Original Article

The Spectrum of Intracranial Hypertrophic Pachymeningitis at an Eastern Indian Tertiary Care Center

Suman Das[1,2], Biman Kanti Ray[2]

[1]Department of Neuromedicine, North Bengal Medical College, Darjeeling District, West Bengal, [2]Department of Neuromedicine, Bangur Institute of Neurosciences, Kolkata, West Bengal, India

Abstract

Introduction: Hypertrophic pachymeningitis (HP) is a treatable, rare inflammatory disease, either primary or secondary to systemic causes. **Aims:** To characterize the etiology, clinical manifestations, and treatment outcomes of HP patients and determine the factors influencing the radiological resolution of the pachymeningeal enhancement and recurrence of symptoms within the follow-up period. **Materials and Methods:** We collected data for this prospective observational study between March 1, 2021 and May 31, 2022, at the Bangur Institute of Neurosciences, Kolkata, and the patients were followed for a 6-month period. Demographic, clinical, laboratory, and treatment-related data were collected. A univariate logistic regression model was used for comparison between patients with and without radiological resolution of pachymeningitis and between patients with and without symptom recurrence. **Results:** Among 44 patients, the male: female ratio was 1.2:1. The median age at disease onset was 35.5 (28.5–49.5) years. The etiologies were idiopathic (56.8%), tuberculosis (22.8%), immunoglobulin G subtype 4 (IgG4) disease (9.2%), other infections (6.8%), and neoplastic (4.4%). Headache was the most common presentation (95.4%), followed by cranial neuropathies (68.2%). Optic and oculomotor neuropathies were the most common. In terms of radiological features, 27.27, 29.54, and 43.18% of patients had diffuse, focal regular, and focal irregular enhancement, respectively. Temporal (50%), followed by cavernous sinus (38.63%) enhancement, was the most common. Recurrence occurred in 36 and 50% of idiopathic and IgG4-related HP cases, respectively. Mycophenolate mofetil was added to their steroid regimen with no further recurrences. **Conclusion:** The cohort had a marked absence of (antineutrophil cytoplasmic antibodies) ANCA-associated HP. The severity of clinical manifestations or distribution of pachymeningitis did not differ significantly among the etiological groups. The presence of idiopathic etiology and focal regular enhancement had a significantly higher chance of radiological resolution. The response to therapy was satisfactory. Recurrence was significantly related to shorter steroid courses (<median duration of 5.2 months).

Keywords: Hypertrophic pachymeningitis, idiopathic, IgG4, tuberculosis, recurrence, resolution

Introduction

Hypertrophic pachymeningitis (HP) is a rare fibrosing inflammatory disease characterized by localized or diffuse thickening of the cranial or spinal dura mater. It can be idiopathic/primary (no identifiable cause) or secondary (co-existent cause identified).[1] The secondary causes can be infective (tubercular or bacterial meningitis, neurosyphilis, borreliosis, cryptococcosis, mucormycosis, aspergillosis), inflammatory immunoglobulin G subtype 4 (IgG4)-related disease (RD), rheumatoid arthritis, Behcet's disease, systemic lupus, mixed connective tissue disease, antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis], and miscellaneous causes (hemodialysis, mucopolysaccharidosis, neoplasia, postsurgical, drugs like hydralazine, propylthiouracil, cocaine, and allopurinol, and intrathecal drug administration).[2-5] The crude prevalence rate was 0.949/100,000 in a Japanese study.[6] The predominance of case reports and series and the relatively low number of research articles make the exact delineation of the epidemiology of HP difficult.[7] Gadolinium contrast-enhanced magnetic resonance imaging (CEMRI) is the gold standard for diagnosis. It also helps in differentiating other causes of dura mater thickening like intracranial hypotension.[7] In this study, we prospectively investigated 44 patients diagnosed with HP, the largest sample size described from India till date. We aimed to characterize the etiology, clinical manifestations, and treatment outcomes of HP in an eastern Indian population and identify the factors influencing the radiological resolution and recurrence of the symptoms of HP.

Materials and Methods

Study setting

This study was conducted at the Neuromedicine department of the Bangur Institute of Neurosciences, Kolkata, in eastern India,

Address for correspondence: Dr. Suman Das, Department of Neuromedicine, North Bengal Medical College, Darjeeling, West Bengal - 734 012, India.
E-mail: dr.sumands@gmail.com

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after institutional ethics committee approval (IPGMER/IEC/2022/030).

Study design

Prospective observational study.

Inclusion criteria

The diagnosis was based on dura mater enhancement in CEMRI T1 sequences, which was not explained by intracranial hypotension syndrome.

Methods

All patients with HP diagnosed between March 1, 2021 and May 31, 2022, were included in the study by the consecutive sampling technique after written informed consent. Postdischarge, every patient was followed for a 6-month period on an outpatient basis. There was no case of consent refusal or dropout during the follow-up period. Their demographic, clinical, laboratory, and treatment-related data were collected. We investigated all the patients by performing complete hemogram with erythrocyte sedimentation rate (ESR) and biochemical investigations (renal, liver, and thyroid function tests, C-reactive protein and electrolytes), cerebrospinal fluid study (CSF) (opening pressure, cell count and type, glucose, protein, Gram and Ziehl-Neelsen (ZN) stain, culture, cartridge-based nucleic acid amplification test for tubercle bacilli, adenosine deaminase (ADA)), autoantibodies testing (antinuclear antibody, rheumatoid factor, and p and c ANCA), serum angiotensinogen converting enzyme (ACE) and IgG4 levels, venereal disease research laboratory (VDRL), hepatitis B and C and HIV (human immunodeficiency virus) serologies, chest radiography [X rays or contrast-enhanced computed tomography (CECT) as when needed], and abdominal ultrasound or CECT.

We categorized the enhancement in CEMRI based on their pattern, distribution, and location. Distribution was categorized according to the following standards: lesions involving >50% of the intracranial compartment were denoted as "diffuse enhancement," and the rest as "focal enhancement."[7] We defined "irregular" enhancement as the existence of nodules, whereas "regular" enhancement was defined as linear enhancement without any nodules.[7] In all cases, CEMRI preceded the lumbar puncture.

Data analysis

The clinical, demographic, and radiological parameters were compared between the groups using the Pearson Chi-squared test for categorical variables and the Mann–Whitney *U* test for all continuous variables. The continuous variables were expressed as median and interquartile range (IQR). The determination of the factors influencing the resolution of pachymeningeal enhancement in CEMRI was the primary outcome. The recurrence of symptoms within the 6-month follow-up period was the secondary outcome. The outcomes were analyzed by univariate logistic regression modeling. P value < 0.05 was considered statistically significant.

