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RESEARCH

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Clinical and radiological profile of cavernous sinus syndrome: a study from eastern part of India

Vinayak Narayan Rodge[1], Adreesh Mukherjee[1], Samar Biswas[1*], Suchitra Majumdar[2] and Goutam Gangopadhyay[1]

Abstract

Background Cavernous sinus syndrome (CSS) consists of a variable combination of involvement of the 3rd-to-6th cranial nerves. The etiologies vary across studies, and it has a significant impact on the outcome. This study was done to delineate the etiology, clinico-radiological profile and outcome of CSS. In this prospective study, patients were recruited consecutively over 2 years, and were followed up for at least 6 months. MRI of the brain and orbit with contrast was done, and other relevant investigations were performed to arrive at a specific etiology. Tolosa-Hunt Syndrome (THS) was defined in accordance with the second edition of the International Classification of Headache Disorders (ICHD-II).

Results Of the 92 patients studied, THS was the predominant diagnosis, followed by Tuberculosis, fungal infection, aneurysm, neoplastic and Sjögren's syndrome. Cranial nerves commonly involved were 3rd, 4th, 6th and 5th. The optic nerve was affected in 54.3% of patients. The non-THS patients showed the greater occurrence of proptosis, complete ophthalmoplegia, involvement of optic nerve and cranial nerves 7th–10th. Nasal blockage was present in fungal infection. MRI revealed more frequent involvement of orbit in non-THS cases. Bony erosions, ICA narrowing, intracranial extension and involvement of paranasal sinus were seen in fungal infection and neoplasm. THS patients improved with corticosteroid therapy, although, there was recurrence in 8 patients.

Conclusions THS and tuberculosis were the most common cause of CSS. Clinical and radiological features were useful in distinguishing among the etiologies. Most of the patients responded to treatment, although, recurrence was seen in THS.

Keywords Cavernous sinus syndrome, Fungal, Magnetic resonance imaging, Tolosa-Hunt syndrome, Tuberculosis

Background

Cavernous sinus is a complex venous space situated on either side of the sphenoid sinus and the sella turcica, and it consists of the carotid artery, cranial nerves and sympathetic fibers [1]. Cavernous sinus syndrome (CSS) signifies the involvement of cranial nerves located in the cavernous sinus. This includes a variable combination of the third, fourth, fifth (V1, V2) and sixth cranial nerves (CN), and the oculosympathetic fibers [2]. The clinical features consist of headache, diplopia, ptosis, facial numbness, dimness of vision and proptosis.

*Correspondence:
Samar Biswas
biswassamar66@gmail.com
[1] Department of Neurology, Bangur Institute of Neurosciences, Institute of Post Graduate Medical Education and Research, 52/1A, Sambhu Nath Pandit Street, Kolkata 700025, India
[2] Department of Ophthalmology, Institute of Post Graduate Medical Education and Research, Kolkata, India

Ophthalmoplegia is the prominent finding, associated with trigeminal nerve and optic nerve involvement. The common etiologies for CSS are neoplasms, infection, non-infectious inflammation and vascular (aneurysms, fistula) [3, 4]. Trauma has also been listed as a likely cause [2]. An Indian study noted tumors, fungal infections and Tolosa-Hunt syndrome (THS) as the most frequent etiologies [5]. The relative proportion of these etiologies differs across the various studies. Fernández and colleagues [3] documented an overwhelming presence of tumors (63%), whereas Bhatkar and colleagues [5] found a much lower prevalence (28.8%). Inflammation was the commonest cause in another large series [6]. The outcome of CSS has been described in some of the studies, and it varies according to the etiology [5]. However, often information on follow-up is lacking. Moreover, patients with treatable causes of CSS can also rarely have an unfavorable course.

Detailed studies on CSS are sparse in this part of the world. Hence, we conducted this prospective study from eastern India to delineate the etiology and clinico-radiological profile of CSS along with its outcome.

