Clinical features of immunoglobulin G4-related disease with central nervous system involvement: an analysis of 15 cases

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Abstract

Objective

Immunoglobulin G4-related disease (IgG4-RD) is a systemic disease that affects various organs of the body. The aim of this study is to elucidate the clinical characteristics of IgG4-RD with central nervous system (CNS) involvement.

Methods

Among 589 patients with IgG4-RD in a prospective single-centre cohort study in Peking Union Medical College Hospital, 15 patients had CNS involvement. The clinical data including demographic features, symptoms, involved organs, laboratory findings, radiological results, pathology, treatment and outcome were analysed.

Results

Seventeen patients, including nine men and six women, had IgG4-related neuropathy, with an average age of 49.8±12.3 years. IgG4 related hypophysitis was the most common manifestation, accounting for 40% (6/15) of cases, followed by hypertrophic cranial pachymeningitis (n=4), hypertrophic spinal pachymeningitis (n=2), intracranial mass (n=2), cavernous sinus and orbital disease (n=1). Most patients had multi-organ involvement, with the most common extra-CNS manifestations were Mikulicz disease (MD) and lymphadenitis in 5 (33.3%) cases. Serum IgG4 levels were elevated in 12/15(80%) patients and the median value was 438.5 (104, 2250)mg/dL. Fourteen cases underwent biopsy, of which tissue was taken directly from CNS lesions in 4 cases. All patients received treatment with glucocorticoids (GCs) combined with immunosuppressants, including cyclophosphamide, tacrolimus, mycophenolate mofetil, and tripterygium glycosides. Complete remission was achieved in 3/15 (20.0%) patients, and 11/15 cases (73.3%) achieved partial remission.

Conclusion

IgG4-related CNS involvement is a rare and distinct entity of IgG4-RD. Treatment with corticosteroids combined with immunosuppressive agents yielded favourable responses.

Key words

immunoglobulin G4-related disease, central nervous system, meningitis, hypophysitis

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a newly recognised immune-mediated fibro-inflammatory disease with increased serum IgG4 levels, lymphoplasmacytic infiltrate enriched with IgG4-positive plasma cells and distinctive stori-form fibrosis of affected organs. It is potentially a multi-organ disorder, and has been described in various organ systems, including the salivary gland, lacrimal gland, pancreas, biliary tract, lymph node, kidney, lung, retroperitoneum, thyroid, nervous system, skin, etc. (1-3). In 2006, Kamisawa *et al*. reported the first case of IgG4-RD hypophysitis (4). Gradually idiopathic hypertrophic pachymeningitis was found to be a part of IgG4-RD (5, 6), then peripheral neuropathy (7, 8) and inflammatory pseudotumour of the nervous system (9, 10) were reported.

In recent years, four large retrospective cohort studies demonstrated that neurological symptoms are rare clinical manifestations of IgG4-RD, with an incidence rate ranging from 1.7–3.2% (11-14). Due to its rarity, only a few case reports and evidence reviews have been published on this subject (15, 16). To strengthen the literature in this area, we retrospectively analysed and summarised the clinical, laboratory, imaging and pathological features and treatment of 15 patients with IgG4-related central nervous system (CNS) involvement.

Methods

Study design and study population

This study represents an analysis of patients drawn from a prospective longitudinal cohort study of patients with IgG4-RD conducted in the outpatient rheumatology clinic of Peking Union Medical College Hospital (PUMCH), a large tertiary care referral hospital in Beijing, China, from January 2011 to April 2018.

The study protocol was registered on a public-access clinical trial database (http://www.clinicaltrials.gov; no. NCT03023371) and approved by the Ethics Committee of Peking Union Medical College Hospital (no. 442). All enrolled patients consented to attend this cohort study and signed written informed consent.

In brief, patients presenting for care with definite, probable or possible IgG4-RD according to the 2011 comprehensive diagnostic criteria for IgG4-RD (16) were recruited. Definite IgG4-RD was defined as having all of the following characteristics: (i) organ enlargement, mass or nodular lesions, or organ dysfunction; (ii) a serum IgG4 concentration >135 mg/dL; and (iii) histopathological findings of >10 IgG4+ cells per high power field (/HPF) and an IgG4+/IgG+ cell ratio of >40%. A diagnosis of possible IgG4-RD required (i) and (ii), in the setting of negative results on histopathology or lack of histopathological examination. Probable IgG4-RD required (i) and (iii), in the setting of normal serum IgG4 levels. Patient with malignancy or other autoimmune diseases were excluded. The study was approved by the PUMCH ethical review board and written informed consent was obtained from each patient prior to participation in any study activities.

