Original Article

A Series of Biopsy-proven Patients with Immunoglobulin G4-related Neurological Disease

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Abstract

Aim: To study the clinical presentation, radiological findings, and therapy responsiveness of patients with biopsy-proven immunoglobulin G4 (IgG4)-related neurological disease. **Methods:** The study was conducted between January 2016 and March 2018 from the Department of Neurology and Pathology of Nizam's Institute of Medical Sciences. Patients with neurological symptoms and biopsy suggestive of IgG4-related disease (IgG4-RD) were included. These patients were studied for their demographic pattern and clinical presentation. The presence of serological markers such as vasculitic profile and IgG4 levels was analyzed. Radiological findings were studied in detail. Therapeutic agents used and the response to therapy were assessed. **Results:** There were six cases with IgG4-related neurological disease which were all hypertrophic pachymeningitis. The age ranged from 35 to 64 (mean = 46) years. The clinical presentation was acute in one, subacute in two, and chronic in three patients. The most common presenting symptom was headache (4), followed by gait and/or urinary disturbances (2), paraparesis (1), and diplopia (1). IgG4 levels were elevated in 50% of them. Pseudotumor-like mass and sinovenous thrombosis, not described previously, were seen in one patient. All the patients were treated with oral or intravenous steroid. Rituximab was given in three patients; azathioprine was the steroid-sparing agent in one patient. Those with acute/subacute onset of presentation had an excellent response to steroids. All the patients with a chronic duration of their symptoms received empirical anti-tuberculous therapy before a definitive diagnosis of Ig G4-RD was made. **Conclusions:** The characterization of patients with IgG4-related neurological disease based on the understanding of the clinical spectrum increases the confidence in the clinician to resort to early immunosuppression, thereby having prognostic implications.

Keywords: Compressive myelopathy, hypertrophic pachymeningitis, immunoglobulin G4, steroid response, storiform fibrosis

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a novel disease that affects multiple organs or tissues. IgG4-bearing plasma cells infiltrate the tissues and form tumefactive masses that lead to tissue destruction.[1] The classical histopathological features are storiform fibrosis, obliterative phlebitis, lymphoplasmacytic infiltrates, and increased tissue eosinophils.[2]

Single-organ involvement of IgG4-RD was well established with various eponym syndromes[3,4] [Table 1]. Involvement of nervous system was recognized initially with isolated reports of hypophysitis and hypertrophic pachymeningitis and recently as perineural disease.[5,6] The current series is a compilation of cases of IgG4-related neurological disease from a single center in South India.

Aims and methods

The aim of this study is to analyze the clinical presentation, serological and radiological findings, and therapy responsiveness in patients with IgG4-RD with neurological manifestations.

Inclusion criteria

Patients with the diagnosis of IgG4-related neurological disease, clinically and with histopathological confirmation, were included in the study. In addition, those patients with biopsy suggestive of IgG4-RD even when the biopsy was done for other indications such as suspected tumor in a patient with compressive myelopathy or a patient with chronic tuberculous meningitis not responding to antituberculous therapy (ATT) were also included.

Exclusion criteria

Patients with definite infectious, inflammatory, or neoplastic etiology for their neurological disease and those not willing to consent for either biopsy or serological investigations due to any reason were excluded. Patients with granulomatous inflammation with or without necrosis on meningeal biopsy, suggestive of tuberculosis or sarcoidosis, were excluded.

Methods

Informed consent was obtained from all the participants. Patients with complaints of headache, visual disturbances,

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Table 1: Patterns of organ involvement of immunoglobulin G4-related disease