Methods

This was a prospective study carried out at a tertiary care institute in eastern India over a period of 2 years (2017–2019). The patients were recruited consecutively from the departments of Neurology and Ophthalmology, and were followed up for at least 6 months. The study was approved by the institutional ethics committee and written informed consent was obtained from the patients. For inclusion in the study, the diagnostic criteria of CSS were the involvement of two or more of the third, fourth, fifth (V1, V2) or sixth cranial nerves, or the involvement of one of them in the presence of a radiologically confirmed cavernous sinus lesion [3]. The study excluded patients with a single cranial nerve involvement in the absence of a definite radiological lesion, post-traumatic cases, patients less than 12 years of age and patients who could not be followed up for at least 6 months.

After detailed history and examination of the patients, relevant investigations were performed to arrive at a diagnosis. Investigations included complete hemogram, total and differential leukocyte count, erythrocyte sedimentation rate, fasting and postprandial blood glucose levels, serum HbA1c, and renal, liver and thyroid function tests. Other tests comprised Antinuclear antibodies (ANA), ANA profile, Anti-Ro (SS-A), Anti-La (SS-B), Antineutrophil cytoplasmic antibodies (ANCA), Serum Angiotensin-converting enzyme (ACE), Chest X ray and Mantoux test. Serum IgG4 level, nasal scraping and endoscopic biopsy were done in selected patients. Magnetic resonance imaging (MRI) of the brain and orbit with gadolinium contrast was obtained for all the patients (unless contraindicated), and MR angiography was advised in selected patients. The visual evoked potential was also performed. A cerebrospinal fluid (CSF) study was done in indicated cases. If required, additional investigations were performed to arrive at a specific etiology.

The diagnosis of THS was defined in accordance with the second edition of the International Classification of Headache Disorders (ICHD-II) [7]. These patients were followed up for at least 1 year (2 years in several cases) for a definite diagnosis and also to record any recurrence. THS formed a large section of the patients of CSS. For comparative analysis, other etiologies were taken together as the non-THS group. To differentiate from the infective causes, an analysis was also performed taking Tuberculosis and fungal infection together.

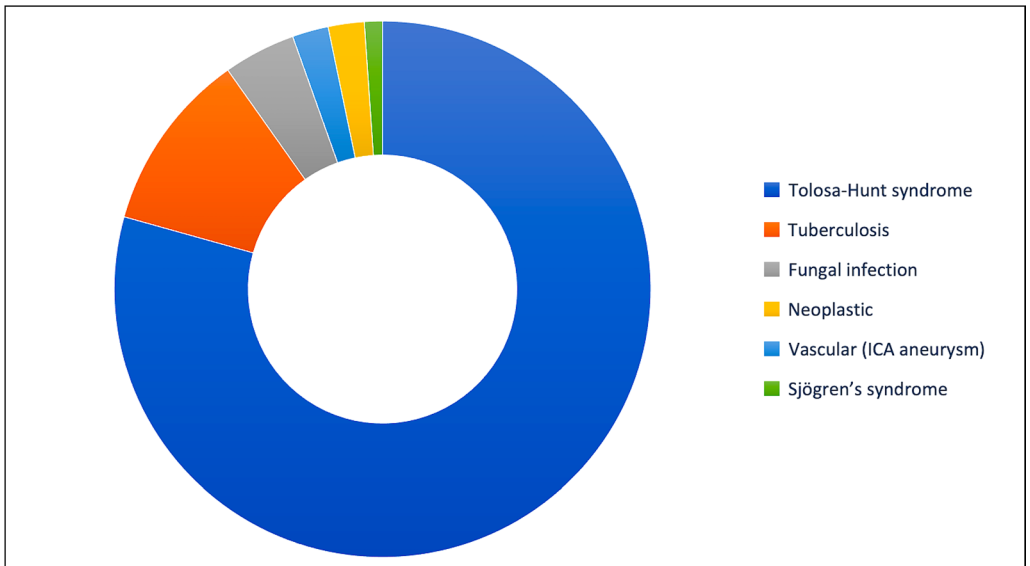
All the patients were treated according to the etiology, following standard protocols including surgical treatment. THS patients received corticosteroids with taper according to the response.