Results

Table 1 shows the distribution of the demographic, clinical, radiological, and laboratory findings among the patients of varied etiology.

The male:female ratio was 1.2:1. The distribution of the etiologies did not differ significantly between genders. The other infections group comprised bacterial infections ($N = 2$) and rhino-orbito-cerebral mucormycosis ($N = 1$). The neoplasms were acute myeloid leukemia and an inflammatory myofibroblastic tumor ($N = 1$ each). Among the two HP cases due to bacterial infections, one patient had chronic suppurative otitis media (CSOM), and one had right parietal bone osteomyelitis.

Headache, the most common presentation, was more frequently holocranial. Hemicranial headaches were usually correlated with the distribution of hypertrophied pachymeninges. Frontal and periorbital pain usually occurred in patients with localized cavernous sinus lesions or frontal pachymeningeal involvement. The patient with cluster headache had unilateral tentorial pachymeningitis. Apart from the cluster headache, other patients had chronic daily dull, aching headaches without autonomic manifestations, nausea/vomiting, and photo/photophobia.

Cranial neuropathies, the second most common presentation, affected the nerves II–VIII. In descending order of affection, the optic, followed by oculomotor and abducens, were most frequently affected. The patients with seizures had focal onset clonic seizures with impaired awareness. About 6.8% of patients had encephalopathy and motor deficits (hemiparesis). The patient with spinal pachymeningitis had paraparesis.

There was a history of fever among three patients with tuberculous (TB) pachymeningitis. The patient with acute myeloid leukemia (AML) had weight loss. The mucormycosis-associated HP patient had soft tissue and bony erosions, with a discharging sinus over the left malar region. None had scleritis, epistaxis, cough, hemoptysis, salivary adenitis, lymphadenopathy, abdominal pain, muscle pain, or hematuria.

Focal irregular enhancement [Figure 1] exceeded focal regular [Figure 2] and diffuse pachymeningeal enhancement [Figure 3a, 3h]. Temporal lobar pachymeningeal enhancement was the commonest. Patients with raised intracranial pressure (ICP) had radiological evidence of distension of the perioptic nerve sheaths, protrusion of the optic nerve heads, and flattening of the posterior globe. Two (4.5%) patients with idiopathic HP and features of raised ICP had concomitant cerebral venous sinus thrombosis involving the transverse, sigmoid, and straight sinuses, as evidenced in contrast magnetic resonance venography (MRV). All of them had CSF opening pressures >20 cm water. In total, three idiopathic HP patients (6.8%) had FLAIR (Fluid-attenuated inversion recovery) hyperintensities without DWI (diffusion-weighted imaging) restrictions in

Table 1: The distribution of the demographic, clinical, radiological, and laboratory findings among the patients of varied etiologies

Parameters	Types of HP				
	Idiopathic, *n*=25 (56.8%)	TB, *n*=10 (22.8%)	IgG4 RD, *n*=4 (9.2%)	Other infections, *n*=3 (6.8%)	Neoplastic, *n*=2 (4.4%)
Demographics					
Age	41.4 (32.5–50)	35.5 (23.5–40)	33.5 (31.5–35.5)	10 (25–53)	
Sex [M=24, F=20]	M-14, F-11	M- 6, F-4	M-1, F-3	M-1, F-2	M-2, F-0
Time from symptoms onset to diagnosis (months) [3.06 (2.1–6.9)]	3 (1–4.75)	1.5 (1–2.12)	1.75 (1.12–2)	6 (5–7)	
Clinical features					
Headache (*n*=41, 94.5%)	Holo-16	Holo-2	Holo-1	Hemi-2	Holo-1
[Holo-43%	Hemi-3	Hemi-4	Hemi-1	FP-1	
Hemi-23%	FP-4	FP-3	FP-2		
FP-23%	Cluster-1				
Cluster-2%]					
Cranial neuropathies (*n*=30, 68.2%)	CN II-15	CN III-2	CN II-2	CN III-1	CN II-1
[II-40%,	CN III-3	CN IV-1	CN III-2	CN IV-1	
III-18%,	CN IV-2	CN VI-2	CN IV-1	CN V-1	
IV-11%	CN V-3	CN VII-1	CN VIII-1	CN VI-1	
V-7%	CN VI-4				
VI-16%	CN VIII-2				
VII-9%					
VIII-5%]					
Seizures (*n*=4, 9%)	2	2	-	-	-
Encephalopathy (*n*=3, 6.8%)	1	2	-	-	-
Raised ICP (*n*=4, 9%)	2	2	-	-	-
Diabetes (*n*=5, 11%)	4	-	-	1	-
Radiological features					
Pattern of affection	D- 7	D- 3	D- 1	D- 0	D- 1
[D-27.27%	FR-7	FR-3	FR- 2	FR- 1	FR- 0
FR-29.54%	FI-11	FI- 4	FI-1	FI- 2	FI- 1
FI-43.18%]					
Area of affection	Cavernous sinus-14	Temporal HP-4	Cavernous sinus-2	Temporal HP-1	Fronto parieto temporal HP-1
[Temporal-50%	Temporal HP-12	Tentorium-3	Fronto-temporal HP-1	Parietal HP-1	Temporal and tentorial HP-1
Cavernous sinus-38%	Tentorium-7	Falx-1	Tentorium-1	Cavernous sinus with temporal HP-1	
Tentorium-25%	Frontal HP-5	Frontoparietal HP-2			
Frontal-20%	Parietal HP-3	Diffuse-1			
Parietal-16%	Falx cerebri-3	Occipital HP-1			
Falx-9%]					
Laboratory features					
Leucocytosis (*n*=4, 9.09%)	-	2	-	2	-
Raised ESR (*n*=7, 15.9%)	1	5	1	-	-
CSF pleocytosis (*n*=7, 15.9%)	3	3	1	-	-
Raised CSF protein (*n*=11, 25%)	5	5	1	-	-

IgG4 RD=IgG4 related disease, M=male, F=female, D=diffuse enhancements, FR=focal regular enhancements, FI=focal irregular enhancements, holo=holocranial headache, hemi=hemicranial headache, frontal=frontal headache, FP=frontal/periorbital headache, cluster=cluster headache, CN=cranial nerve, ICP=intracranial pressure, many patients had multiple sites of involvement, ESR=erythrocyte sedimentation rate, CSF=cerebrospinal fluid, IgG4=immunoglobulin G subtype, HP=hypertrophic pachymeningitis

the brain parenchyma adjacent to the inflamed meninges, suggestive of venous edema [Figures 2b, 3c].

