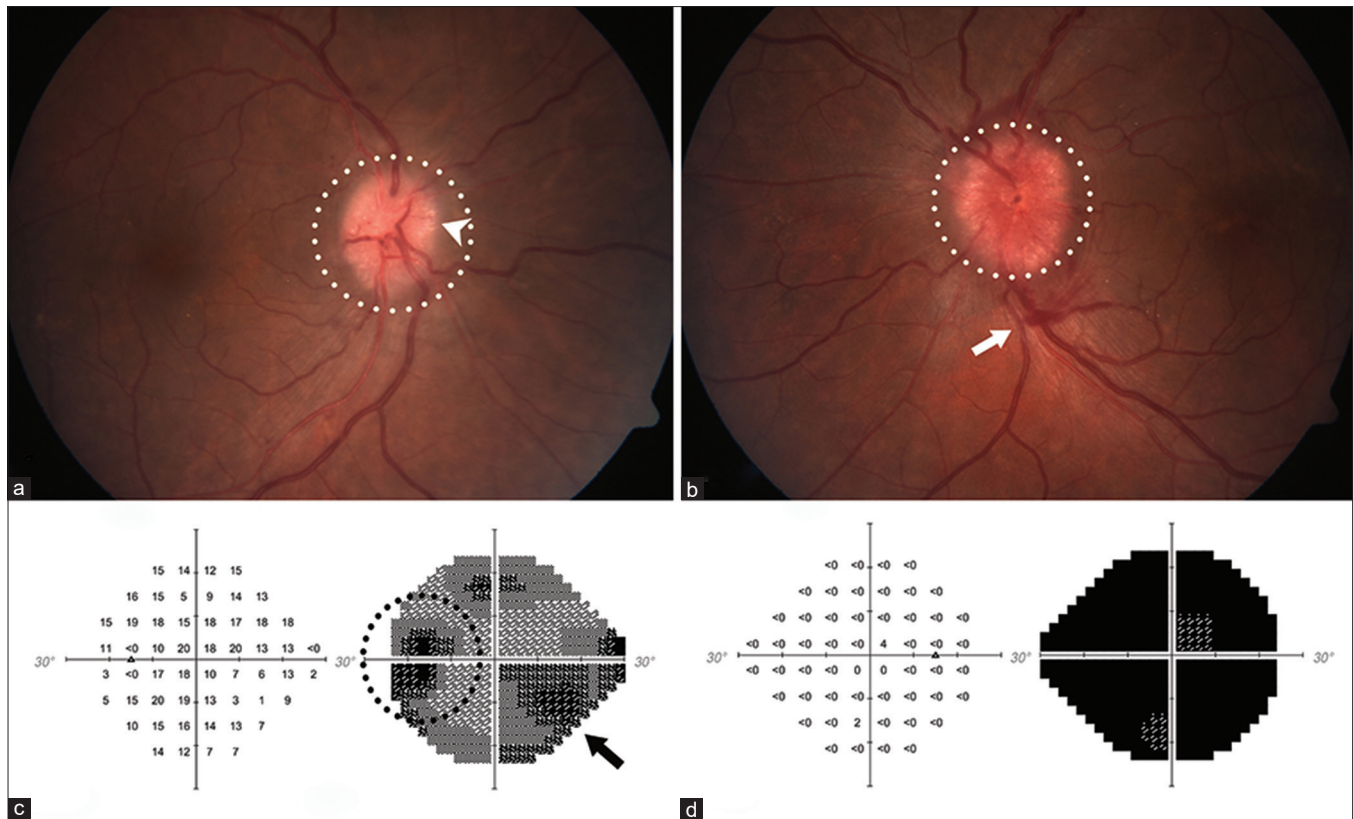


Figure 4: (a–d) Fundus photograph and visual fields of a patient with chronic CVST initially diagnosed as bilateral nonarteritic ischemic optic neuropathy (NAAION). Note presence of bilateral disc edema (dotted white lines, (a, b)), superficial peripapillary hemorrhages (white arrow), and refractile bodies (white arrowhead), suggestive of chronic disc edema. Automated perimetry (gray scale) showed enlargement of blind spot (black circle) and inferonasal field defect in the left eye (figure 4c) and advanced field defect in the left eye (figure 4d)