Statistical analysis was done using SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). Categorical variables were expressed as frequency (percentage) and compared across groups using the Pearson Chi-squared test/ Fisher exact test as applicable. Continuous variables were expressed as mean and standard deviation and compared between groups using the Mann–Whitney U test. Logistic regression analysis was done to assess the ability of variables to predict THS. A P value at the level of < 0.05 was considered as significant.

Results

Of the total 92 patients of CSS included in this study, females (62%) outnumbered males (38%). The mean ($\pm$ SD) age at presentation was 44.16 ± 15.32 years (range 12–78 years), and the majority of the patients (64.1%) belonged to the 31–60 years age group. The mode of presentation was categorized as acute (onset-to-presentation duration—up to 1 week), subacute (duration > 1 week up to 1 month) and chronic (duration > 1 month) [5]. The most common presentation was subacute (n = 44, 47.8%), followed by chronic (n = 38, 41.3%), and the rest (n = 10, 10.9%) was acute. In 19 (20.7%) patients, a definite etiology could be arrived at (tuberculous, fungal, aneurysm, neoplastic and Sjögren's syndrome), whereas, the other 73 (79.3%) patients were diagnosed as THS after reasonable exclusion of possible etiologies (Fig. 1). None of the patients were HIV positive.

Headache was the most common symptom and was present in almost all the patients. Other frequent symptoms were diplopia, ptosis and facial numbness (Table 1). Dimness of vision was present in 47 (51.1%) patients. Clinically, the cranial nerves commonly involved were



Etiology		Number of patients (%)
Possible Tolosa-Hunt syndrome		73 (79.3)
Tuberculosis		10 (10.9)
Fungal infection	Aspergillosis	3 (3.3)
	Mucormycosis	1 (1.1)
	Total	4 (4.3)
Neoplastic	Meningioma	1 (1.1)
	Pituitary macroadenoma	1 (1.1)
	Total	2 (2.2)
Vascular (Internal carotid artery aneurysm)		2 (2.2)
Sjögren's syndrome		1 (1.1)

Fig. 1 Etiology of cavernous sinus syndrome

3rd, 4th, 6th and 5th. The 3rd CN was involved bilaterally in 3 (3.3%) patients. The pupils were spared in 12 (13%) cases of 3rd CN palsy. Complete ophthalmoplegia was seen in 28 (30.4%) patients. Regarding the 5th CN, the ophthalmic (V1) division was affected more frequently than the maxillary (V2) division, while the mandibular division (V3) was involved in only 2 patients. The optic nerve was affected in 50 (54.3%) patients indicating an anterior extension of the lesion, and it was bilateral in two of them. Overall, only 3 (3.3%) patients had bilateral CSS. Other cranial nerves (7th–10th) were involved in less than 10% of cases.

There were some significant differences in the clinical and radiological features according to etiology (Table 2). Compared to THS, non-THS patients (as a group) showed a greater occurrence of proptosis, complete ophthalmoplegia, and involvement of optic nerve and cranial nerves 7th–10th (Table 3). Proptosis maintained this significant difference in logistic regression analysis. Nasal blockage was seen only in fungal infection. These differences also persisted when THS was compared with infective causes (as a group). The only significant clinical distinction between THS and Tuberculosis was proptosis. In addition to nasal blockage ($p = 0.001$), involvement of cranial nerves 7th–10th was more frequent in fungal infection ($p = 0.041$) compared to Tuberculosis. THS and non-THS groups were similar in terms of age ($p = 0.803$) and mode of presentation ($p = 0.215$). MRI revealed a greater involvement of the orbit in the non-THS group. Orbital pathology was more common in fungal infection than Tuberculosis ($p = 0.015$). Moreover, bony erosions, internal carotid artery (ICA) narrowing, intracranial extension and involvement of the paranasal sinus were seen only in fungal infections and neoplasms. Focal meningeal enhancement was noted in Tuberculosis, fungal infection, neoplasm and Sjögren's syndrome. MRI was normal in one patient of possible THS. He was diagnosed on the basis of typical clinical features after exclusion of other causes and improvement with corticosteroid.