Organ involved	Disease	Eponym if any
Salivary gland	IgG4-related sialadenitis	Mikulicz's disease (1892)
Parotid gland	IgG4-related parotitis	
Submandibular gland	IgG4-related submandibular gland involvement	
Lacrimal gland	IgG4-related dacryoadenitis	Küttner's tumor (1896)
Testis	Ig G4 related epididymo-orchitis, paratesticular pseudotumor	
Mammary gland	Mastitis	
Orbit	Orbital inflammatory pseudotumor	
	Pan-orbital inflammation	
	Orbital myositis	
Thyroid gland	IgG4-related thyroiditis	Riedel's thyroiditis (1896)
Peritoneum	Retroperitoneal fibrosis	Morbus Ormond's tumor
Pancreas	Autoimmune pancreatitis type 1	
Gallbladder	Sclerosing cholangitis	
	IgG4-related cholecystitis	
Liver	IgG4-related hepatopathy	
Aorta and arteries	Aortitis or periarteritis	
Lung and pleura	IgG4-related pneumonitis, pleuritis or mediastinitis	
Lymph nodes	IgG4-related lymphadenopathy	
Kidney	Tubulointestinal nephritis	
	Membranous glomerulonephritis	
	Pyelitis	
Neurological involvement.	IgG4-related pachymeningitis	
	Hypophysitis	
	Perineural disease	

IgG4=Immunoglobulin G4

multiple cranial nerve dysfunction, and motor, sensory, or cerebellar symptoms who were encountered in the neurology outpatient department or in the emergency services underwent detailed neurologic evaluation with documentation of their deficits. The presence of constitutional symptoms such as fever, asthenia, weight loss, and symptoms pertaining to involvement of cardiovascular, respiratory, or gastrointestinal system was noted. All the patients underwent magnetic resonance imaging (MRI) (both plain and after gadolinium contrast administration) of either the brain or the spine. Laboratory parameters such as complete blood picture, erythrocyte sedimentation rate (ESR), urine analysis, renal and liver function tests, C-reactive protein, and viral markers were collected. Cerebrospinal fluid (CSF) with opening pressure was obtained after a lumbar puncture, and CSF cell count, protein, and sugar were analyzed. CSF was also sent for Gram stain, Ziehl–Neelsen, Venereal Disease Research Laboratory, and Indian ink stain and further cultured for aerobic and anaerobic bacteria, tuberculosis, and fungi. Tubercular GeneXpert was obtained. Malignancy was ruled out by CSF cytology for malignant cells. Vasculitic profile was obtained from all the patients. It included the presence and titres in the serum of antinuclear antibodies (ANA), anti-double stranded DNA (anti-ds DNA) antibodies,anti neutrophiic cytoplasmic antibodies with two patterns (c-ANCA and p-ANCA) ,antibodies to cyclic citrullinated peptides (anti -CCP) and Ig M rheumatoid factor (RA factor). Serum and CSF angiotensin-converting enzyme (ACE) levels, chest radiograph, and ultrasound abdomen and pelvis were done. Few of them underwent whole-body positron emission tomography (PET) scan. If the preliminary workup was negative, meningeal biopsy was done after periodic acid–Schiff (PAS) and acid-fast bacilli (AFB) staining which were negative and only those patients with IgG4-RD on IgG4 stains were studied further. The IgG4 immunohistochemistry (IHC) was done on a fully automated immunostainer (horse radish, Xmatrx, Biogenex, India) using IgG4 monoclonal antibody by horseradish peroxidase polymer technique (Biocare Medical, Pacheco, CA, USA). Serum levels of IgG4 were analyzed in biopsy-confirmed patients. These patients were treated with steroids, either oral prednisolone or intravenous pulse methylprednisolone (based on the severity of the symptoms), and clinical response was noted. Some of them needed steroid-sparing agents such as azathioprine or rituximab. The long-term outcome and relapses were assessed on follow-up with scoring of disability with modified Rankin scale (mRS) at 3 months.

Results

Demographics and clinical features

The age of the patients ranged between 35 and 64 years with a mean of 46 years. Female: male ratio was 5:1. Two were from urban and four from rural background. By convention, patients were classified into three groups based on the duration of their symptoms: acute (less than a month), subacute (1–6 months), and chronic (more than 6 months). Three (50%) of them had chronic duration of their symptoms (3–4 years), while two had a subacute onset and one had an acute onset [Table 2].

The chief complaint was headache in 4 (67%) individuals. Two (33.3%) patients had gait disturbances (in the form of spastic gait and magnetic gait) while 1 (16%) had double vision and 1 (16%) had symptoms pertaining to dorsal myelopathy. One patient had constitutional symptoms of fever and weight loss, mimicking systemic infection. One patient was incidental diabetic with well-controlled sugars.