For the purposes of the current analysis, all patients in the cohort who presented with CNS disease were included. In our cohort, no case presented peripheral nervous system disease.

Measures

Sociodemographic and clinical data

As part of the prospective longitudinal cohort study, sociodemographic data (sex and age), initial disease symptoms, history of allergies and physical examination data were recorded.

Laboratory data collected included complete blood count (CBC), liver and renal function, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum immunoglobulin levels, IgG subclasses, total IgE levels, rheumatoid factor and antinuclear antibodies (ANAs) were tested.

All patients underwent imaging examinations, including ultrasonography, thoracic and abdominal computed tomography (CT), brain magnetic resonance imaging (MRI) with contrast, or positron emission tomography computed tomography (PET-CT).

Fourteen patients (93.3%) underwent biopsy. Four patients underwent biopsy directly derived from the lesion of CNS and eleven patients underwent biopsy

of the extra-cranial affected organs. Details are shown in Table I.

Whole body organ involvement was evaluated by symptoms, signs, radiographic or other imaging examination or tissue biopsies. Patients were followed and evaluated at 1, 3, and 6–10th months after initiation of glucocorticoid therapy with immunosuppressants.

Outcomes of interest

Complete remission (CR) was defined as total resolution of all IgG4-RD symptoms, normalisation of all involved organs, and marked decrease in serum IgG4 levels. Partial remission (PR) was defined as improvement or reduction in the main involved lesions. No change (NC) was defined as an absence of marked changes in mass sizes, organomegaly and/or symptoms. Disease relapse was defined as clinical symptoms recurred or imaging findings were worsened with or without IgG4 level increased.

Statistical analysis

All statistical analyses were performed by SPSS v. 17.0 (SPSS, Chicago, IL, USA). Descriptive statistics were used to describe clinical data, including means ± standard deviations for normally distributed data and medians (interquartile ranges) for non-parametric data. The normally distributed data between two groups was analysed using independent-samples *t*-tests. A two-tailed *p*-value <0.05 was considered statistical significant.

Data availability statement

The anonymised data within this article will be shared on request by any qualified investigator.

Results

Patient demographic characteristics

Of 589 patients with IgG4-RD recruited as part of the prospective longitudinal cohort study, a total of 15 patients were diagnosed IgG4-related CNS involvement, including 9 men and 6 women (M:F = 1.5:1). The mean age at diagnosis of this subgroup was 49.8±12.3 years, ranging from 16 to 62 years, and mean disease duration before diagnosis was 14.0 (6.0, 84.0) months. The demographic characteristics of patients with IgG4-related CNS disease were similar to the overall cohort of patients of IgG4-RD. Two patients (13.3%) had history of allergic reactions during the course of disease, including allergic skin rash and drug allergy history.

Eleven cases (73.3%), three cases (20.0%), and one case (6.7%) were diagnosed as definite, probable and possible IgG4-RD, respectively.

Clinical manifestation

All 15 cases presenting with neurological manifestations involved the central nervous system (CNS). According to different lesion sites, we divided them into five groups. IgG4-related pituitary involvement (Group 1) was the most common manifestation, accounting for 6 cases (40.0%), followed by hypertrophic cranial pachymeningitis (HCP) (Group 2, n=4, 26.7%), hypertrophic spinal pachymeningitis (HSP) (Group 3, n=2, 13.3%), intracranial mass (Group 4, n=2, 13.3%), cavernous sinus and orbital disease (Group 5, n=1, 6.7%) (Table I).

The main clinical symptoms were diabetes insipidus in 6 cases (40.0%), followed by headache in 4 cases (26.7%), vision reduced, numbness and weakness respectively in 2 cases each (13.3%), epilepsy and orbital pain respectively in 1 case each (6.7%). Of the 6 patients with pituitary involvement, all cases presented with diabetes insipidus. Of the 4 patients of HCP, 3 patients presented with headache and 1 patient with ocular pain and loss of vision due to optical nerve and extra-ocular muscle involved. Case 8 was diagnosed for HCP secondary to IgG4-RD according to histopathology. He had presented with mental and cognitive dysfunction, was diagnosed as "vasculitis" in the local hospital and achieved remission after glucocorticoid therapy 7 years ago.