Table 1 Clinical features of cavernous sinus syndrome

Clinical features	Number of patients (%)
Presenting symptoms	
Headache	90 (97.8)
Diplopia	86 (93.5)
Ptosis	84 (91.3)
Facial numbness	83 (90.2)
Dimness of vision	47 (51.1)
Proptosis	14 (15.2)
Hearing loss	6 (6.5)
Nasal blockage	4 (4.3)
Facial deviation	4 (4.3)
Nasal regurgitation / nasal intonation	1 (1.1)
Clinical examination	
CN III	88 (95.7)
CN IV	87 (94.6)
CN VI	84 (91.3)
CN V	
Total	83 (90.2)
V1 (Ophthalmic)	56 (60.9)
V2 (Maxillary)	39 (42.4)
V3 (Mandibular)	2 (2.2)
CN II	50 (54.3)
CN VIII	6 (6.5)
CN VII	4 (4.3)
Horner syndrome	3 (3.3)
CN IX, X	1 (1.1)

CN cranial nerve

The THS patients improved with corticosteroid therapy, although, the duration of treatment varied according to the response. There was the recurrence of symptoms in 8 patients of THS after stopping corticosteroid. No other etiology of CSS showed recurrence. The timing of the recurrence varied from 3 months to 1 year. It recurred twice in 2 patients. However, all the recurrences responded to corticosteroids. Patients with Tuberculosis were treated with first-line anti-tuberculosis drugs for a total of 18 months (divided into intensive and continuation phases). In 2 patients, the regimen was modified due to adverse effects on the first-line drugs. Corticosteroids were used in adjunct for the first 2 months. All of the patients had a good outcome with a resolution of symptoms of CSS (usually within the first 3 months), although, radiological improvement lagged behind. Patients with fungal infection received appropriate anti-fungal drugs and surgical intervention. However, residual deficits were present in 2 (50%) patients at 1 year of follow-up. Patients with aneurysm and neoplastic lesion were treated at the Neurosurgery department of our institute. Sjögren's syndrome responded well to treatment without any relapse.

Discussion

This is the largest series of CSS (and THS) patients from eastern India to date. The majority of the patients had a subacute-to-chronic presentation, similar to a previously published Indian study [5]. A study from Taiwan, however, noted mostly an acute onset in THS patients [8]. The prolongation in the present study might be due to a delayed presentation of acute onset cases or a more protracted course itself. A definite etiology was established in about one-fifth of the cases in this study, while the rest were diagnosed as possible THS. The proportion of THS and other etiologies of CSS has varied in different studies. Strictly Neurosurgical studies show a preponderance of tumors and other surgical entities [9]. However, other large series, including multidisciplinary studies, have documented a variety of etiologies, both medical and surgical (Table 4). Overall, the frequent causes are neoplasms, infection, non-infectious inflammation, vascular and trauma [2, 3, 5, 6]. The present study comprises an exceptionally large number of THS patients. There was likely an underrepresentation of surgical etiologies, as our institute is a Neurology tertiary referral center and caters to a higher number of medical cases. Further studies are required to know whether there is a true sociodemographic or ethnic variability.

THS was followed by infective etiology (tuberculosis and fungal). Tuberculosis has been documented previously as a rare cause of CSS [5, 10]. A recent Indian study on multiple cranial nerve palsies showed Tuberculosis as important etiology, although, it was relatively rare in CSS (1/8 cases of Tuberculous involvement) [11]. The present study highlights an important role of Tuberculosis as a treatable cause of CSS especially in the Indian context. Fungal infection was reported in several studies on CSS, mostly consisting of Mucormycosis and Aspergillosis [2–5]. None of the patients with fungal infection in the present study was HIV positive, however, 3 (out of 4) were diabetic. The patient with Sjögren's syndrome had a favorable outcome with immunosuppressive therapy. Although cranial neuropathies are well described in Sjögren's syndrome including total external ophthalmoplegia [12], it is a rare cause of CSS.