Serological data

ESR was elevated in two patients to the tune of 60–90 mm in the 1st h. CSF glucose was normal in all patients (more than 2/3rd of the corresponding serum level). Two patients had cellular response in the CSF (30 and 50 cells/mm^3). Protein elevation was seen in three patients and ranged 80–85 mg/dl. Serum ACE levels were normal in all patients. None of them had peripheral eosinophilia or abnormalities in vasculitic profile. IgG4 levels were elevated in 3 (50%) patients (ranged between 2.45 and 4.73 g/l) and were normal (0.03–2 g/l) in 3 (50%) patients [Table 2]. Total serum IgG levels were normal in all patients and ranged between 1.21 and 1.63 g/l).

Table 2: Clinical manifestations, immunoglobulin G4 levels, and therapy response of the patients with neurological manifestations of immunoglobulin G4-related disease

	Age (years)	Sex	Duration	Neurological deficits	Anatomical diagnosis	IgG4 levels (mg/dl)	Treatment given	Course change in mRS from baseline to at 3 months
1	64	Male	2 months	Right 3, 4, 5a, 5b, 6 cranial nerve [Figure 1a]	Right cavernous sinus involvement extending till petrous apex	2450 (increased)	Oral prednisolone (1 mg/kg body weight)	Improved 1-0
2	40	Female	2 weeks	Compressive myelopathy	Cervical 6-dorsal 5 vertebral body level, extra-medullary involvement	1920 (normal)	Intravenous methyl prednisolone followed by oral prednisolone	Improved 4-2
3	36	Female	4 years	Headache-spastic paraparesis [Figure 1b-f]	Parasagittal falcine, Superior sagittal sinus thrombosis, Pseudotumor like masses in bilateral frontal and occipital lobe	4730 (increased)	Intravenous methyl prednisolone followed by oral prednisolone and maintenance with injection rituximab	Near static 3-2
4	52	Female	4 years	Magnetic gait, urinary disturbances, dementia	Diffuse pachymeningeal involvement	3250 (increased)	Oral prednisolone and injection rituximab	Septic shock 4-6
5	35	Female	5 months	Headache	Diffuse pachymeningeal involvement	1860 (normal)	Oral prednisolone, azathioprine	Improved 1-0
6	42	Female	4 years	Headache resembling sinusitis - followed by seizures 1.5 years later [Figure 3]	Right frontal focal pachymeningitis followed by resolution 5 months later	1762 (normal)	Oral prednisolone, injection rituximab	Improved 2-0

IgG4=Immunoglobulin G4, mRS=Modified Rankin scale

Imaging

All the patients had pachymeningitis, focal in 4 (67%) individuals (Patient No. 1, 2, 3, and 6), and two had diffuse involvement (n = 4, 5). Isolated cavernous sinus involvement [Figure 1a] was seen in 2 (33%) patients. Spinal cord involvement extending for a long segment from C6-D5 was seen in 1 (Patient No. 2) individual. Another peculiar finding was pseudotumor-like masses involving frontal lobes and bilateral occipital lobes in one patient [Figure 1b and c]. This patient also had sinovenous thrombosis involving superior sagittal sinus due to trapping of the sinus in the obliterative fibrosis between the layers of thickened meninges [Figure 1d and f]. Hypophyseal involvement or leptomeningeal involvement was not seen in any of them.

Two of the patients underwent whole body 2-[18F]-fluoro-2-deoxy-D-glucose PET–computed tomography (CT) imaging as a part of their workup for the etiology (Patient No. 4 and 6), which revealed a normal study.

Biopsy

Histopathological confirmation was in all (100%) patients and was the basis of inclusion. All the pathological specimens were initially analyzed for the gross pathology with hematoxylin and eosin stains, PAS and AFB stains, as well as cultures for aerobes, anaerobes, fungi, and tubercular before IHC staining for IgG4. IgG4-stained plasma cell ratio of more than 50 cells/high-power field satisfied the definitive diagnosis of IgG4-RD. Lymphocytic infiltration with plasma cells was seen in all the specimens (100%), while storiform fibrosis and obliterative phlebitis were seen in 5 (83%) and 2 (33.4%), respectively. No eosinophilia was seen in the tissue. IgG4 staining was seen in all of them [Figure 2], satisfying the diagnosis.