The most common manifestations included dacryoadenitis and/or sialadenitis (Mikulicz disease, MD) and lymph node lesions respectively in 5 cases (33.3%), thyroiditis in 4 cases (26.7%), interstitial pneumonia (ILD) in 3 cases (20.0%), retroperitoneal fibrosis, mastoiditis, orbital disease in 2 cases (13.3%), pancreatitis, sclerosing cholangitis, rhinosinusitis, interstitial nephritis and skin involvement respectively in 1 case (6.7%). According to clinical manifestation and image finding without pathology, possible rhinosinusitis (RS) in 7 other cases and mastoiditis (MS) in 1 other case (Table I).

If possible RS and MS manifestation were not included, the number of organs involved outside of the CNS ranged from zero to four. There were three cases (20.0%) with more than 3 additional organs involved, one case (6.7%) with 3 additional organs involved, five cases (33.3%) with 2 additional organs involved and five cases (33.3%) with one additional organs involved. Case 11 had no extra-CNS affected except possible IgG4 related rhinosinusitis.

Laboratory data

Of the 15 patients, elevated serum IgG4 (>135mg/dL) was detected in 12 patients (80.0%), as 3 cases of pachymeningitis (3/6, 50%) and 9 cases with other phenotypes (9/9,100%). The median serum IgG4 level before treatment was 438.5(104, 2250) mg/dL. The mean serum IgG4 level in hypophysitis patients (group1) (1394.3±1158.7 mg/dL) was higher than pachymeningitis patients (group 2 and group 3) (165.0±144.0 mg/dL), p=0.027. Of the 15 patients, elevated serum IgG was detected in 8 cases (53.3 %) and the mean serum IgG was 18.4±9.4 g/L.

The mean serum IgG level in the hypophysitis patients (Group 1) 27.7±10.7 g/L was higher than in the pachymeningitis patients (Group 2 and Group 3) (11.8±3.23 g/L), p=0.007. Elevated eosinophil count in the peripheral blood was detected in 4 cases (26.7%) (reference range: 0.05×10^9/L-0.2×10^9/L), with a median of 0.06 (0.02, 0.32) $\times10^9$/L. The total IgE levels were measured in 12 patients, of which 10 cases (67.7%) elevated, with a median of 316(62.3, 668) KU/L (reference range: <60KU/L). Elevated ESR detected in 12 cases (80.0%), with a median of 28 (10, 54) mm/h. Elevated CRP detected in 9 patients (60.0%), with a median of 6.3 (1.55, 35.8) mg/L (reference range: <3mg/L). Complement C3 and C4 were test in 9 cases. Of them, C3 decreased in 1 case with 0.48g/L (reference range:

Table I. Clinical characteristics of IgG4-RD with CNS-involvement.

Group	n.	Age / Sex	Symptoms of CNS	Extra-CNS involvement	IgG4 (mg/dL)	IgG (g/L)	MRI findings	Biopsy Tissue	Histopathology LI	SF	OP	IgG4+/ HPF	IgG4/ IgG(%)
1	1	48/M	diabetes insipidus	MD RPF RS?	1980	19.8	pituitary stalk enlarged	SG	+	+	-	20	>40%
1	2	16/M	diabetes insipidus	AIP MD SC LN	2970	30.2	pituitary stalk enlarged	Liver	+	+	-	>20	40%
1	3	58/M	diabetes insipidus	RPF MD LN	532	31.5	pituitary stalk enlarged	LG	+	+	-	>10	>40%
1	4	44/F	diabetes insipidus	RS	167	11.01	the sellar region enlarged	RS	+	+	-	>20	>40%
1	5	52/F	diabetes insipidus	LN ILD IN LG RS?	2250	32	pituitary and suprasellar mass	LG	+	+	-	30	40%
1	6	56/F	diabetes insipidus	TG	5300	17.5	pituitary stalk enlarged	Thyroid	+	+	-	>20	>40%
2	7	55/M	headache	TG RS? MS?	279	16.1	dura mater thickened and enhanced	N/A					
2	8	57/M	headache	TG	401	11.9	dura mater thickened abnormal signals in parenchymal	dura mater	+	+	-	>10	40%
2	9	62/F	headache	TG MS	78	10.8	dura mater thickened in right middle cranial fossa	MS	+	+	-	50	50%
2*	10	50/F	orbital pain vision reduced	MD OD RS?	237	8.34	dura mater thickened and enhanced, left optic nerve thickened and enhanced	LG	+	+	-	15	>40%
3	11	56/M	numbness unstable gait	RS?	78.5	8.6	spinal cord (C1-C3) enlarged spinal cord mass in spinal cord (T1-T9)	dura mater	+	+	-	>50	40%
3	12	31/M	numbness and weakness of lower limbs	LN RS? MS?	30.5	8.0	mass around spinal cord (T8-L1)	dura mater	+	+	-	>10	40%
4	13	56/M	headache	MD Skin	2470	25.9	right basal ganglia mass	intracranial mass SMG	+ +	+ +	- -	NA >50	NA 40%
4	14	49/F	epilepsy	ILD MS	394	18.7	left temporal mass	Lung Mastoid	+ +	+ +	+ -	>10 >50	>40% >40%
5	15	62/M	vision reduced	OD SM ILD LN RS?	2250	31.1	bilateral cavernous sinus enlarged inferior orbital soft tissue	LN	+	-	-	>10	>40%