Headache was the commonest symptom of CSS, followed by diplopia and ptosis. This is in accordance with the usual presentation of CSS in different studies and signifies the localization of the lesion in the cavernous sinus affecting the 3rd, 4th and 6th cranial nerves. Studies on CSS documented a similar trend, while one of them showed a slightly greater involvement of the 6th CN compared to the 3rd CN [5]. Although in the minority

Table 2 Clinical and radiological features of the different etiologies of Cavernous sinus syndrome

	Tolosa Hunt Syndrome (n = 73) n (%)	Tuberculosis (n = 10) n (%)	Fungal Infection (n = 4) n (%)	Vascular (Aneurysm) (n = 2) n (%)	Neoplasm (n = 2) n (%)	Sjögren's Syndrome (n = 1) n (%)
Clinical features						
Headache	71 (97.3)	10 (100)	4 (100)	2 (100)	2 (100)	1 (100)
Diplopia	67 (91.8)	10 (100)	4 (100)	2 (100)	2 (100)	1 (100)
Ptosis	66 (90.4)	10 (100)	4 (100)	2 (100)	1 (50)	1 (100)
Proptosis	2 (2.7)	5 (50)	4 (100)	2 (100)	1 (50)	–
Nasal blockage	–	–	4 (100)	–	–	–
CN III	70 (95.9)	10 (100)	4 (100)	2 (100)	1 (50)	1 (100)
CN IV	69 (94.5)	10 (100)	4 (100)	2 (100)	1 (50)	1 (100)
CN VI	65 (89)	10 (100)	4 (100)	2 (100)	2 (100)	1 (100)
CN V	65 (89)	10 (100)	4 (100)	2 (100)	1 (50)	1 (100)
CN II	35 (47.9)	8 (80)	4 (100)	1 (50)	1 (50)	1 (100)
Complete Ophthalmoplegia	16 (21.9)	4 (40)	4 (100)	2 (100)	1 (50)	1 (100)
Other CN (VII, VIII, IX, X)	2 (2.7)	1 (10)	3 (75)	–	–	1 (100)
Radiological features (structures involved)						
Cavernous sinus	72 (98.6)	10 (100)	4 (100)	2 (100)	2 (100)	1 (100)
Orbital apex	33 (45.2)	2 (20)	4 (100)	2 (100)	1 (50)	1 (100)
Orbit	–	2 (20)	4 (100)	2 (100)	1 (50)	–
Paranasal sinuses	–	–	4 (100)	–	1 (50)	–
Bony erosions	–	–	3 (75)	–	2 (100)	–
ICA narrowing	–	–	3 (75)	–	2 (100)	–
Intracranial extension	–	–	1 (25)	–	2 (100)	–
Focal meningeal enhancement	–	3 (30)	1 (25)	–	2 (100)	1 (100)

CN cranial nerve, *ICA* internal carotid artery

(13%), yet, the pupils were spared in some of the cases of 3rd CN palsy. Hence, despite pupillary involvement being commonly noted, exceptions were there. In a previous study, 43.8% of patients with 3rd CN palsy had sparing of the pupil [5].

Facial numbness was due to the involvement of the 5th cranial nerve. The ophthalmic (V1) division was affected more frequently than the maxillary (V2) division, while the mandibular division (V3) was involved in only 2 patients. This might be explained by the location and extent of the lesion in the cavernous sinus. According to the Ishikawa classification, combined ophthalmic nerve and ocular motor nerve involvement denotes a middle type, whereas, involvement of the maxillary division indicates a posterior type of cavernous sinus lesion [6]. The 5th CN was affected more frequently in the present study compared to previous reports [2, 5]. However, the subjective nature of numbness and the sensory examination of the 5th CN might account for some variability. The optic nerve was involved in about half of the patients suggestive of an anterior type of CSS [6]. Previous studies documented a lower prevalence of optic nerve involvement in CSS [2, 3, 5]. Cranial nerves 7th–10th were involved in less than 10% of cases, signifying the spread of the lesion beyond the cavernous sinus.