Therapy received

All the patients in the cohort had clinical and histological features consistent with IgG4. They were initially treated with steroids, either pulse methyl prednisolone or oral prednisolone based on the severity of their symptoms. Those with acute/subacute presentation (50%) had an excellent response to steroids (1 mg/kg body weight of oral prednisolone for 6 weeks followed by taper in the dosage over next 3 months and stopped during follow-up based on the clinical response) (Patient No. 1 and 2). The response was appreciated within 2 weeks to a month. Patients with a chronic course were treated with rituximab after initial treatment with oral steroid or intravenous pulse methyl prednisolone (Patient No. 3) at a dose of 1 g pulse over 5 days. One elderly female (Patient No. 4) with magnetic gait, dementia, and urinary disturbances was initially treated with ATT, following a provisional diagnosis of tuberculous pachymeningitis. However, failing a clinical response, she underwent a biopsy confirmation of IgG4-RD and was started on steroids followed by rituximab for maintenance immunosuppression. She deteriorated 7 months later after an initial response and succumbed to urosepsis and septic shock while on rituximab. Another patient (Patient No. 3)

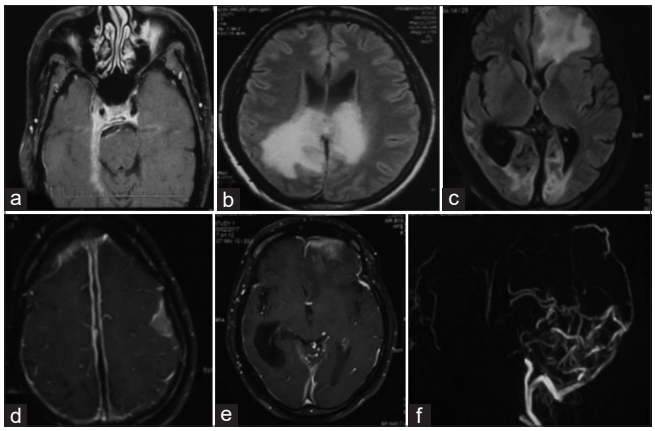

Figure 1: (a) Contrast-enhanced magnetic resonance imaging of the patient with right-sided ophthalmoplegia showing enhancement along the cavernous sinus and along the tentorium cerebelli (Patient 1). (b and c) Magnetic resonance imaging fluid-attenuated inversion recovery sequence showing tumor-like masses along the splenium and bilateral occipital lobes and left frontal lobe. (d and e) Magnetic resonance imaging T1-weighed images after gadolinium contrast showing enhancement along falx cerebri and cerebelli with cerebrospinal fluid loculated in between. (f) Magnetic resonance venography showing nonvisualization of the superior sagittal sinus suggesting obliterative phlebitis and organized collaterals (Patient 3)

had spastic paraparesis and was treated elsewhere with ATT. She also had venous thrombosis of superior sagittal sinus for which she was started on anticoagulants [Figure 1]. Owing to the nonresponse to treatment, she underwent biopsy and was confirmed as IgG4-RD, for which she was started on pulse intravenous methylprednisolone followed by rituximab. She has a nearly static course (mRS 3–2). Another patient (Patient No. 6) was a 42-year-old female with recurrent sinus headache and underwent functional endoscopic sinus surgery and biopsy of maxillary sinus was normal. MRI brain was done when she had a cluster of seizures, which showed right frontal focal pachymeningitis, biopsy of which proved to be IgG4-RD. She responded very well [Figure 3a and b] to steroids and rituximab. Azathioprine 50 mg twice a day was the oral steroid-sparing agent in another patient (Patient No. 5) with isolated headache and diffuse pachymeningeal involvement.

