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Idiopathic hypertrophic pachymeningitis: Features of 9 patients and a literature review

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Abstract

Introduction: Idiopathic hypertrophic pachymeningitis (IHP) is a rare disorder presenting with headache, cranial and spinal neuropathy. This study is to explore the clinical, laboratory and imaging changes; treatment; and clinical outcomes of idiopathic hypertrophic pachymeningitis (IHP). *Methods*: This was a retrospective evaluation of 9 patients (5 men and 4 women; mean age: 53.6 years), their clinical features, laboratory tests, cerebral spinal fluid (CSF) analysis, MRI results, pathological features, treatment and clinical outcomes from a tertiary centre in Qingdao, North East China. The serum IgG4 was negative for all the cases. *Results*: Headache was the most common symptom (7/9), followed by oculomotor, trigeminal, abducens and facial nerve neuropathies, and limb numbness in one case. Two cases showed increased ESR and CRP, and four were positive for ANA or anti-SSA antibodies. On CSF analysis, 2/7 had increased pressure, and 4/7 showed lymphocytosis and high protein levels. MRI revealed a thickening and enhancement of the dura, mainly involving bilateral tentorium (85%), falx cerebri (57%), and cerebellar hemisphere (57%). The tissue biopsy of dura mater in three cases showed thickened collagen fibers, lymphocytosis and focal necrosis, with similar but not identical features to IgG4-related sclerosing disease. Most patients were treated with corticosteroids, and 79% showed improvement. The abnormal thickness and enhancement of the dura mater disappeared in one case. *Conclusion*: Gadolinium-enhanced MRI serves as the key preliminary investigation for the diagnosis and evaluation of the clinical course for IHP. Majority of patients have good respond to steroid.

Keywords: Idiopathic hypertrophic pachymeningitis, IgG4-related disease, MRI

INTRODUCTION

Hypertrophic pachymeningitis (HP) is a rare disorder that causes localized or diffused thickening of the dura mater, affecting both the spinal and cranial dura mater. The clinical manifestations include headache, cranial neuropathy, ataxia, seizures and myelopathy, depending on the sites involved.[1] The prevalence of HP is 0.949/100.000 in Japan according to a survey in 2014[2], and no prevalence data are available from China or other Asian countries.

Regarding the pathogenesis of HP, it can be secondary to other diseases such as infections (including bacterial and viral infections, syphilis, Lyme disease and tuberculosis), autoimmune disorders (such as systemic lupus erythematosus, rheumatoid arthritis, and vasculitis), sarcoidosis and neoplasms.[3] Cases with no known etiology are termed "idiopathic" hypertrophic pachymeningitis (IHP), a substantial percentage of which was recently identified as IgG4-related sclerosing disease (IgG4-RD).[4] MRI, particularly with gadolinium enhancement, is commonly used to diagnose IHP, while biopsy and pathological examination of the dura mater confirm the diagnosis.[5]

Recently, retrospective studies have been performed for the clinical and imaging characterization of HP in China[6] and Portugal.[7] However, studies on IHP are rare in Asia, except for one conducted in China in 2014.[3]

METHODS

We conducted the present retrospective study at our hospital, a university and tertiary referral hospital in Qingdao, North East China. Patients were identified from the electronic medical record system using the terms "hypertrophic

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pachymeningitis". The study period was set from 2012 to 2020. The clinical files of each patient were retrieved and examined, and patients with possible etiologies such as neoplastic, infectious or autoimmune disease were excluded from the study. We also excluded patients with typical clinical manifestations of IgG4-RD in other organs or an increased serum IgG4 concentration. The diagnosis of IHP was made from clinical features, MRI changes and pathological examination (Case 4, 6 and 7).

The clinical features of these patients, including their symptoms, age of onset, disease course and physical examination findings, were documented. Further data included laboratory examinations, CSF analysis and MRI results comprising T1, T2, diffusion, fluid attenuation inversion recovery, gradient echo, and T1 with gadolinium enhancement. Treatments and follow-ups were also collected whenever available. Statistical analysis was performed using SPSS software.

RESULTS

Five men and four women were included in this study, with an age range of 33 to 72 years and an average age of 55.6 years. It is noteworthy that there were two patients diagnosed with HP excluded from this study, who had increased IgG4 levels. One was a 72 y/o male, who had emphysema and pulmonary nodules, with serum IgG4 of 1.37g/L. The other one was a 54 y/o male, who had systemic vasculitis, kidney dysfunction and diabetes mellites, with serum IgG4 of 3.22g/L.