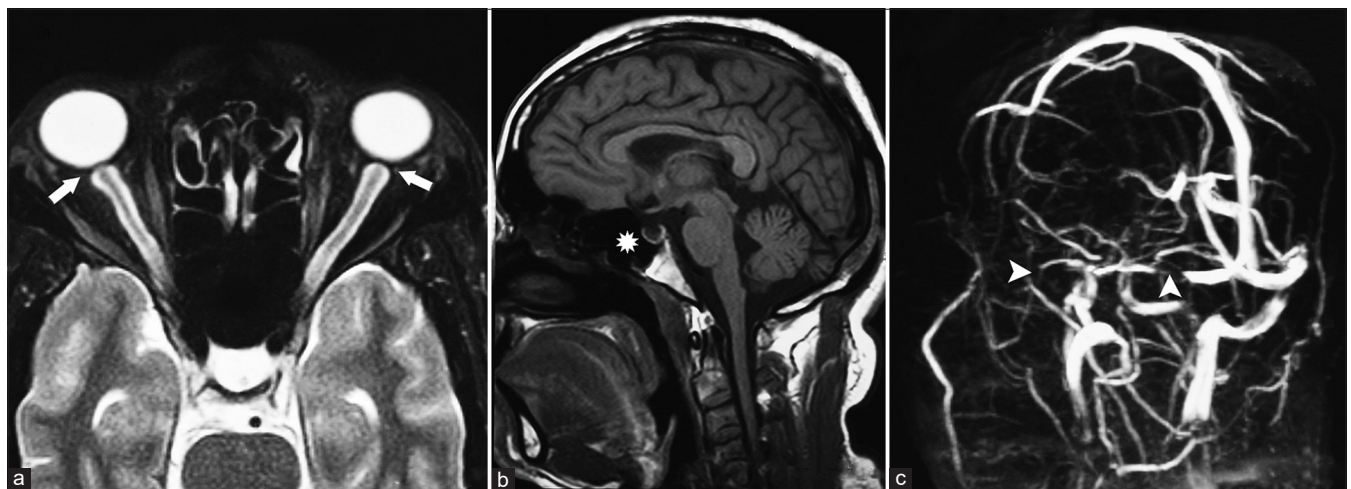


Figure 5: (a–c) Composite picture showing magnetic resonance imaging (MRI) and venogram (MRV) of the same patient as in Figure 4 (suspected bilateral NAAION) showing flattening of sclera at optic nerve head-globe junction (white arrow), dilatation of the perioptic nerve sheath (a), empty sella (white asterisk, (b)). MRV (c) shows filling defects in the right transverse and sigmoid sinuses (white arrowhead)

ophthalmologists, which could be due to differences in their training and exposure to such cases. Possible reasons for diagnostic dilemma were presentation with only intracranial hypertension, unilateral disc edema, coexisting systemic diseases, and type of work-up obtained. Ferro *et al.*^[26] suggested that the diagnosis of CSVT was delayed in patients presenting

with intracranial hypertension ($P = 0.04$) as compared to those presenting with other focal neurological symptoms/seizures/ altered sensorium. Further, patient demographics (middle-aged men) and concomitant conditions such as prior history of accelerated hypertension prompted physicians to consider diagnosis of NAAION and malignant hypertension (systemic

blood pressure: 200/110 mm Hg). Fig. 4 and 5 show representative fundus findings, visual fields at presentation, MRI brain, and MRV findings of patient initially thought to have bilateral NAAION.

All patients with unilateral disc edema were considered to have optic neuropathy and not CSVT [Table 3]. For example, one middle-aged woman with good vision was initially diagnosed as incipient NAAION after pseudodisc edema was ruled out [Table 3].^[8]

Above observations suggest that following factors could have contributed to *not diagnosing CSVT at initial presentation*: (a) lack of hypothesis generation (IIH, NAAION vs. CSVT), (b) not paying weightage to demographics (middle-aged men vs. younger women), and (c) associated systemic history (presence of blood pressure, and absence of other focal/generalized neurological symptoms). Further logistic regression analysis suggested “*not obtaining appropriate neuroimaging (MRV)*” was associated with alternate diagnosis in our series [E supplement Table 2].