THS was the predominant etiology in the present study. Headache, diplopia and ptosis were the most frequent symptoms. The commonest cranial nerve involved was 3rd, followed by 4th, 6th and 5th. The pattern of involvement of these cranial nerves in THS varies in different studies. A previous Indian study documented 3rd CN involvement in every patient of THS [13]. However, other cranial nerves were affected to a lesser extent, with the 5th CN being involved in 50% of patients and the 4th and 6th CN in less than 20%. Similar to the present study, optic nerve involvement was present but less common [13]. In a Korean study on THS, 6th CN (72.7%) was affected more frequently than 3rd and 4th CN (45.5% each) [14]. A study from Qatar found visual disturbance in 96.8% of patients with THS [15]. It also noted the involvement of the 3rd and 6th CN most frequently, while 4th and 5th (V1) CN were much less affected [15]. This difference in the pattern of involvement of the cranial nerves may be due to the variability in the extent of the lesion within and anterior to the cavernous sinus. Also, a delay in the presentation and diagnosis may lead

Table 3 Comparison of clinical and radiological features between Tolosa Hunt syndrome and other etiologies

	Tolosa Hunt Syndrome (n = 73)	Non-THS[#] (n = 19)		Infective[‡] (n = 14)		Tuberculosis (n = 10)	
	n (%)	n (%)	P value	nN (%)	P value	n (%)	P value
Clinical features							
Headache	71 (97.3)	19 (100)	1.000	14 (100)	1.000	10 (100)	1.000
Diplopia	67 (91.8)	19 (100)	0.3388	14 (100)	0.5836	10 (100)	1.000
Ptosis	66 (90.4)	18 (94.7)	0.3376	14 (100)	0.5921	10 (100)	0.59
Proptosis	2 (2.7)	12 (63.2)	< 0.001*	9 (64.3)	< 0.001*	5 (50)	< 0.001*
Nasal blockage	–	4 (21.1)	0.0014*	4 (28.6)	< 0.001*	–	–
CN III	70 (95.9)	18 (94.7)	1.000	14 (100)	1.000	10 (100)	1.000
CN IV	69 (94.5)	18 (94.7)	1.000	14 (100)	1.000	10 (100)	1.000
CN VI	65 (89)	19 (100)	0.1983	14 (100)	0.3445	10 (100)	0.5869
CN V	65 (89)	18 (94.7)	0.6793	14 (100)	0.3445	10 (100)	0.5869
CN II	35 (47.9)	15 (78.9)	0.0199*	12 (85.7)	0.0168*	8 (80)	0.0903
Complete Ophthalmoplegia	16 (21.9)	12 (63.2)	0.0013*	8 (57.1)	0.0181*	4 (40)	0.2436
Other CN (VII, VIII, IX, X)	2 (2.7)	5 (26.3)	0.0037*	4 (28.6)	0.0055*	1 (10)	0.3231
Radiological features							
Cavernous sinus	72 (98.6)	19 (100)	1.000	14 (100)	1.000	10 (100)	1.000
Orbital apex	33 (45.2)	10 (52.6)	0.6127	6 (42.9)	1.000	2 (20)	0.1731
Orbit	–	9 (47.4)	< 0.001*	6 (42.9)	< 0.001*	2 (20)	0.0132*
Paranasal sinuses	–	5 (26.3)	< 0.001*	4 (28.6)	< 0.001*	–	–
Bony erosions	–	5 (26.3)	< 0.001*	3 (21.4)	0.0034*	–	–
ICA narrowing	–	5 (26.3)	< 0.001*	3 (21.4)	0.0034*	–	–
Intracranial extension	–	3 (15.8)	0.0077*	1 (7.1)	0.1609	–	–
Focal meningeal enhancement	–	7 (36.8)	< 0.001*	4 (28.6)	< 0.001*	3 (30)	0.0013*

CN cranial nerve, *ICA* internal carotid artery

[#] Non-THS (Non-Tolosa Hunt Syndrome)—comprises all patients other than Tolosa Hunt Syndrome

[‡] Infective—comprises Tuberculosis and fungal infection

*Significance at $p < 0.05$

to a greater involvement of the cranial nerves, although, it is not possible to conclude this from the present study. Thus, THS is characterized by headache/ periorbital pain, diplopia and ptosis, with a variable combination of involvement of 3rd–6th cranial nerves. Additionally, the optic nerve may be affected, signifying a more anterior lesion. Although rare, involvement of the facial nerve has also been reported in THS [16].