CNS: central nervous system; HCP: hypertrophic cranial pachymeningitis; HSP: hypertrophic spinal pachymeningitis; MD: Mikulicz disease; SC: sclerotic cholangitis; RPF: retroperitoneal fibrosis/periaortitis; AIP: autoimmune pancreatitis; ILD: interstitial lung disease; RS: rhinosinusitis, MS: mastoiditis; LN: lymphadenopathy or lymph node; IN: interstitial nephritis; LG: lacrimal gland involvement of lacrimal gland; OD: orbital disease; TG: thyroiditis; SM: submaxillaritis; SMG: submandibular gland; LI: Lymphoplasmacytic Infiltration; SF: storiform fibrosis; OP: occluded phlebitis .
*Combined with optic neuropathy. NA: not available.

0.73–1.46g/L). Anti-nuclear antibody low titre positive in one case and negative in the other cases. Rheumatoid factor (RF) elevated in 1 case, 76.5U/ml (reference range: <20U/ml), others were negative. In Case 8 the p-ANCA assay revealed low-titre 1:10 positive by immunofluorescence method while the anti-MPO antibody using the ELISA method was negative. Cerebral spinal fluid (CSF) examination was tested in 4 patients who were diagnosed as IgG4 related hypertrophic pachymeningitis. The pressure of CSF slightly elevated range 180–230 mmH2O, with elevated protein levels (0.72±0.18g/L, reference range: 0.15–0.45g/L) of CSF in all.

Imaging features

All patients underwent MRI examination. Imaging findings of MRI associated with nerve system included pituitary enlargement (n=6, 40.0%), abnormal the cerebral dura mater thickened (n=4, 26.7%), abnormal spinal dura mater thickened (n=2, 13.3%), brain parenchymal mass (n=2,13.3 %), optic nerve thickened (n=2, 13.3%), cavernous sinus enlarged and inferior orbital soft tissue (n=1, 6.7%). Additional details regarding neuroimaging findings of MRI are shown in Table I. Four patients underwent PET-CT and two of them (Case 1 and Case 7) underwent brain PET-CT. A slightly increased uptake of pituitary stalk was found in Case 1 and in Case 8 the dura mater was found thickened with no increased uptake.

Histopathological results

Histopathological biopsy was performed in 15 patients. Four underwent biopsy directly derived from the lesion of CNS. In three of the 4 cases, a large number of lymphocytes and plasma cells were infiltrated with obvious fibrosis, and IgG4 staining was positive (>10/HPF). Case 13 underwent biopsy in local hospital and had a consultation in our hospital without immunohistochemical analysis. Eleven patients underwent biopsy of the extra-cranial involved organs, including lacrimal gland (n=2), mastoid (n=2), lymph node (n=2), thyroid (n=1), submandibular gland (n=1), paranasal sinus (n=1), liver biopsy (n=1), lung (n=1) and retroperitoneal mass (n=1). Case 13 underwent both basal ganglia mass biopsy and Case 14 underwent both lung biopsy and mastoid biopsy. Details of all biopsies are shown in Table I.