The most common symptoms were headache (7/9), pain or numbness of the face (2/9), ptosis and diplopia. Headache was commonly described as localized or diffuse, continuous, with no specific character, progressive worsening and refractory to medication such as NSAIDs. In half of the cases, the cranial nerves were affected, with the oculomotor (2), trigeminal (2), abducens (2) and facial (3) nerves being the most common. The glossopharyngeal and hypoglossal nerves were also affected in one case. Only one patient showed limb numbness due to frontal cortex involvement. Six cases had a chronic course (>1 month), while three cases showed a subacute course (>7 and <30 days).

Most cases showed some abnormalities in laboratory tests. Two cases showed increased high ESR and CRP. Three cases were positive for autoimmune antibodies, among which two had ANA (1:100) and two had anti-SSA(+). No patient was symptomatic for Sjögren's syndrome, systemic vasculitis or other autoimmune disease. The serum IgG4 level of all patients were normal (<2g/L). One patient with a history of thyroiditis had high TG-Ab. Of 7 cases that had undergone lumbar puncture, all showed some abnormalities in CSF analysis. Two (29%) cases showed increased pressure (230-270 mmH2O), three (43%) had a high WBC (10-34 $*10^6$/L), and three (43%) showed high protein levels (0.62-2.8 g/l). All patients had normal glucose levels (not shown in the table). MRI disclosed focal or diffuse thickening and enhancement of the dura, mainly including the bilateral tentorium (85%) and falx cerebri (57%), cerebellar hemisphere (57%), peri-cavernous sinus (25%) and posterior fossa. (Figure 1)

Pathologic results were obtained in 3 cases (Case 4, 6 and 7). One patient (Case 4) was subjected to a dura mater biopsy because of the mass effect of a thickened tentorium, which showed inflammatory cell infiltration comprising many lymphocytes, thickened collagen fibers and focal necrosis (Figure 3a and 3b). Immunohistochemical staining showed partial expression of CD68(++), s-100 and epithelial membrane antigen (EMA) (+) (data not shown). Similar pathologic changes were seen in Case 6 and 7 (Figure 4a, 4b, 5a and 5b).

All the patients were treated with corticosteroids, among whom 3 cases with severe symptoms were administered pulsed methylprednisolone (500-1000 mg/day) followed by prednisone. Only one patient (Case 7) who had relapse with a decreasing dosage of prednisone was given azathioprine at 50 mg bid , and had good response. Six of eight patients were followed up from 3 months to 8 years. We compared the MRI results before and after therapy of Case 7 (Figure 2). Interestingly, the symptom (headache) of case 4 was relieved, although the CSF test obtained in her most recent hospitalization showed a pressure of 280 mmH2O, which was even higher than that 8 years previously. Most patients' symptoms were relieved with corticosteroids from 20 to 80 mg/day only, and 2 patients showed relapse. Unfortunately, Case 2 was lost to follow up, possibly because his headache did not improve.

DISCUSSION

Although the histopathological features, frequency and demographic characteristics of IHP have many similarities with IgG4-RD, little is known about the pathogenesis of IHP.[1]less frequently, in both locations simultaneously. Numerous

Table 1: Clinical features, laboratory tests, MRI results, treatment and outcome of 9 patients with IHP