Proptosis, complete ophthalmoplegia, and involvement of optic nerve and cranial nerves 7th–10th distinguished non-THS patients from THS. All of these were more common in non-THS patients, with proptosis being the most significant discriminator. The nasal blockage was unique to the fungal infection. These features also differentiated THS from the infective etiologies group (Tuberculosis and fungal infection taken together). Tuberculosis was the second most common etiology in the present study, and proptosis was its only significant clinical distinction from THS. Compared to Tuberculosis, fungal infection had a greater involvement of 7th–10th CN (in addition to nasal blockage).

While comparing THS with other symptomatic painful ophthalmoplegia (SPO), Hung and colleagues noted a greater occurrence of atypical symptoms and radiographical findings in SPO [8]. The atypical symptoms included bilateral headache or hemicranial headache other than orbital dominant pain, and orbital pain preceding ophthalmoplegia by over 2 weeks or developing after it [8]. In their study on CSS, Fernández and colleagues documented pain at the onset of the disease and 3rd CN involvement to be associated with THS, whereas, lack of pain and V2 involvement were linked with tumor [3]. Bhatkar and colleagues observed an association of fungal CSS with severe visual loss, nasal blockage and diabetes mellitus [5]. Additionally, they noted significant proptosis in vascular etiologies [5]. An Indian study on multiple cranial nerve palsies revealed the involvement of non-cavernous sinus locations in non-THS etiologies such as tumor and tuberculosis [11]. Optic nerve involvement in the form of orbital apex syndrome was also more common in non-THS cases, especially fungal infection and tumor [11]. The present study also showed more frequent

Table 4 Cavernous sinus syndrome in various studies

Present study (n = 92)	Bhatkar et al. [5] (n = 73)	Keane [2] (n = 151)	Fernández et al. [3] (n = 126)
Average age at presentation (years)			
44.16 ± 15.32 (range 12–78)	44. 45 ± 14.7 (range 11–70)	39 (range 15–72)	55.5 (range 18–83)
Gender (%)			
Female—62 Male—38	Male—64 Female—36	Male—59 Female—41	Female—58 Male—42
Mode of onset (%)			
Acute—10.9 Subacute—47.8 Chronic—41.3	Acute—24.7 Subacute—27.4 Chronic—47.9	–	–
Side involved (%)			
Right—42.4 Left—54.3 Bilateral—3.3	Bilateral—16.4	Right—49 Left—47 Bilateral—4	Right—53 Left—42 Bilateral—5
Etiology (%)			
THS—79.3 Tuberculosis—10.9 Fungal—4.3 Neoplastic—2.2 Vascular—2.2 Others (Sjögren's syndrome)—1.1	Neoplastic—28.8 Fungal—24.6 THS—23.2 Vascular—6.8 Others—16.4	Tumor—30 Trauma—24 Inflammation/questionable inflammation—23 Surgery—11 Vascular—6 Infection—5 Others—1	Tumor—63 Vascular—20 THS—13 Others—4
Recurrence in THS (n)			
8	2	-	3
Symptoms (%)			
Headache—97.8 Diplopia—93.5 Ptosis—91.3 Facial numbness—90.2	Headache—97.2 Diplopia—90.4 Ptosis—68.4 Facial numbness—56.2	-	Diplopia—66 Periocular pain—35 Facial paresthesia—15
Cranial nerves involved (%)			
CN III—95.7 CN IV—94.6 CN VI—91.3 CN V—90.2 CN II—54.3	CN III—78.1 CN IV—68.4 CN VI—82.1 CN V—V1 (46.5), V2 (30.1), V3 (8.2) CN II—23.2	CN III—99.3 CN IV—33.1 CN VI—94.7 CN V—38.4 CN II—39.1	CN III—66 CN IV—31 CN VI—58 CN V—V1 (38), V2 (24) CN II—19

CN cranial nerve, *THS* Tolosa-Hunt syndrome

involvement of optic nerve and 7th–10th CN in non-THS patients.