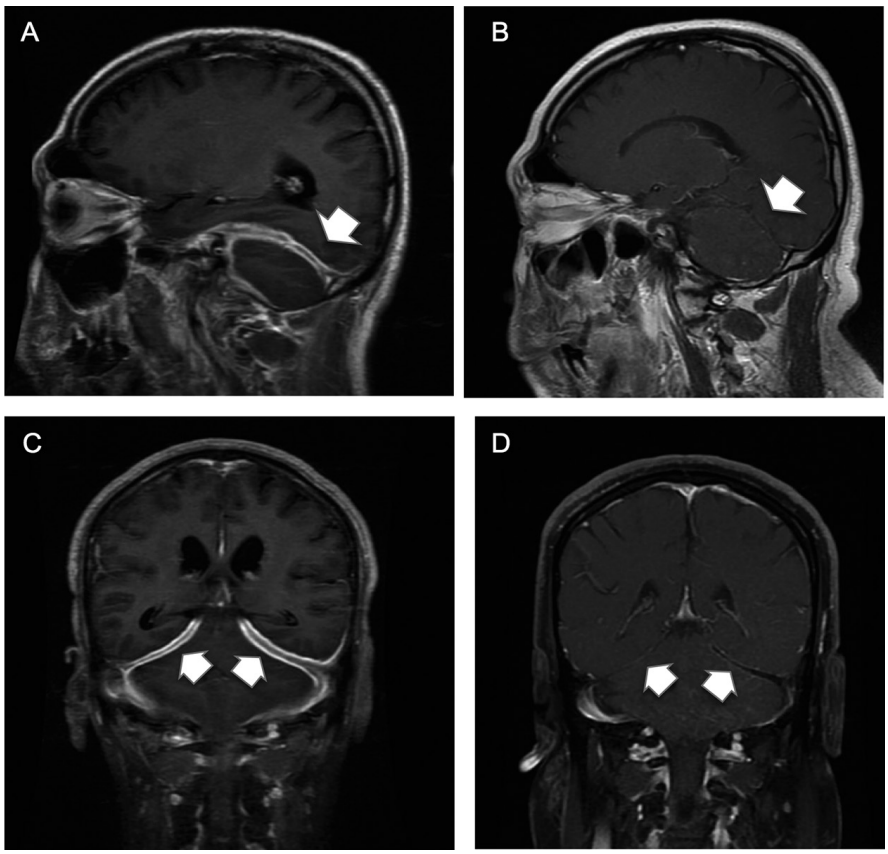

Fig. 1. Magnetic resonance imaging of a patient (Case 7) with IgG4-related hypertrophic pachymeningitis (arrowheads) (**A** and **C**) showing resolution of dural thickness 2 years after therapy (**B** and **D**).

Table II. Treatment and follow-up course of IgG4-RD with CNS involvement.

Group	n.	Induction therapy	F/U (m)	IgG4 (mg/dL) / IgG(g/L)	Outcome
1	1	GC+CTX+MTX	21	224/7.49	PR
1	2	GC+MMF	36	1540/22.46	PR
1	3	GC+MMF	30	151/9.32	PR
1	4	GC+CTX	12	16.8/11.85	PR
1	5	GC+CTX	30	349/15.07	PR
1	6	GC+MMF	3	223/11.6	PR
2	7	GC+CTX	36	39.5/9.12	PR#
2	8	GC+TG	21	36.3/10.2	CR
2	9	GC+CTX	9	38.0/8.42	PR
2*	10	Rituximab GC+CTX+TG	9	42.2/9.19	PR
3	11	GC+CTX	30	85.6/12.1	CR
3	12	GC+CTX	6	36.5/14.2	NC
4	13	GC+CTX	36	145/8.69	PR#
4	14	GC+CTX	33	692/16.06	CR
5	15	GC+TAC	60	153/13.3	PR

GC: glucocorticoids; IM: immunosuppressant; TAC: tacrolimus; MTX: methotrexate; TG: tripterysium glycosides; F/U(m): months of follow-up.
IgG4/IgG shows the recent result of follow-up. *Combined with optic neuropathy. #relapse during maintenance therapy.