Among patients with tubercular HP, tuberculomas were seen in four patients, and tubercular abscess [Figure 1i] in one patient, which exhibited lipid-lactate peaks at 1.3 ppm in MR spectroscopy. Two patients had concomitant basal leptomeningeal enhancements. One patient had communicating hydrocephalus, and one patient had vasculitis of the right intracranial internal carotid, middle, and posterior cerebral arteries [Figure 3d] and resultant cerebral infarcts [Figure 3c and e]. 1 patient had dorsolumbar spinal pachymeningitis [Figure 3b].

The factors affecting the resolution of the pachymeningeal enhancement are analyzed in Table 2. Idiopathic HP had significantly higher radiological resolution than other etiological subgroups of HP. However, none of the cases

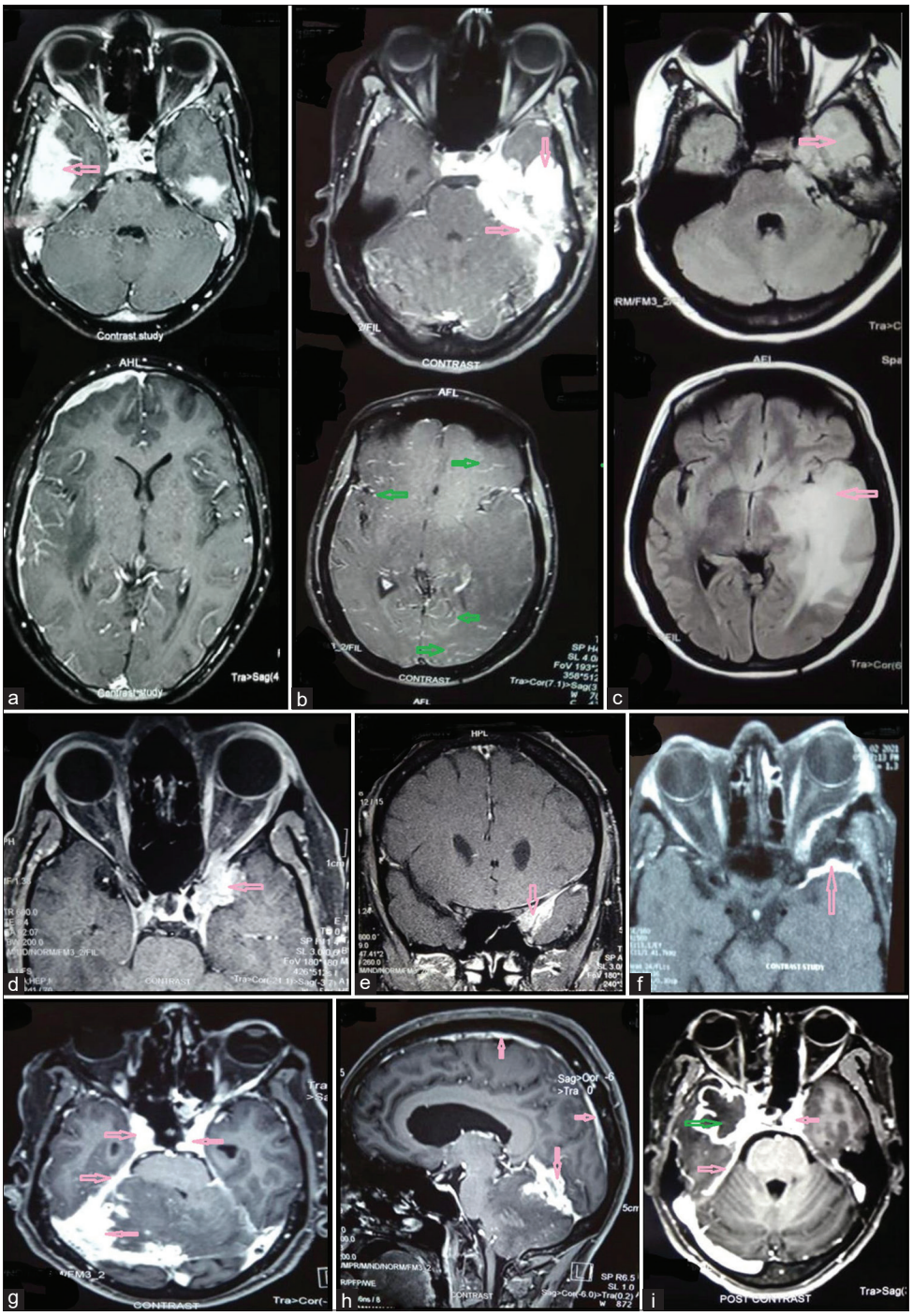

Figure 1: Focal irregular HP. (a) T1 contrast image: patient with AML with nodular pachymeningitis of bilateral temporal lobes (right > left) and patchy involvements of right frontoparietal regions (marked with pink arrows). (b) T1 contrast image and (c) T2 FLAIR image: Patient with TB HP with nodular pachymeningitis involving the left temporal region and the tentorium cerebelli (marked with pink arrows), along with subtle leptomeningeal enhancements (marked with green arrows). Edema is seen in the adjacent brain parenchyma with mass effect (marked with pink arrows). (d) T1 contrast axial image and (e) T1 contrast coronal image: patient with IgG4-RD having focal nodular enhancements involving left cavernous sinus, orbital apex, and medial temporal region (marked with pink arrows). (f) T1 contrast image: patient with idiopathic HP with nodular pachymeningitis involving the left temporal region (marked with pink arrow). (g) T1 contrast axial image and (h) T1 contrast sagittal image: patient with TB HP with nodular enhancements of left tentorium, bilateral medial temporal and cavernous sinus regions, along with falx cerebri (marked with pink arrows). (i) T1 contrast image: patient with TB HP having nodular enhancements of bilateral medial temporal and cavernous sinus regions and bilateral tentorium cerebelli (marked with pink arrows). There is a TB access in the right temporal lobe (marked with green arrow)

of TB HP were radiologically resolved, although all of them symptomatically improved. Focal regular HP had significantly higher resolution than other patterns of involvement.