MRI Brain was instrumental in delineating the cavernous sinus lesions and their extension into other regions. Nearly half of the THS patients showed the involvement of the orbital apex in addition to the cavernous sinus. Similarly, Arthur and colleagues found orbital apex involvement in about 30% of cases of THS [13]. Other studies have also noted the involvement in the orbital apex/ superior orbital fissure in several THS patients [14, 15, 17]. In the present study, the non-THS group had greater involvement in the orbit. Bony erosions, ICA narrowing, intracranial extension and involvement of the paranasal sinus were seen in fungal infection and neoplasm. Focal meningeal enhancement was seen in infective and neoplastic cases and Sjögren's syndrome. In the study by Bhatkar and colleagues, fungal CSS was associated with bone erosion, paranasal sinus disease and narrowing of ICA on MRI, whereas, orbital apex involvement favored THS [5]. In another study, invasion beyond the cavernous sinus such as the sellar fossa and paranasal sinus, and focal narrowing of the intra-cavernous ICA were suggestive of non-THS etiology [8]. However, the inflammatory process in THS can sometimes cause narrowing of the adjacent ICA as well [4, 8].

THS showed a good response to corticosteroid therapy. However, there was a recurrence in 8 patients after stopping corticosteroid, and it was delayed by up to 1 year. No other etiology of CSS showed recurrence. Tuberculosis had a good outcome with appropriate treatment. On

the other hand, residual deficits were common in fungal infections. Previous studies have also noted favorable outcome in THS [5, 13, 14]. However, recurrence was present in most of the studies on THS [13–15]. The frequency of recurrence varied and the duration of follow-up seemed to play an important role as recurrence was documented at an interval of even 7 years [13]. Arthur and colleagues observed a reduced rate of recurrence in THS patients treated with steroid-sparing agents [13]. As described in the series on invasive fungal sinusitis by Thurtell and colleagues, fungal infections usually have a less favorable response, especially if treatment is delayed [18].

The present study has some limitations. Most of the patients were of THS, and hence there was a disproportionate representation of other etiologies, which makes their comparison less robust. There are several previous reports of THS cases turning out to be some other disease on follow-up. Although this study followed up patients of THS for at least 1 year, this does not definitively rule out the future possibility of a different etiologic diagnosis. However, the period of follow-up was reasonably long to exclude such possibilities and note any recurrence of symptoms.

Conclusions

THS was the commonest cause of CSS in the present study, followed by Tuberculosis. In addition to the 3rd–6th cranial nerves, the optic nerve was frequently affected. Some of the clinical and radiological features were useful in differentiating the various etiologies. Compared to THS, the presence of proptosis, complete ophthalmoplegia, and involvement of optic nerve and cranial nerves 7th–10th were more common in non-THS patients. Proptosis was the most significant discriminator. Nasal blockage was exclusive to the fungal infection. MRI revealed bony erosions, ICA narrowing, intracranial extension and involvement of the paranasal sinus in fungal infection and neoplasms. Among the non-neoplastic cases, fungal infection had a poorer outcome. THS improved with corticosteroid therapy, however, recurrences occurred during follow-up. Thus, patients with CSS, especially THS, should be followed up regularly to evaluate the response to treatment as well as to detect early signs of recurrence.

Abbreviations

CN	Cranial nerves
CSS	Cavernous sinus syndrome
ICA	Internal carotid artery
MRI	Magnetic resonance imaging
SPO	Symptomatic painful ophthalmoplegia
THS	Tolosa-Hunt syndrome

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Author contributions

VNR, AM, SB and GG were involved in the conception and design of the work. VNR, AM, SB and SM were involved in acquisition of data. All the authors contributed to analysis and interpretation of data. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional ethics committee (IPGME&R Research Oversight Committee) dated 11-05-2017 (No. IPGME&R/IEC/2017/296). Written informed consent was obtained from all patients included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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