Of note, in three patients, the diagnosis of CSVT was not confirmed in an MRV brain done without contrast and MRV brain with contrast was subsequently needed to confirm the diagnosis. MRV brain has its own limitations and might not be able to distinguish completely between congenital venous sinus hypoplasia vs. CSVT, and at times it might be inconclusive. In these cases, review of the source images for MRV is useful in differentiating between CSVT and congenital hypoplasia.^[28] Also, other techniques such as MRV brain with contrast, digital subtraction angiography and MRI black-blood imaging may be needed in CSVT.^[28-31]

Despite the novelty of the study in looking at patients with subacute/chronic CSVT, current study has the limitations of being retrospective and having a small sample size. Our patients were initially evaluated by general ophthalmologists, general neurologists, and ophthalmologists/neurologists practicing neuroophthalmologists. Initial work-up was dictated by working diagnosis of the primary physician and were not necessarily uniform. *However, it allowed us to understand the possible reasons for the initial diagnosis.* Further this suggests need for uniform training and disseminating recommendations for evaluation of patients with papilledema and other conditions.

Nearly half of the patients were lost to follow-up after establishing the initial diagnosis, and the follow-up investigations were obtained according to discretion of the treating physician. Hence, the data related to visual outcomes was available only for a small subset of patients. Therefore, these results should be viewed with caution. Similarly, data about prothrombotic abnormalities at presentation and follow-up, repeat neuroimaging was limited.

Conclusion

Our study suggests that patients with subacute/chronic CSVT often present with isolated intracranial hypertension, optic disc edema/atrophy and can be a diagnostic challenge. Unilateral disc edema, absence of other focal/generalized neurological symptoms/signs, and not obtaining MRV at initial work-up might lead to delay in diagnosis. Further our study suggests that middle-aged patients, men, and nonobese patients are more likely to have subacute/chronic CSVT than IIH. In addition, even unilateral disc edema, especially persistent and

without other signs on MRI orbits/rain with contrast, should raise suspicion of CSVT. We recommend performing MRI brain with contrast and MRV brain to establish diagnosis in all patients with papilledema and especially in patients whose demographic and clinical features raise greater suspicion. Further, prothrombotic profile should be performed in discussion with treating neurologist/hematologist to establish the underlying etiology at appropriate time (subacute/chronic CSVT – at the time of diagnosis; acute CSVT after at least 6 weeks of initial episode).

Acknowledgements

We would like to thank Dr. Akhila Acharya for her help with the professional English language editing. We also thank Dr Harsha L Rao for his clarifications with statistical interpretation. We also thank all our neuroradiologists, and especially Dr. D Ravi Varma, Consultant Neuro-radiologist, Citi Neuro Centre, Hyderabad, India and Dr. P Srinivasa Perraju, Consultant Neuro-radiologist, Vijaya Medical Centre, Visakhapatnam, India who helped with accurate interpretation of the neuroimaging findings of our patients. We also thank all the neurologists who have involved in the care of the patients in the series.

Financial support and sponsorship

Hyderabad Eye Research Foundation (HERF), Hyderabad, Telangana, India.

Conflicts of interest

There are no conflicts of interest.

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E-supplement Table 1: Systemic and prothrombotic abnormalities observed in the study patients

Systemic abnormality	Prothrombotic abnormality
Hypertension alone -1	Hyperhomocysteinemia - 6
Hypothyroidism -1	Protein C deficiency -2
Ulcerative colitis -1	Polycythemia vera-2
Diabetes and hypertension-4	Protein S deficiency- 1
Hypothyroidism and diabetes mellitus 3	Factor VIII deficiency- 1
	Thrombocytosis -1
	Methyl-tetra-hydro-folate reductase (MTHFR) gene mutation -1

E-supplement Table 2: Univariate analysis showing the effect of various characteristics influencing initial diagnosis other than cerebral sinus venous thrombosis