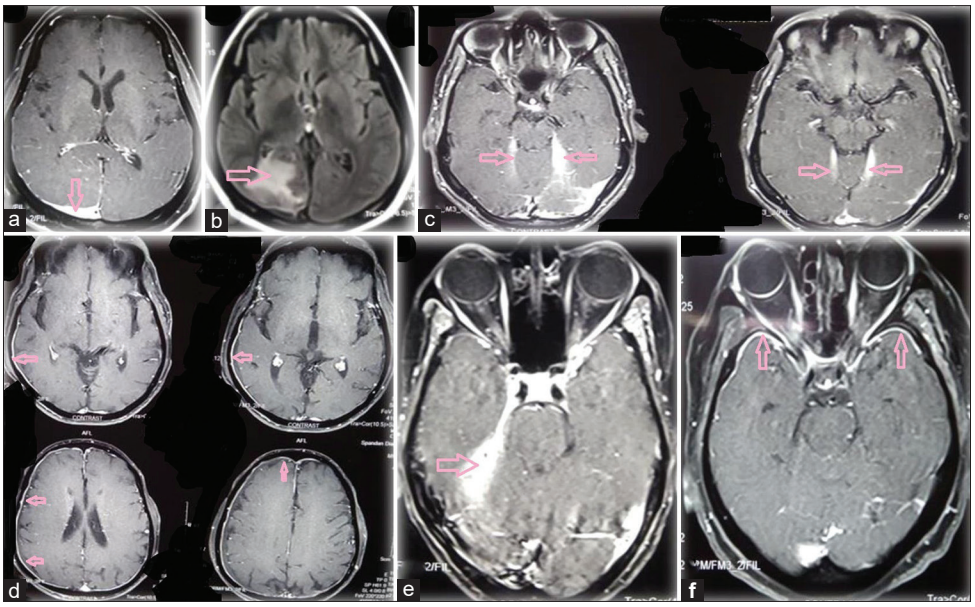

Figure 2: Focal regular HP. (a) T1 contrast image, (b) T2 FLAIR image: patient with idiopathic HP involving the right occipital region (focal regular enhancement) with edema in the adjacent cortex, with mild mass effect (marked with pink arrows). (c) T1 contrast image: bilateral tentorial focal regular enhancements in a patient with TB HP (marked with pink arrows). (d) T1 contrast image: right-sided frontal, parietal, and temporal focal regular pachymeningeal enhancements in a patient with idiopathic HP, presenting with right hemicranial headache (marked with pink arrows). (e) T1 contrast image: patient with idiopathic HP with right tentorial and bilateral anterior temporal region focal regular enhancements (marked with pink arrows)

Table 2: The factors affecting the radiological resolution of pachymeningeal enhancements

Parameters	Resolution in MRI [*n*=13, 29.54%]	Unresolved HP [*n*=31, 70.46%]	*P*
Age (years)	38.6 (28.2–50.2)	32.4 (29–49.5)	0.6
Female sex (*n*=20)	7 (53.8%)	13 (41.9%)	0.52
Etiology			
Idiopathic (*n*=25)	11 (84.6%)	14 (45.2%)	0.02
TB (*n*=10)	0	10 (32.3%)	0.04
IgG4 (*n*=4)	1 (7.7%)	3 (9.7%)	1
Other infections (*n*=3)	1 (7.7%)	2 (6.4%)	1
Malignancy (*n*=2)	0	2 (6.4%)	1
Pattern of enhancements			
Diffuse (*n*=12)	4 (30.8%)	8 (25.8%)	1
FN (*n*=19)	1 (7.7%)	18 (58.1%)	0.002
FR (*n*=13)	8 (61.5%)	5 (16.1%)	0.004
Sites of affection			
Temporal (*n*=22)	4	18	1
Cavernous sinus (*n*=17)	4	13	0.7
Tentorium (*n*=11)	2	9	1
Frontal (*n*=9)	1	8	0.68
Parietal (*n*=7)	1	6	1
Falx cerebri (*n*=4)	1	3	1
Occipital (*n*=1)	0	1	1
Treatment			
Duration of steroid therapy (months)	4.8 (3.3–6.3)	4.2 (3.5–5.9)	*P*=0.8

FR=Focal regular enhancements, MRI=Magnetic resonance imaging, TB=Tuberculosis., IgG4=Immunoglobulin G subtype, HP=Hypertrophic pachymeningitis, FN=Focal nodular enhancement

The median (IQR) values for patients with leucocytosis, raised ESR, CSF lymphocytic pleocytosis, and raised CSF protein were 12600 leucocytes (11580–17548)/mm^3, 30 (25–40) mm in 1st hour, 18 (12–36) cells/mm^3, and 56 (49–66) mg/dL, respectively. None had anemia, thrombocytopenia, positive ANA/ANCA, HIV/VDRL/Hepatitis B and C serologies, or elevated serum ACE levels. Only one patient with TB HP had evidence of healed old pulmonary TB on a chest radiograph. CSF had elevated ADA levels in two patients with TB HP. All the four patients with IgG4-RD had elevated serum IgG4