Case	Age/ sex	Symptoms	Disease course	Cranial nerves involved	Laboratory tests	CSF tests	MRI dural thickening location	Treatment	Follow-up	Outcome
1	65/F	Headache and numbness of the right face	2 weeks	V	Anti-TG: 346.59 IU/ml	-	Bilateral tentorium, frontal lobe and convex surface of the cerebellar hemisphere	Prednisone (40 mg- 20 mg- 8 mg daily)	5 years	V nerve dysfunction, improved
2	40/M	Headache	3 months	-	ANA(-); Anti-O: 229 IU/mL	Pressure 140 mmH2O, WBC $8*10^6$/L PR 0.69 g/L, IgG 41.4 mg/L	Diffuse dura mater, narrowing of the bilateral lateral ventricles and sulcus gyrus	Pulsed methyl-prednisolone 500 mg/day followed by Prednisone 80 mg/day	-	Not well improved
3	33/M	Pain in the right face	6 months	V, VII	ANA(-)	Pressure 230 mmH2O, WBC $10*10^6$/L, IgG 39.6 mg/L	Diffuse dura mater	Dexamethasone 10 mg/day	1 year	Improved
4	43/F	Headache	3 years	-	ESR 28.3 mm/h, CRP 18.9 mg/l, anti-SSA(+)	Pressure 270 mmH_2O, WBC $15*10^6$/L, Cl 120 mmol/L	Bilateral tentorium	Biopsy confirmed the diagnosis. Prednisone 30 mg/day, followed by decreasing dosage	8 years	Headache improved. Pressure 280 mmH2O in latest CSF test.
5	66/F	Dizziness, headache and diplopia	1 month	III, IV, VI, VII	RF 13.4 IU/ml, ANA(-)	Pressure 100 mmH2O, WBC $10*10^6$/L, PR 1.2 g/l	Bilateral tentorium, posterior part of the falx cerebri	Prednisone 50 mg/day, decreasing dosage	1 year	Diplopia relapsed with decreasing dosage
6	65/F	Headache and ptosis of the left eye	2 years	III, VI, VII, IX, XII	ESR 35 mm/h, CRP 29.3 mg/l, ANA: (1:100); anti-SSA(+)	Pressure 150 mmH2O, WBC $34*10^6$/L, IgG>108 mg/L	Bilateral temporal, parasellar, tentorium, and posterior fossa	Pulsed methyl-prednisolone 500 mg/ day followed by prednisone 80 mg/day	6 months	III nerve dysfunction, improved
7	60/M	Headache	2 months	-	ANA(-)	Pressure 150 mmH2O, WBC $10*10^6$/L, PR 0.62 g/L	Bilateral tentorium and falx cerebri	Prednisone 80 mg/ day, decreasing dosage with azathio-prine 50 mg bid	3 months	Asymptomatic
8	57/M	Headache	8 days	-	ANA (1:100)	-	Bilateral tentorium and pericavernous sinus	Prednisone 50 mg/day	-	Asymptomatic at discharge
9	72/M	Numbness of right lower limb	1week	-	ANA(1:100)	Pressure 130 mmH2O, WBC $50*10^6$/L (monocytes 96%), PR 2.8 g/L	Left medial frontal lobe and falx cerebri	Methylprednisolone 80 mg/day followed by prednisone 40 mg/day	3 months	Asymptomatic at discharge

Anti-TG, anti-thyroglobulin antibody; ANA, antinuclear antibodies; Anti-O, anti-streptolysin O antibody; Anti-SSA, anti-Sjögren's syndrome-related antigen A; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; PR, protein; WBC, white blood cell; IgG, immunoglobulin G.