Treatment and outcomes

All patients were treated with glucocorticoids (GC) (0.5-1.0mg/kg body weight/day, almost 30–60mg/d) combined with immunosuppressants. Three cases were treated with methylprednisolone pulse (1g/d for 3 days) therapy. The initial dose of GC therapy was continued for 1 month, then gradually tapered by 5mg every 7-14 days until reaching a maintenance dose of 5–10mg/day. Patients treated with immunosuppressants (n=15) such as cyclophosphamide (CTX, n=8), mycophenolate mofetil (MMF, n=3), tacrolimus (TAC, n=1), tripterygium glycosides (TG, n=1), CTX plus TG (n=1), CTX plus methotrexate (MTX, n=1). Case 10 received Rituximab without remission before combined with high dose GC and IM.

The treated patients were followed up for an average of 21.8±12.0 months (range 3–60 months). Of these, 3/15 (20.0%) patients achieved CR, and 11/15 (73.3%) achieved PR, 1/15 (6.7%) experienced no change. Case 7 and Case 13 relapsed during maintenance with prednisone 10mg/d with leflunomide (LEF) and azathioprine (AZA), and achieved partial remission again after using high dose GCs plus CTX again. The therapeutic history of all 15 patients is shown in Table II.

Discussion

Central nervous system involvement in IgG4-related diseases was rare to our knowledge (18). In this study of patients meeting the criteria for IgG4-RD at a large tertiary referral hospital in Peking, China, we found that 15/589 (2.5%) patients presented with nervous system involvement, all originating in the CNS. As only limited cases of CNS involved in IgG4-RD patients were reported and the clinical features of patients have not been characterised by clarity. It is the largest number of cases of retrospective study in IgG4-RD with CNS involvement and reveals a substantial prevalence of nervous system involvement in IgG4-RD patients.

The most common CNS manifestations of IgG4-RD are hypophysitis and pachymeningitis. Of six patients with pituitary involvement, the common manifestation was diabetes insipidus. As reported, IgG4-related hypophysitis could also present with hypopituitarism, such as reduced libido, hypogonadism, hypothyroidism, and hypoadrenalism. These patients usually went to an endocrinology clinic first and should be excluded such as pituitary adenoma, granulomatosis with polyangiitis, Langerhans cell hystiocytosis, neoplasia, infection, sarcoidosis etc. (19). Obviously elevated serum IgG4 was detected in these cases and it was much higher than the pachymeningitis

group before treatment. However, clues as to the underlying diagnosis may be apparent from elevated serum IgG4 levels and the concurrence of systemic features of IgG4-RD.

IgG4-related pachymeningitis patients were divided into two groups according to location, such as HCP and HSP. The prominent manifestation of cranial pachymeningitis involved was headache, which occurred in 80% of patients with HCP. In two patients who had spinal cord involvement, numbness and weakness of the limbs was the first symptom. The location of spinal lesion in Cases 11 and 12 were mainly located in thoracic segment, which was consistent with the literature report of HSP (3). Brain parenchymal disease secondary to IgG4-RD is very rare, and spinal cord parenchymal involvement has not been reported yet (18). Symptoms of IgG4-related brain parenchymal involvement depend on the location of lesion. Case 13 who had right basal ganglia mass presented with headache and Case 12 who left temporal mass presented with epilepsy. Case 15 was a special patient who presented with orbital pain and reduced vision due to cavernous sinus, orbital and optic neuropathy involvement. Regarding the special location of the lesion, we allocated this case to a separate group. We noticed that both Case 10 and Case 15 had ocular muscle involvement, but none presented with diplopia and restrictions in ocular movements.

Similar to other studies, most cases had other organs involved besides CNS except one case who just had suspicious rhinosinusitis (RS). MD and LN involvement were the most common concurrence. While according to image findings with/without pathology, RS (8/15, 53.3%) and mastoiditis (MS) (4/15, 26.7%) were much higher than the proportion of those phenotypes in IgG4-RD patients overall. As In our previous study, Lin (11) *et al*. reported every phenotype in 118 cases of IgG4-RD, the proportion of rhinosinusitis and mastoiditis were 12.7% and 0%. Though without pathology, we could not distinguish IgG4-related RS/MS from common RS/MS and allergic disease, such high concurrence rate might also be an interesting finding. As we noticed most of RS/MS associated clinical symptoms and imaging manifestations were alleviated after treatment. The specific mechanism is not clear and needs further study. We suspect inflammation maybe to spread from the adjacent organ due to paranasal sinus and mastoid are adjacent to meningeal and parenchyma. In addition, the assessment of CNS lesions commonly used MRI examination, may improve the detection rate of RS and MS.