Discussion

Here, we describe the clinical presentation of six patients with biopsy-confirmed IgG4-RD, between January 2016 and March 2018. The total number of other patients with hypertrophic pachymeningitis during this period was 29, with established diagnosis of tuberculous meningitis in 12, sarcoidosis in 3, malignancy related in 1, idiopathic in 10, and hypertrophic meningitis with elevated serum IgG4 levels in 3 patients. These three patients with elevated serum levels of IgG4 levels had clinical and imageological evidence of hypertrophic pachymeningitis (2) and neuropathy (1), but did not undergo the biopsy either due to milder nature of their symptoms/failed to consent. They were not included in the study to minimize

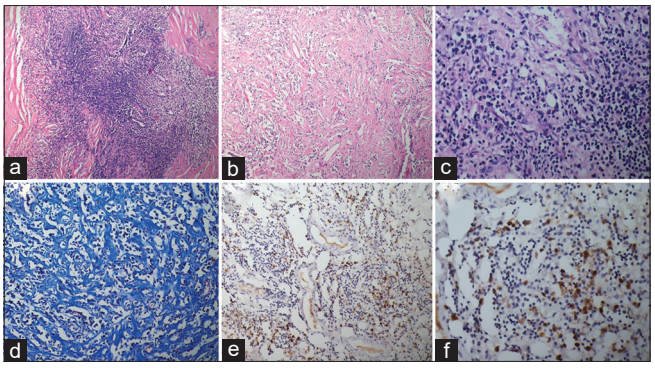

Figure 2: (a) Dural biopsy showing extensive inflammation and (b) fibrosis with (c) dense plasma cell infiltrate. (d) The fibrosis highlighted by Masson's trichrome. (e and f) Intense positivity for immunoglobulin G4 in the plasma cells

the confounders such as ANCA-associated vasculitis that may mimic IgG4-RD with elevated serum IgG4 levels.[7]

IgG4-RD has been reported initially in nonneurological conditions. The involvement of nervous system is far less common and was described as a case report of Mikulicz disease complicated by autoimmune hypophysitis.[8] None of our patients had hypophyseal involvement. Isolated central nervous system (CNS) involvement, as in our series, though rare has been described in the literature.[9] Large prospective studies of systemic IgG4-RD in 118 Chinese patients[10] and another retrospective study on 235 patients from Japan[11] showed no CNS manifestations [Table 3]. A retrospective study of 125 patients with neurological symptoms showed meningeal involvement in three patients and perineural involvement in one.[6] None of our six patients manifested any perineural disease. Another large multicentric study of IgG4-RD with neurological involvement was described by Lu *et al*. in 33 patients with histological confirmation of IgG4-RD.[17] Our series was relatively small with only 6 patients, but all of them were from a single center and data were obtained over a short span of 2 years.

Inflammatory pseudotumor-like presentation with direct brain involvement is rare. We had 1 patient (Patient No. 3) with tumor-like mass involving left frontal lobe and bilateral occipital lobes. In addition, she had sinovenous thrombosis stemming due to encasement of the superior sagittal sinus in the obliterative fibrosis. Such a scenario has not been described so far. Another patient had compressive myelopathy mimicking an en plaque meningioma. Case reports of compressive myelopathy due to IgG4-RD are well described in the literature.[18]

Seventy to ninety percent of patients with IgG4-RD have elevated IgG4 levels in the serum.[17] Among the biopsy-proven six patients, there were equal numbers of patient with normal and elevated levels of IgG4 levels not yielding a diagnostic tool [Table 2]. Serum IgG levels were not elevated in any of them. Carruther *et al*.[19] proposed low specificity and poor positive predictive levels of IgG4 levels in the serum. However, their study was in patients with systemic IgG4-RD and not in