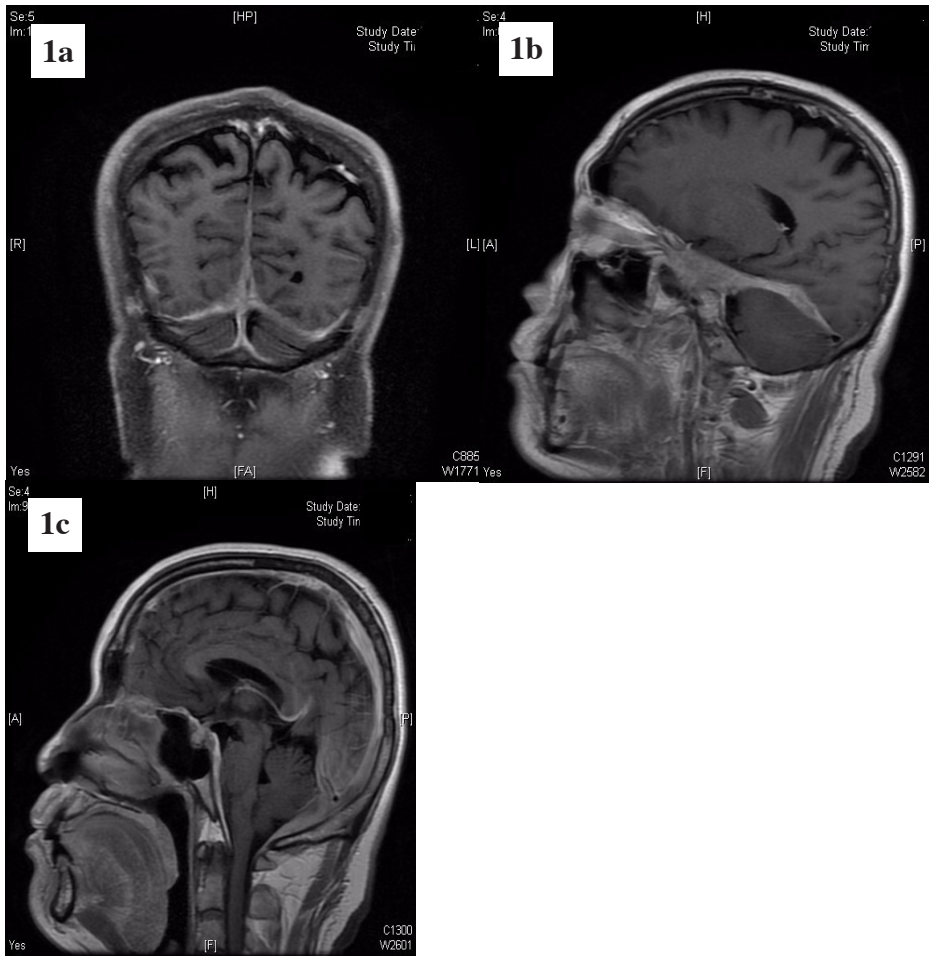

Figure 1. Gadolinium-enhanced T1-weighted MR imaging of Case 8, showing diffuse and wide thickening of the tentorium and falx cerebri in the coronal (**1a**) and sagittal views (**1b** and **1c**).

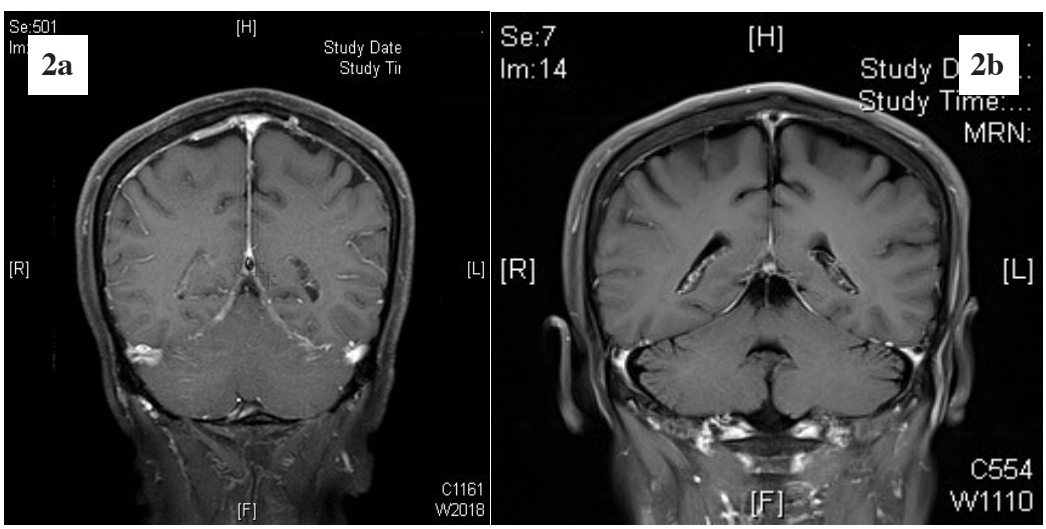

Figure 2. Linear enhancement of the dura mater on coronary enhanced T1-weighted MR imaging (**2a**), and the diminishment of this change in the follow-up study (**2b**).

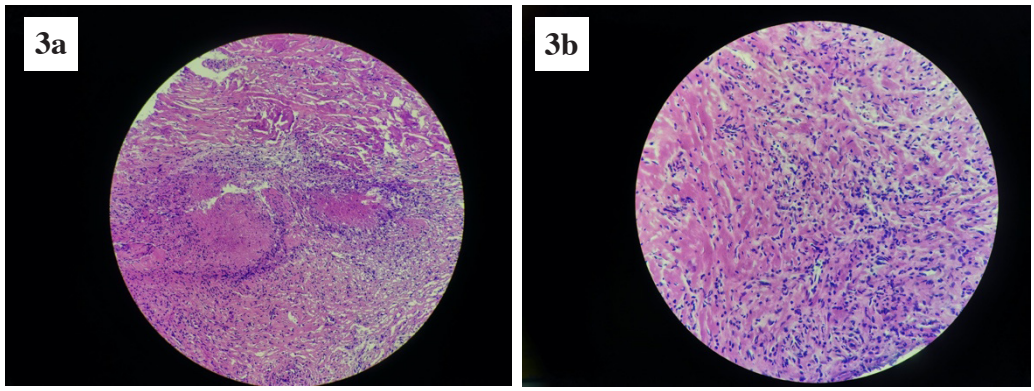

Figure 3. Histopathological findings revealed hypertrophic pachymeningitis with fibrosis and focal necrosis (**3a**; hematoxylin-eosin staining; original magnification, *200) and many infiltrated lymphocytes (**3b**; hematoxylin-eosin staining; original magnification, *400).