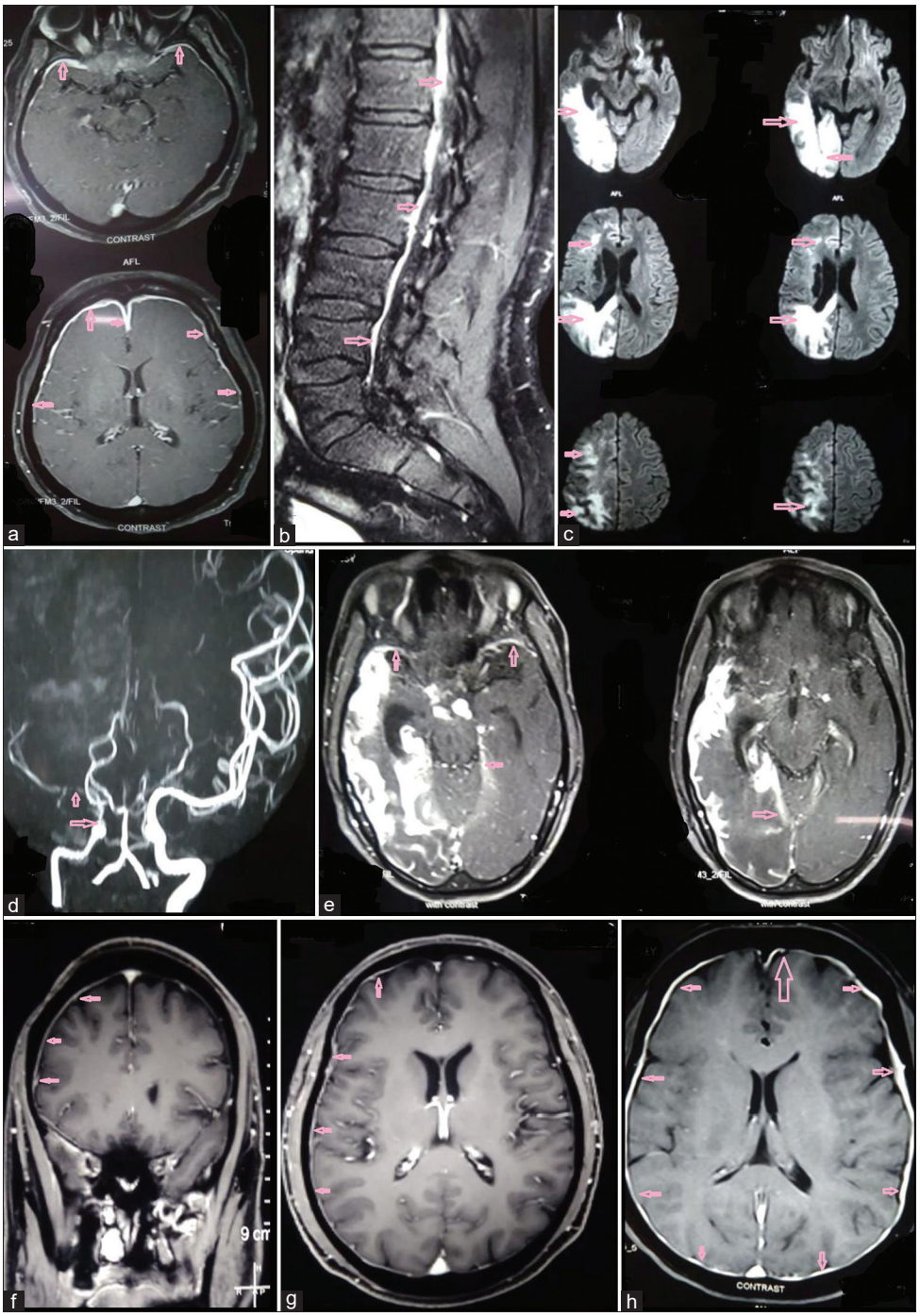

Figure 3: Idiopathic HP, "other infections" associated HP, spinal HP, complications of HP. (a) T1 contrast image: patient with idiopathic HP having bilateral enhancements in frontal, parietal, and temporal regions (marked with pink arrows) (b) T1 contrast image: patient with TB having dorsolumbar HP (marked with pink arrows) (c) DWI image (d) MR angiography, (e) T1 contrast image: patient with TB HP with arteriopathies having diffusion restrictions in the right frontal, parietal, temporal, and occipital lobes. The caliber of right ICA and MCA are reduced, along with focal arteriopathy in the right posterior cerebral artery. There is contrast uptake in subacute infarcted tissues, and there are focal pachymeningeal enhancements of bilateral anterior temporal, and tentorium cerebelli regions (marked with pink arrows) (f) T1 contrast axial image (g) T1 contrast coronal image: patient with right parietal bone osteomyelitis (post-debridement status), with underlying pachymeningeal enhancements (marked with pink arrows) (h) T1 contrast image: patient with idiopathic HP having bilateral enhancements in frontal, parietal temporal, and occipital regions (marked with pink arrows)

levels [137.5 (136.5–140.9) mg/dL]. In the presence of organ involvement (HP) and elevated serum IgG4 levels >135 mg/dL, our patients were classified as possible IgG4- RD as per the 2020 revised diagnostic criteria.[8] All the patients had normal renal, liver, and thyroid functions. The patients with cerebral venous sinus thrombosis (CVST) had normal homocysteine, protein C, protein S, and antithrombin III levels and lacked Leiden factor V mutations.

All patients with idiopathic and IgG4-RD were treated with intravenous pulse methylprednisolone for five days. This was followed by oral prednisolone at 1 mg/kg/day for 8 weeks and a subsequent taper. Although headaches resolved completely in all patients, some patients were left with residual disabilities due to cranial neuropathies. Residual reduced visual acuity following optic neuropathy, residual extraocular muscle weakness with resultant squinting, and residual sensorineural hearing loss were noted in three, two, and one idiopathic HP patients, and in one, one, and 0 patients with IgG4-RD, respectively.

The median duration of steroid therapy in these two groups combined was 4.5 (3.1–6.4) months. A shorter duration of steroid therapy was significantly associated with the recurrence of symptoms [Table 3]. Patients who relapsed after the stoppage of steroid therapy were restarted on steroids. They again had a good response, similar to the first episode. The subsequent tapering was slow, and we planned long-term continuation at low doses. We also started the additional immunomodulator mycophenolate mofetil (MMF), and they did not relapse further during the study period. Only two patients with idiopathic HP who had severe symptoms at onset (CVST) were also initiated on MMF from the beginning of their treatment, and they did not experience relapses of symptoms. Acenocoumarol was added to maintain their International Normalized Ratio between 2 and 3, and acetazolamide was used to reduce the ICP.

In addition, one patient, who was initially suspected to have idiopathic HP, had severe persistent holocranial headache despite two courses of pulse methylprednisolone, followed by oral prednisolone. He also had a sequential bilateral visual loss. He was initiated on rituximab cycles (1 g at 2-week intervals, followed by every 6-monthly infusion). His dural biopsy was done after the third cycle of rituximab therapy. It showed dense lymphohistiocytic infiltration by plasma cells and eosinophils. There was a storiform pattern of fibrosis which stained positive for reticulin. However, the characteristic of obliterating phlebitis was lacking, which differentiated it from IgG4-RD. No granulomas, giant cells, or fungal elements were seen; ZN, Periodic acid-Schiff, and Giemsa stains were negative. CD138 (plasma cells), CD68 (histiocytes), and S100 (histiocytes) were positive, and CD1a was negative. The features were suggestive of an inflammatory myofibroblastic tumor. His headache was completely unresponsive to therapy, and he also developed bilateral optic atrophy.

Patients with TB HP received four antitubercular drugs (ATD) (isoniazid, rifampicin, pyrazinamide, and ethambutol) from the directly observed treatment centers during their 2-month intensive phase. The 10-month continuation phase comprised of isoniazid, rifampicin, and ethambutol. None had serious adverse effects from ATD. They also received oral prednisolone (1mg/kg/day) for 8 weeks, followed by a slow taper over the next 4 weeks. Two patients had partial resolution of their headaches, and others had complete resolution; three had residual cranial neuropathies (extraocular muscle weaknesses).