In laboratory tests, elevated of serum IgG4 is an important feature of IgG4-RD, which list in one of diagnostic standard. Compared to Lin (11) reported elevated of serum IgG4 (>135mg/dL) detected in 97.5% cases, whereas in pachymeningitis, only 50.0%. It's difficult to differentiate from granulomatosis with polyangiitis, Erdheim-Chester disease, lymphoma and sarcoidosis etc. In this regard, for those patients with normal serum IgG4 levels, the combination of clinical manifestation, histopathology and responding well to glucocorticoid treatment should be important clues for the diagnosis of IgG4-RD. Cerebral spinal fluid (CSF) examination was tested in 4 patients exhibited elevated pressure and protein levels. A study (20) reported intrathecal IgG synthesis with oligoclonal bands and intrathecal IgG4 was detected in IgG4-related pachymeningitis patient.

Radiologic examination is very important for the diagnosis and evaluation of IgG4-RD. MRI / enhancement MRI is widely used to evaluate CNS lesions. Ultrasonography, CT and PET-CT are helpful to assess the involvement of the whole body. In our study, all patients underwent MRI / enhanced MRI for CNS lesions. On T2-weighted MRI, fibrotic hypertrophic meninges are thickened and relatively hypointense, with foci of hyperintensity being suggestive of inflammation that can be confirmed using gadolinium-enhanced T1-weighted MRI (3). Because of the high degree of uptake by normal underlying brain tissue, 18F-FDG PET-CT examination imaging of brain is generally of low utility (18). IgG4-related pachymeningitis is more readily detected with 11C methionine PET (MET-PET), which has low uptake in the normal brain (21).

Histopathological biopsy was performed in 14/15 patients, of which 4 cases underwent central nervous system lesions biopsy. Intracranial mass biopsy of Case 12 shown lymphocyte and eosinophil infiltration, IgG4 staining is positive, which should be differentiated with infectious lesion, Kimura disease and inflammatory disease such as eosinophilic granulomatous vasculitis. Accounting for concurrence of MD manifestation, significantly elevated serum IgG4, histopathology of the submandibular gland biopsy and effective response to glucocorticoid therapy, the patient was diagnosed IgG4-RD finally. Three other cases showed typical IgG4-RD histology characteristics, such as lymphocytes and plasma cells infiltrated, accompanied by fibrosis and positive IgG4 staining. Due to CNS lesions especially pituitary are difficult to obtain tissue, elevated serum IgG4 is a key clue and we also have to take biopsy from other organs including lymph nodes, lacrimal glands, salivary glands (22), sinuses and others (23).

As there was no single criterion for neurological disease secondary to IgG4-RD, this retrospective study refers to the 2011 IgG4-RD criteria (17). According to the criteria, 12 cases, 3 cases and1 case were diagnosed as definite, probable and possible IgG4- RD, respectively. After exclude other inflammatory, infectious and tumour disease, clinical improvement after steroid therapy is important clue for us to make clinical diagnosis.

Because of its rarity, no randomised clinical trials have been performed and there is no guideline for neurology disease secondary to IgG4-RD. Considering that CNS lesions may cause serious irreversible damage to the nervous system, referred to neuropsychiatric lupus erythematosus treatment strategy, we treated them with median-high dose of GCs treatment combined with IM. Through follow-up, 20.0% cases achieved CR, 73.3% cases were partially improved, and only one case of HSP did not respond well to therapy. Notably, all the hypophysitis patients who presented with diabetes insipidus did not regain pituitary function and needed long-term antidiuretic hormone replace-

ment therapy despite serological and radiographic resolution after treatment. Two patients relapsed when treated with low-dose GC with IM. After increasing the dose of GC and adjusting suppressant agents, they achieved PR again. Case 9 is an elderly woman who had severe diabetes and glaucoma and did not tolerate high-dose GCs. After 3 times of intrathecal injection (with methotrexate 10mg combined with dexamethasone 10mg), her symptoms of severe headache, earache and vertigo improved. B-cell depletion with rituximab could be a candidate choice in combination with glucocorticoids (3, 18).

Overall, neurological disease secondary to IgG4-RD is a rare and particular clinical phenotype and is being increasingly recognised. The most common manifestations are hypophysitis and pachymeningitis, which have a good response to GCs combined with immunosuppressive agents.

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