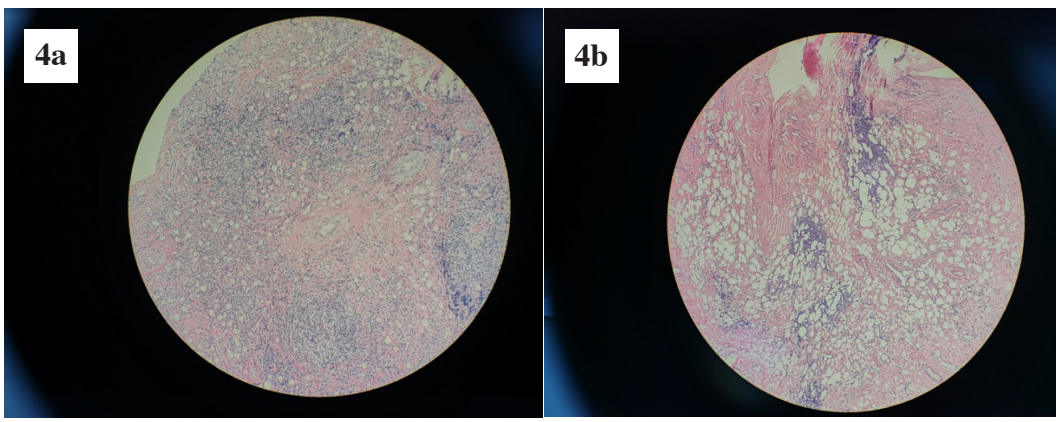

Figure 4. Dense fibrosis and lymphocytic infiltration can be seen in Case 6 (**4a**, hematoxylin-eosin staining, original magnification, *100; **4b**, *400).

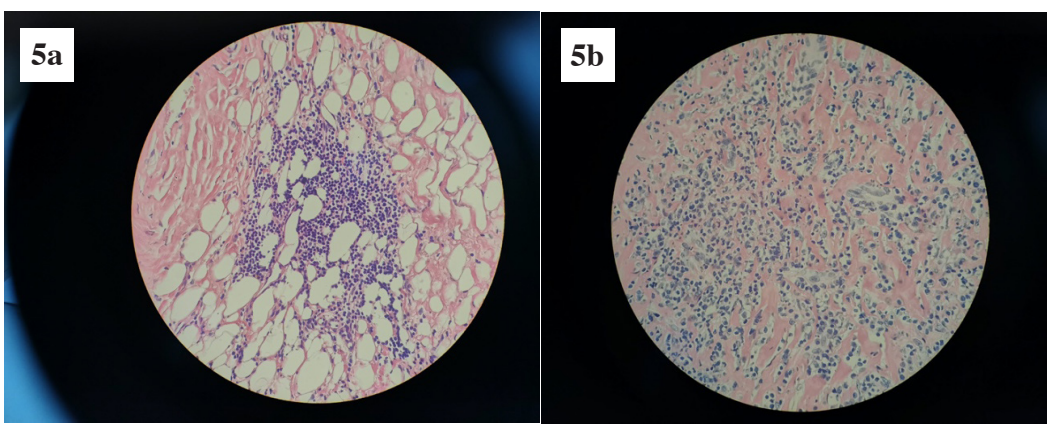

Figure 5. In Case 7, the fibrotic tissues were obviously hypertrophic with abundant inflammatory cells and collagenization of interstitial tissues can be seen (**5a**, hematoxylin-eosin staining, original magnification, *100; **5b**, *400).

clinico-pathological entities cause thickening of the pachymeninges. Indeed, HP is a potential manifestation of many different diseases, but the diagnosis often remains uncertain. Cases in which the pachymeningitis has no known aetiology are termed "idiopathic" HP (IHP Patients with IgG4-RD present with constitutional features, pulmonary manifestations, autoimmune pancreatitis, retroperitoneal fibrosis, lacrimal or salivary gland enlargement associated with a high serum IgG-4 level.[4] In this study, we excluded patients with other etiologies, including IgG4-RD, to study the idiopathic subset of HP. According to previous report, IHP affect men more than women, involving patients mostly in their 60s.[8] There was no gender difference (1:1) among our cases, although the number of our patients is small.