The patient with CSOM was treated with injections of ceftriaxone and vancomycin for 4 weeks, followed by oral cefuroxime, topical ear drops containing fluroquinolone with steroids, and a modified radical mastoidectomy. The diabetic patient with rhino-orbito-cerebral mucormycosis was treated with an injection of amphotericin B 1 mg/kg/day for 4 weeks,

Table 3: The factors affecting the recurrence of symptoms

Parameters	Recurrence of symptoms [*n*=11, 25%]	No recurrences [*n*=33, 75%]	*P*
Age (years)	36.2 (27.7–39.5)	39.8 (21.8–42.4)	0.56
Female sex	4 (36.4%)	16 (48.5%)	0.7
Etiology			
Idiopathic (*n*=25)	9 (81.8%)	16 (48.4%)	0.99
TB (*n*=10)	0	10 (30.3%)	0.08
IgG4 (*n*=4)	2 (18.2%)	2 (6.1%)	0.55
Other infections (*n*=3)	0	3 (9.1%)	0.56
Malignancy (*n*=2)	0	2 (6.1%)	1
Pattern of enhancements			
Diffuse (*n*=12)	3 (27.3%)	9 (27.3%)	1
FN (*n*=19)	6 (54.5%)	13 (39.4%)	0.48
FR (*n*=13)	2 (18.2%)	11 (33.3%)	0.4
Sites of affection			
Temporal (*n*=22)	4	18	0.7
Cavernous sinus (*n*=17)	3	14	0.74
Tentorium (*n*=11)	3	8	0.69
Frontal (*n*=9)	2	7	1
Parietal (*n*=7)	2	5	0.1
Falx cerebri (*n*=4)	1	3	1
Occipital (*n*=1)	0	1	1
Treatment			
Duration of steroid therapy (months)	3.8 (3–4.9)	5.2 (3.2–6.2)	0.00148

followed by oral posaconazole 300 mg daily for 6 months. Strict euglycemia was ensured, and necrotic tissues were surgically debridged. The patient with right parietal bone osteomyelitis and a discharging sinus [Figure 3f, 3g] was treated with injections of meropenem and vancomycin for 8 weeks, followed by oral linezolid. Surgical debridement of necrotic tissues and removal of a segment of the parietal bone was done. Patients in this group showed complete resolution of symptoms following therapy for their primary infections.

The patient with AML was treated with the standard chemotherapy regimen as determined by the hematologist. Although he went into hematologic resolution, his pachymeningeal enhancement persisted at the end of the follow-up period [Figure 3a].

Discussion

There were nine previous publications from India, five of which were case series. The first clinical study was published by Sobha *et al.*[9] followed by Barvalia *et al.*[10] A continuation of the same series was published by Jagiasi *et al.*[11] followed by Gupta *et al.*[12] We describe 44 cases, the largest cohort published from India till date. The cases were diagnosed over a time period of 15 months, which was grossly shorter compared to previous Indian and foreign studies [Table 4]. Rare diseases can be geographically disparate and of a heterogeneous nature. Moreover, the insufficiency of epidemiological data and the lack of earlier publications from eastern India make it difficult to ascertain the reason for the clustering of HP cases during the study period.

The median age of presentation in our study was comparable with the studies of Sylaja *et al.*[4] and Sobha *et al.,*[9] but much lower than the other Asian and western studies. Although higher female prevalence was seen in the majority of the Asian studies, western studies by Kupersmith *et al.*[20] and Mekinian *et al.*[19] reported male predominance in their cohorts. In India, we and Sobha *et al.*[9] also had more male patients. Although some studies found no sex predominance in the whole cohort, the distribution of etiologies differed between genders.[7] Xiao *et al.*[7] reported viral and tubercular HP only in females and bacterial HP only in males; idiopathic HP and ANCA-associated HP had male and female predominance, respectively. Yokoseki *et al.*[15] also reported an elderly female predominance among patients with p-ANCA vasculitis. However, Mekinian *et al.*[19] reported male predominance even in ANCA-associated HP patients.

Likewise, in other Asian and western studies, we also found idiopathic HP to be the most common. However, interestingly, we did not encounter any ANCA-associated HP cases. Higher proportions of ANCA-associated HP were described by Japanese[4,15] and Chinese[7,16] studies, and even exceeded idiopathic variants in the studies by Yokoseki *et al.*[15] and Bi *et al.*[21] [Table 4]. Indian studies[9-11] reported a lower proportion of ANCA-associated HP. The proportions of TB and IgG4 disease-related HP in our study were comparable to other Indian and foreign studies [Table 4]. The median duration from symptom onset to diagnosis of HP was much shorter than the average 22-month period described by Xiao *et al.*[7] We found a minimum time gap for TB HP and a maximum for HP associated with other infections, whereas Xiao *et al.*[7] described the shortest (0.6 ± 0.4) month interval for bacterial meningitis and the longest (25 ± 36) month interval for idiopathic HP.

Similar to other studies, headache was the most common symptom in our study. Wang *et al.*[22] reported chronic daily headaches, especially chronic migraine, as the most common headache type among six HP patients studied over 6 years. Although, our patients had chronic daily headaches, they did not have migrainous features. Cluster headache is extremely rare in HP, with only one case reported previously in a 71-year-old man.[18]

We found cranial neuropathies to be the second most common manifestation. However, Thai studies[13,23] reported cranial neuropathies to be more common than headaches. Two patterns of cranial neuropathies correlated to the site of dural inflammation have been described. The cavernous sinus to superior orbital fissure (affecting the 2nd–6th nerves) and falcotentorial to posterior fossa dural involvement (affecting 3rd–12th nerves).[17] Optic neuropathy was most common in our study, similar to the reports of Jagiasi *et al.,*[11] Bi *et al.*,[21] and Xiao *et al.*[7] Xiao *et al.*[7] even reported optic neuropathy to be the commonest cranial neuropathy in all the subgroups of HP: idiopathic, ANCA-related HP, TB, and bacterial/viral meningitis-related HP. We found the oculomotor and the abducens to be the next most commonly affected cranial nerves. Thai studies[13,24] and the Indian study by Gupta *et al.*[12] also described the oculomotor and the abducens nerves as the most commonly affected nerves, exceeding optic neuropathy. The abducens nerve was the second most commonly affected in the study by Jagiasi *et al.*[11] and in the idiopathic HP group of Xiao *et al.*[7]

The frequency of seizures in the idiopathic and TB HP groups in our study was higher than the 6.25% cases in Xiao *et al.'s*[7] study (in the same etiological groups). Sakdee *et al.*[13] reported seizures in 2.4% of cases among idiopathic and IgG4-related HP groups. We noted raised ICP and papilledema in patients with idiopathic HP due to CVST and among TB HP patients without CVST. CVST had been described in 13% of patients in the study by Chen *et al.*[16] and also in IgG4 and ANCA-related HP due to dural inflammation and ensuing local hemodynamic changes.[14,25] Xiao *et al.*[7] reported raised ICP among 29% of patients in their study (31% in idiopathic HP, 43% in ANCA-related HP, and 25% in TB HP groups). In contrast to some studies, where severe features (seizures, focal deficits, raised ICP) insinuated secondary etiologies,[11] we found such features in the idiopathic group too.