Characteristic	Pearson's coefficient	P
Age	58.8	0.13
Gender	4.5	0.10
Average duration of symptoms (overall)	33.7	0.48
Duration of symptoms less than 14 days	0.30	0.58
Other focal/generalized neurological symptoms	4.4	0.11
Body mass index (BMI) > 30	6.80	0.15
Unilateral disc edema	11.7	0.003
Associated disc pallor	0.59	0.75
Initial MR Venogram/CT Venogram	24.4	<0.001
Contrast used in initial imaging	3.3	0.19

This table shows that only unilateral disc edema at presentation and lack of obtaining MRV/CTV at initial workup were the only two factors that significantly led to initial misdiagnosis

e-supplement Table 3: Comparison of key clinical and demographic features in our series as compared to the important landmark studies showing subacute/chronic CSVT

Authors	ISCVT ⁽¹⁾	Biousse ⁽⁴⁾	Narayan ⁽¹¹⁾	Uzar ⁽¹²⁾	Yadegari et al. ^(13,a)	Nithyanandam et al. ⁽¹⁵⁾	Liu et al. ⁽¹⁶⁾	Current Study
Number of patients	624 (391 subacute/chronic)	59 (total 160)	428	47	53	60	65	43
Age (mean, range)/median (IQR), years	39.1 (16-86) Median: 37	36 (11-71)	31.3 (8-65)	30.2 (5-65)	33.7 years (17-60)	28 (20-58)	33.8 (9-70)	37 (IQR=27-47) Range: 36-60
Gender (% female)	74.5%	58.7%	47.3%	66%	40 (75.8%)	57%	45 (69.2)	25.6%
Median duration of symptoms (days)	4	NR	16.1	NA		NR	NR	30 (15-180)
Presentation:								
ACUTE CSVT (Percentage, %)	37.2%	62.2%	14.2%	19.1%	26.4%	NR	NR	Nil ^b
SUBACUTE and chronic CSVT (Percentage, %)	55.5%+7.2%	36.8%	72.8%+12.3%	48.9% + 31.9%	73.65%	NR	NR	30 (69.7%) + 13 (31.3%)
HEADACHE (%)	88.8%	93%	88.3%	80.8%	83%	65%	87.7%	58.1%
NAUSEA/VOMITING (%)	NR	NR	69.6%	NR	54.7%	56.6%	30.8%	27.9%
TVO (%)	NR	NR	NR	NR	NR	10%	NR	14%
VISUAL LOSS/IMPAIRMENT/ BLURRING OF VISION (%)	13.2%	NR	22.1%	4.3%	33.3%	33.3%	49.2%	79%
DIPLOPIA (%)	13.5%	NR	29.3	4.3%	33.3%	20%	21.5%	25.6%
PAPILLEDEMA (%)	28.3%	86%	63.4	38.3%	86%	46.6%	53.8%	81.4%
6 TH NERVE PALSY (%)	13.5%	15%	NA	4.3%	30.7%	36.6%	NR	25.6%
Outcomes	86.6% no/minimal/mild impairment. Visual loss exceptional	93% complete recovery, 3 had optic atrophy	Favorable outcomes defined as independent status in 74.3% Visual outcomes not separately reported	85.1% complete recovery, 6.4% recovered with sequelae and 8.5% died; visual outcomes not separately reported	Mortality rate 3.8% Vision improvement: 94% without vision loss; 60% with unilateral and 73% with bilateral vision loss at presentation	58.3% improved on medical management, 28.3% after shunt 3 (5%) had optic atrophy	Average visual acuity: 20/25 (20/15 to light perception); 40% had Visual field defects	Visual outcomes With disc pallor: median BCVA improvement: 0 (IQR: -0.01 to 0.20) logMAR Without disc pallor: median BCVA improvement: 0.07 (IQR: 0-0.1) logMAR

*Data refers to the population of the patients from those with symptoms of isolated intracranial hypertension alone as relevant to the current study; ^bNone as the study included only patients with subacute/chronic CSVT; NR=not reported. This table suggests that unlike many studies, patients in our series more likely to be men, tended to be older, had greater prevalence of blurred vision and papilledema, and sixth cranial nerve palsy than most studies, while headaches were less frequent