Headache was the most common symptom at presentation, the pathogenesis of which may be inflammation and hypertrophy of the dura mater and increased intracranial hypertension[9], seen in 30% of our patients. Cranial nerve palsy was another frequent symptom probably due to compression by the hypertrophied dura mater.[6] Previous studies have reported that the optic nerve followed by the abducens nerve and other ocular motor nerves were most frequently involved in IHP.[3,8,10] The specific nerve involved were related to the sites of thickening of the dura mater. Multiple cranial neuropathy were observed in our Case 5 (III, IV, VI, VII) and Case 6 (III, VI, VII, IX, XII), and the enhancement of the dura mater in these cases was diffuse, including the bilateral tentorium and posterior part of falx cerebri ub Case 5, tentorium and posterior fossa in Case 6. We did not observe optic nerve dysfunction in our cases, perhaps partly because the patients with visual symptoms may have been referred to the ophthalmology service, with the diagnosed being missed and not captured in this study. It is noteworthy that limb numbness was the chief complain of Case 9, a 72-year-old male, which could have led to a misdiagnosis of stroke.

Kupersmith *et al*. reported that the ESR levels were elevated in 41% of their IHP patients[8], which is seen in 25% of our cases. CRP levels were also increased in our Cases 4 and 6. This is likely to reflect the underlying inflammatory reaction.

The differential diagnosis for HP is broad and includes other autoimmune disease. Interestingly, we observed that 3 of our cases were positive for ANA or SSA without other clinical features of autoimmune disease.

CSF analysis is an important evaluation for the diagnosis of IHP. The opening pressure can be increased, with variable biochemistry changes in IHP.[8] Our Case 4, with high CSF pressure and pleocytosis but relatively benign disease, appear to indicate that it is not a reliable indicator of the severity of this disease. Half of our patients had elevated protein or high lymphocytes. We suspect it changes reflect the pathological features of IHP, such as lymphoplasmacytic infiltration, obliterative phlebitis, and fibrosis.[11]

Gadolinium-enhanced MRI is helpful in the diagnosis of IHP that can also be used to evaluate disease progression.[4,8] According to previous reports, the tentorium and falx cerebri are most frequently involved[10], consistent with our own case. MRI changes are correlated with the clinical course[8,12] and can be reversed after therapy as seen in some of our cases (Figure 2). The abnormal thickness and enhancement of the dura mater disappeared in Case 7 after the 3-month follow-up, associated with clinical remission. This finding is in contrast to that reported by Masson *et al*., where there was no change.[13] The complete disappearance of imaging abnormality was rare in our patients, unlike that of other previous reports.[3,8]

Pathological examination is the gold standard for the diagnosis of IHP. We found a similar lymphocyte and macrophage infiltrating pattern in our cases, as compared to IgG4-RD, The dura mater of which was mainly involved, while the pia mater, with inflammatory cells lymphocytes, eosinophils and macrophages, can also be affected.[14] However, the characteristic storiform-type fibrosis for IgG4-RD[11] was missing for our cases. This finding indicates that IHP could share similar, but not identical, pathological features with IgG4-RD.

There is still no controlled clinical trial to provide definite guideline to therapy of IHP. Retrospective studies found that corticosteroid treatment is effective for most patients[3,6,8], while immunosuppressive agents can be used for those without a good response to steroids[15], as well as radiotherapy and surgery.[16] Rituximab, a B-cell-depleting agent targeting CD20, appears to be beneficial for IgG4-RD.[17] All the patients were treated with steroids in this study, either with prednisone 40-80 mg/day or pulsed methylprednisolone 500-1000 mg/day. Steroid-sparing agents were not widely used, except for one case who was given azathioprine, likely from the treating physician's personal preference. Most of the patients' symptoms were markedly improved with the treatment. Headache was the first symptom to improve, while cranial

neuropathy showed a slower improvement. More clinical trials are needed to compare the efficacy between different treatment strategies.

In conclusion, IHP is a rare disorder presenting with headache, cranial and spinal neuropathy. The pathological features of IHP are similar, but not identical to IgG4-RD. MRI is the preliminary modality for the diagnosis and is correlated with the clinical course. Steroids are effective for most patients, and more clinical trials are necessary for other treatment modalities.

DISCLOSURE

Ethics: Informed consent was obtained from the patients, and the clinical study was approved by the ethics committee of the Affiliated Hospital of Qingdao University. The patients signed informed consent regarding publishing their data and photographs.

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Conflict of interest: None

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