In our study, focal HP far exceeded diffuse HP, similar to the Thai studies.[13,24] However, intra-national variability was seen in other Indian and Chinese studies. Although Jagiasi *et al.*[11] and Gupta *et al.*[12] reported the vast majority of focal

Table 4: The comprehensive comparison of the cases reported from India

Year of publication	Author, Study site, Time period	No.	M:F ratio	Etiology	Age (yrs)	Clinical features	Pattern of affection
India							
1997	Goyal,[3] Delhi	4	-	Idiopathic	-	-	Diffuse (100%)
2002	Sylaja,[4] Kerala	4	1:3	Idiopathic (75%) TB (25%)	39.5±7.9	Headache (100%) CN (50%) Ataxia (25%)	Diffuse (50%) Focal (50%)
2002	Prabhakar,[5] Chandigarh	3	1:2	Idiopathic (67%) TB (33%)	52±3.5	Headache (100%) CN (100%) Ataxia (33%) Quadriparesis (33%)	Diffuse (66%) Focal (34%)
2008	Sobha,[9] Bengaluru, 10 years	11	1:0.8	Idiopathic (46%) Vasculitis (18%) Sarcoidosis (18%) TB (9%) Wegener granulomatosis (9%)	39.7±10	Headache (64%) CN (73%) Seizures (18%) Hemiparesis (18%)	-
2011	Karthik,[1] Chennai	2	1:1	Idiopathic (100%)	50±10	Headache (100%) CN (50%) Seizures (50%) Hemiparesis (50%)	Diffuse (100%)
2011	Hassan,[13] Pune, 4 years	3	1:2	Idiopathic-67% TB-33%	Mean -51	Headache -67% CN-100%	Diffuse-33% Focal-67%
2019	Barvalia,[10] Mumbai, 5 years 4 months	27	-	Idiopathic (52%) IgG4 RD (11%) Fungal (11%) TB (11%) Sarcoidosis (7%) Wegener granulomatosis (4%) Lymphoma (4%)	-	-	-
2021	Jagiasi,[11] Mumbai, 5 years 7 months	33	1:1.2	Idiopathic (52%) IgG4 RD (12%) Fungal (9%) TB (9%) Sarcoidosis (9%) Wegener granulomatosis (6%) Lymphoma (3%)	44±12	Headache (100%) CN-73% Hemiparesis-1 (3%) Seizures-3 (9%)	Diffuse-3% Focal-97%
2022	Gupta,[12] New Delhi, 5 years	31	-	Idiopathic (58%) Secondary (42%)	40.6±15.7	Headache-87% CN-83.8%	Diffuse-29.1% Focal-70.9%
2023	Index report, Kolkata 1 year 3 months	44	1.2:1	Idiopathic (57%) TB (23%) IgG4 (9%) Other infections (7%) Malignancy (5%)	35.5 (28.5-49.5)	Headache-94.5% CN-65.9% Seizures-9.1% Hemiparesis- 6.8%	Diffuse-27.27% Focal-72.73%
China							
2022	Yao[14]	30	-	Idiopathic (100%)	46 (34.2-56)	Headache (93.3%) CN (66.7%)	Diffuse (60%) Focal (40%)
2019	Chen[16]	22	-	Idiopathic (77%) ANCA vasculitis (9%) IgG4 RD (14%)	-	Headache (82%) CN (68%) Ataxia (18%) CVST (13%)	-
2020	Bi,[21] 6 years 8 months	16	1:1	Idiopathic (26%) ANCA vasculitis (56%) Rheumatoid arthritis (12%) Sjogren (6%)	52.6±13.2	Headache (81.3%) CN (50%) Ataxia (12%) Hemiparesis (12%)	Diffuse (32%) Focal (68%)

Contd...

Table 4: Contd...

Year of publication	Author, Study site, Time period	No.	M:F ratio	Etiology	Age (yrs)	Clinical features	Pattern of affection
2020	Xiao,[7] 13 years	48	1:1	Idiopathic (67%) ANCA vasculitis (15%) TBM (8%) Meningitis (10%) (viral-6%, bacterial-4%)	50±12	Headache (92%) CN (60%) Ataxia (4%) Seizures (6.25%) Hemiparesis (2%)	Diffuse (48%) Focal (42%)
Thailand							
2014	Roongpiboonsopit,[17] 11 years 11 months	32	1:1.9	-	49±16.12	Headache (93.8%) CN (84.4%)	Diffuse (3.1% Focal (96.9%)
2021	Sakdee,[18] 7 years 6 months	84	1:1.5	Idiopathic (64.3%) IgG4 RD (21.4%) ANCA vasculitis (2.4%) Sarcoidosis (2.4%) Aspergillosis (2.4%) TB (2.4%)	51 (38–62)	Headache (65%) CN (92.8%) Seizure (2.4%) Motor weakness (4.7%)	Diffuse (14.3%) Focal (85.7%)
2019	Warittikoon[13]; 13 years	34	1:1.8	Idiopathic (68%) Secondary (32%)	50.5 (8–79)	Headache (50%) CN (85%)	-
Japan							
2014	Yonekawa,[4] 5 years	159	-	Idiopathic (44%) ANCA vasculitis (34%) IgG4 RD (8.8%) Others (13.2%)	58.3±15.8	-	-
2013	Yokoseki,[15] 4 years	36	1:1.1	Idiopathic (25%) p-ANCA (47%) c-ANCA (11%) Other immunological diseases-17%	61 (43–75)	-	-
USA							
2004	Kupersmith[12]	12	3:1	Idiopathic (100%)	55 (39–88)	Headache (91%) CN (83%) Ataxia (17%) Seizures (8%)	-
France							
2018	Mekinian,[19] 6 years 2 months	60	1:0.43	Idiopathic (30%) Erdheim-Chester-(17%) GPA (17%) IgG4 RD-(5%) TB-(5%) Rosai-Dofman disease-(3%) Sarcoidosis (3%) Microscopic polyangiitis-(3%) Cryptococcal meningitis-(2%) Lyme disease-(2%) ENT infection-(2%) Lymphoma-(2%)	55.5 (30–80)	Headache (72%) CN (55%) Encephalopathy (17%) Focal deficits (15%) Seizures (12%) Ataxia (10%)	Diffuse (32%) Focal (68%)

Ages are expressed as mean±standard deviation or median (interquartile range), CN=cranial neuropathy, "-"signifies lack of pertinent information in the article

HP, Sylaja *et al*.[4] reported equal proportions of both, and Prabhakar *et al.*[5] reported a higher occurrence of diffuse HP. In China, the predominance of diffuse HP was reported by Yao *et al*.,[14] focal HP by Bi *et al.*[21] and almost equal proportions by Xiao *et al.*[7] Sakdee *et al.*[13] described much higher regular enhancement (66.7%) than our study, 22.6% irregular patterns, and 9.5% nodular patterns. Xiao *et al.*[7] noted diffuse enhancement in idiopathic, ANCA-related, and viral meningitis-associated HP, whereas TB HP patients had focal enhancement. The irregular pattern was significantly higher in idiopathic HP patients (47%) than in other subgroups of HP. However, a contrasting finding of more regular enhancement in idiopathic HP was noted by Hahn *et al.*[26] among American patients. Xiao *et al.*[7] hypothesized that racial differences may influence the patterns of affection in the pachymeninges. However, other Asian studies[13] comparing idiopathic HP and IgG4-related HP also noted significantly higher regular enhancement in the former group. We did not find significant

differences in the occurrence of the three patterns of enhancement among the different etiological groups.