Table 3: Review of literature of IgG4-related disease

Author	Mean age (range) in years	Male/female number	Year of study	Nature of the study	Pituitary	Meningeal involvement	Peripheral nerve involvement	Special remarks
Lin *et al*.[10] (*n*=118)	53.1 years (19-80)	82/36	2015	Prospective	2	0	0	Systemic IgG4-related disease from China
Inoue *et al*.[11] (*n*=235)	55.2 (24-83)	76/49	2015	Retrospective	0	3	1	Largest cohort with systemic IgG4- related disease
Sekiguchi *et al*.[12] (*n*=166)	67 (35-86)	189/46	2011	Retrospective	0	0	0	Orbital and paravertebral involvement
Tajima and Mito[13]	33	0/1	2012	Case report	0	0	0	Paraneoplastic IgG4 - orbital inflammation, cranial neuropathy due to metastatic breast carcinoma
Lu *et al*.[14]	NA	NA	2014	Case series	0	1	1	IgG4-hypertrophic pachymeningitis, 48% had systemic involvement
Regev *et al*.[15]	50	1/0	2014	Case report	0	0	0	Left hemiparesis, dementia, MRI -parenchymal involvement
Wallace *et al*.[6]	40 (32-50)	2/2	2013	Retrospective case series	0	3	1	Retrospective study of preserved pathology slides over 25 years
Ezzeldin *et al*.[16]	55	1/0	2014	Case report	0	0	0	Spinal cord involvement with systemic IgG4

NA=Not available, MRI=Magnetic resonance imaging, IgG4=Immunoglobulin G4

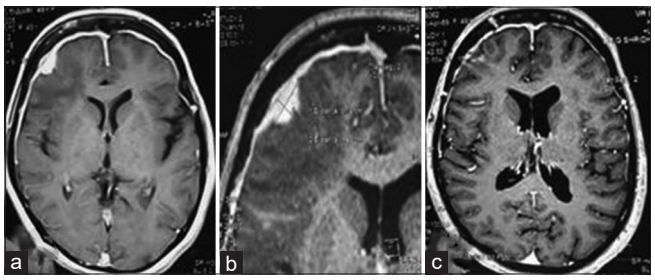

Figure 3: (a and b) Magnetic resonance imaging brain fluid-attenuated inversion recovery showing right frontal lesion which on contrast administration showed nodular pachymeningeal enhancement (Patient 6). (c) Repeat magnetic resonance imaging after 6 months showing complete resolution. The patient was on rituximab

those with isolated CNS involvement. There is a need to further validate the role of IgG4 levels in the serum in patients with isolated neurological involvement. The serological markers might negate the need for invasive biopsies in the future.

No definitive treatment guidelines exist for IgG4-RD of the CNS. A consensus guideline for IgG4-related autoimmune pancreatitis recommend 0.6 mg/kg of steroid for 4 weeks, followed by taper over 3–6 months to maintain at low dose of 2.5–5 mg/day for 3 years.[20] Patients with acute/subacute onset responded well and did not require long-term immunosuppression and were advised a close follow-up. Rituximab is reported to be a promising agent in IgG4-RD[21] and was used in three patients, all with a chronic course. All these patients (Patient No. 3, 4, and 6) were initially treated as tubercular meningitis and one patient also had constitutional symptoms and elevated ESR. The failure to respond to ATT prompted a biopsy and revealed IgG4-RD and the need to stop ATT and start immunosuppressants. Unlike the patients with acute course, patients with a chronic history had variable prognosis, suggestive of a burnout disease with obliterative fibrosis. This could be attributed to both duration of disease and limitations with drug penetration into the fibrosed tissue. Thus, duration of the disease was a greater prognostic factor than the therapeutic agent of choice. Early diagnosis and treatment hold promise of a disability-free status.

Limitations of the study

The limitations rest on the retrospective and observational nature of the study. The sample size was small. These patients have predominant nervous system manifestations and indolent multisystem involvement cannot be ruled out as whole-body PET-CT was not done in all the patients.

Conclusion

IgG4 subset of plasma cells have important role in the etiopathogenesis of IgG4-RD. The constellation of clinical features, imageological findings, IgG4 assay, and histopathological findings aid the clinician in the definitive diagnosis. The characterization of the patients has prospects in studying the natural course of this rare entity and determining the therapeutic response in the long run. There is a need for further research on the role of noninvasive serological markers as a substitute to the invasive meningeal biopsy which is the current gold standard and used in the study.

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Conflicts of interest
There are no conflicts of interest.

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