Although we found temporal lobar enhancement to be the commonest, Sakdee *et al*.[13] reported the highest incidence of cavernous sinus affection (71.4%), followed by the tentorium (54.8%) and the superior orbital fissure/orbital apex (51.2%). Gupta *et al*.[12] also described the cavernous sinus and tentorium cerebelli as the most common sites of involvement (70.9% and 58.1%, respectively). Xiao *et al*.[7] described posterior fossa affection in idiopathic and TB HP, whereas frontal and parietal affection occurred in ANCA-related HP. Abrantes *et al*.[27] described significantly higher anterior and middle cranial fossa affections in the secondary HP group compared with idiopathic HP patients. However, we did not find any significant difference in the distribution of pachymeningitis among the various etiological groups.

Cerebral infarcts associated with HP are rarely described. We found predominantly cortical infarcts due to vasculitis in one patient with TB HP, whereas Jagiasi *et al*.[11] reported basal ganglia infarcts. ANCA-related HP may also be associated with cerebral infarcts.[28] We noted perilesional parenchymal edema, adjacent to the inflamed meninges, possibly due to narrowing of the venous sinuses and compression of the cortical surface by the inflamed, thick, and adherent meninges.[11] The parenchymal edema had a mass effect, as also previously described by other authors in idiopathic HP.[29]

No previous studies investigated the factors affecting the resolution of pachymeningeal enhancement. The significantly higher chance of radiological resolution of idiopathic HP and focal linear enhancement were novel findings in our study. None of the TB HP patients had radiological resolution within the short follow-up period, although on longer follow-up, some studies reported complete resolution.[7,30]

We found a much lower occurrence of leucocytosis, raised ESR, CSF pleocytosis, and elevated CSF protein compared to other studies. Xiao *et al*.[7] reported leucocytosis in 57.1% of cases of ANCA-associated HP and 25% of cases of idiopathic and TB HP. Raised ESR was reported in 42, 73, and 87.5% of cases by Mekinian *et al*.[19], Jagiasi *et al*.[11], and Xiao *et al*.[7] respectively. About 30% of patients in Jagiasi *et al*.' *s*[11] study had ESR >50, which was not encountered in our study. Mekinian *et al*.[19] reported CSF pleocytosis in 47% of cases. Raised CSF protein was noted in 60% of cases by Xiao *et al*.,[7] 53% of idiopathic HP, 100% of ANCA-associated HP, 75% of TB HP, and 67% of viral HP groups.

The patients with idiopathic and IgG4-related HP had a good response to immunotherapy. Only a few patients were left with residual disabilities. Recurrences occurred in 36% of idiopathic HP and 50% of IgG4-related HP. Restarting pulse steroid therapy followed by a very slow taper, along with additional immunomodulators (MMF), kept them in remission during the study period. The uses of azathioprine and rituximab (for recurrently relapsing cases) have also been described. Sakdee *et al*.[13] described recurrences in 26 and 22% of patients with idiopathic and IgG4-related HP, respectively. Possibly the higher rates of recurrences in our study were related to the much shorter steroid courses compared to Sakdee *et al*.' *s*[13] study. Sakdee *et al*.[13] described the median duration of steroid therapy of 9 (6–14) and 10 (7–14) months for idiopathic and IgG4-related HP, respectively. Statistical analysis too showed that a shorter duration of steroid therapy (<median duration of 5.2 months) was associated with higher chances of recurrences [Table 3]. Some Japanese studies even recommend the maintenance of low-dose steroid therapy for up to 3 years.[13] Xiao *et al*.[7] reported recurrences in 12.5 and 14% of cases of idiopathic and ANCA-associated HP, respectively. In his study, two TB HP patients progressed despite adequate therapy, whereas the patients with viral and bacterial meningitis-associated HP resolved after etiological therapy. In our study, the patients with TB-HP had a good response to therapy. Our decision to start ATD was based on the presence of auxiliary evidence of TB, but few studies described the empirical use of ATD.[11] The efficacy of such empirical therapy has not been established[11], and Gupta *et al*.[12] advocated against blind empirical ATD. Sato *et al*.[31] described a rare example of bacterial pachymeningitis of the posterior fossa following chronic suppurative otitis media, where the symptoms and pachymeningeal enhancement were resolved solely by antibiotics without steroids. In our study, too, the patients of the "other infections" group symptomatically recovered after their etiological treatments.

Our study had three important limitations. Because of the short follow-up period of 6 months, we could not ascertain whether more cases would have been radiologically resolved with ongoing therapy. There have been reports of resolution of enhancement on long-term follow-up.[7,13,30] Secondly, we did a meningeal biopsy in only 1 case where the patient consented to surgery due to no response to ongoing therapy. Other patients did not consent to surgery due to a significant response to therapy. With a higher rate of histology, some idiopathic HP patients might have been classified into other etiological categories.[7] Third, due to the small numbers of patients (<5) in different subgroups, multivariate analysis could not be performed on the factors responsible for the radiological resolution of HP.

Conclusion

The eastern Indian HP patient cluster had a male predominance, with a lower age of disease onset. An idiopathic etiology was the commonest, and there was a marked absence of ANCA-associated HP. Headache, followed by optic neuropathy, was the most common manifestations. The diagnosis and follow-up of the cases were predominantly done by noninvasive methods (CEMRI). Focal irregular enhancement exceeded focal regular and diffuse patterns, and affected the temporal lobar pachymeninges most commonly. There was no significant difference in the severity of clinical

manifestations or distribution of pachymeningitis between the idiopathic and secondary etiological groups. Idiopathic variants and focal regular enhancement had a significantly higher chance of radiological resolution. The response to therapy was satisfactory, but recurrences were significantly related to shorter steroid courses.

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Conflicts of interest

There are no conflicts of interest.

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