

Neurological Involvement in a Portuguese Cohort of IgG4-Related Disease

Envolvimento Neurológico numa Coorte Portuguesa de Doentes com Hiper-IgG4

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ABSTRACT

Introduction: Neurological involvement in immunoglobulin G4-related disease (IgG4-RD) is increasingly recognized. Its diagnosis can be challenging due to clinical mimics and difficulty in obtaining nervous system biopsies. The aim of this study was to describe a cohort of neurological IgG4-RD patients.

Methods: Patients were recruited from a neuroimmunology tertiary center. Clinical, laboratory, neuroimaging and histological data were reviewed.

Results: Fifteen patients (60% women), with a median age of 53 years (48.5 – 65.0) were included: 13 (86.7%) classified as possible IgG4-RD, one (6.7%) as probable and one (6.7%) as definitive. The most common neurological phenotypes were meningoencephalitis (26.7%), orbital pseudotumor (13.3%), cranial neuropathies (13.3%), peripheral neuropathy (13.3%), and longitudinally extensive transverse myelitis (LETM) (13.3%). Median serum IgG4 concentration was 191.5 (145.0 – 212.0) mg/dL. Seven in 14 patients had CSF pleocytosis (50.0%) and oligoclonal bands restricted to the intrathecal compartment, while most cases presented elevated CSF proteins (64.3%). Magnetic resonance imaging abnormalities included white matter lesions in four (26.7%), hypertrophic pachymeningitis in two (13.3%), and LETM in two (13.3%). Two patients had biopsy-proven IgG4-RD in extra-neurological sites.

Conclusion: This study highlights the phenotypical variability of the neurological IgG4-RD. Biopsy inaccessibility reinforces the importance of new criteria for the diagnosis of this subset of patients.

Keywords: Immunoglobulin G; Immunoglobulin G4-Related Disease/diagnosis; Nervous System Diseases

RESUMO

Introdução: O envolvimento neurológico na doença associada a imunoglobulina G4 é cada vez mais reconhecido. O seu diagnóstico pode ser desafiante por poder mimetizar outras doenças e ser difícil obter amostras de tecido nervoso. O objetivo deste estudo é descrever uma coorte de doentes com doença neurológica associada a IgG4 (IgG4-RD).

Métodos: Os doentes foram recrutados a partir de um hospital terciário com consulta de Neuroimunologia. Os dados clínicos, laboratoriais, neuroimológicos e histológicos foram obtidos retrospectivamente.

Resultados: Foram incluídos 15 doentes (60% mulheres) com uma idade mediada de 53 anos (48,5 – 65,0): 13 (86,7%) classificados como IgG4-RD possível, um (6,7%) como provável e um (6,7%) como definitivo. Os fenótipos neurológicos mais frequentes foram a meningoencefalite (26,7%), pseudotumor orbitário (13,3%), neuropatias cranianas (13,3%), neuropatia periférica (13,3%), e mielite transversa longitudinalmente extensa (13,3%). A concentração sérica mediana de IgG4 foi de 191,5 (145,0 – 212,0) mg/dL. Sete em 14 doentes tinham pleocitose no líquido cefalorraquidiano (50,0%) e bandas oligoclonais sem espelho sérico, enquanto a maioria dos casos apresentava proteinorráquia elevada (64,3%). As alterações na RM incluíram lesões na substância branca em quatro doentes (26,7%), paquimeningite hipertrofica em dois (13,3%) e LETM em dois (13,3%). Dois doentes tinham confirmação histológica da doença.

Conclusão: Este estudo destaca a variabilidade fenotípica da IgG4-RD neurológica. A inacessibilidade da biópsia reforça a importância de atualizar os critérios de diagnóstico para o subgrupo de doentes neurológicos.

Palavras-chave: Doença Relacionada a Imunoglobulina G4/diagnóstico; Doenças do Sistema Nervoso; Imunoglobulina G

INTRODUCTION

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a fibro-inflammatory disease characterized by tumefactive lesions involving multiple organs, with typical histopathological features and a rapid clinical response to glucocorticosteroids.^{1,2}

Neurological involvement is a recognized feature of IgG4-RD, mainly in the form of diffuse inflammation of the dura mater (hypertrophic pachymeningitis), hypophysitis, and cranial neuropathies (usually associated with orbitopa-

thy).³ Furthermore, peripheral neuropathy, carotid/ intracerebral vasculopathy, and brain/ spinal cord parenchymal lesions have been rarely described.⁴

The diagnosis of IgG4-RD can be challenging due to several clinical mimics, histological intra- and inter-organ variability and absence of elevated IgG4 serum concentration in 30% - 50% of patients with biopsy proven IgG4-RD.^{1,5} In the nervous system, the diagnosis is even more complex given the lack of organ-specific diagnostic criteria (only

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available for head and neck glands, eye, chest, pancreas and biliary tree, kidney, and retroperitoneum) and biopsy inaccessibility in some circumstances.^{6,7}

The available evidence regarding the neurological phenotype in IgG4-RD is even rarer, consisting of case reports and a few case series focusing on specific phenotypes like pachymeningeal involvement.⁸⁻¹²

In this study, we provide a clinical, neuroradiological, and biochemical description of an IgG4-RD cohort from our centre.

METHODS

Patient selection

We retrospectively reviewed all patients with suspected IgG4-RD based on an electronic search of the neuroimmunology outpatient clinical database from a tertiary referral centre. Patients were diagnosed between 2015 and 2022. IgG4-RD was defined according to the 2020 Revised Comprehensive Diagnostic Criteria of the Japanese College of Rheumatology, and further classified in possible, probable and definite.⁶ All the included cases had been sufficiently investigated that alternative diagnoses that were set as exclusion criteria had been excluded. These comprised the following: serological findings of positive antibodies (ANCA, Ro, La, dsDNA, RNP, and Sm) or clinical diagnosis of similar conditions [Sjögren disease, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, sarcoidosis, Castleman disease, primary sclerosing cholangitis, secondary retroperitoneal fibrosis, inflammatory bowel disease (if pancreaticobiliary disease present), Hashimoto thyroiditis (if the thyroid is the only organ involved), tumors].^{6,7}

Serum IgG4 quantifications were obtained using enzyme-linked immunosorbent assay (ELISA) with a cutoff value adapted using the reference value set by our laboratory (14 - 74 mg/dL). Neurological manifestations comprised clinical or radiological evidence suggestive of involvement of the following structures: extra-ocular muscles and levator palpebrae; cranial nerves; meninges; brain or spinal cord parenchyma; pituitary gland; peripheral nerves; plexuses; nerve roots; ganglia; and intracranial or neck vasculature.

Data collection

Demographic, clinical, laboratory, imaging and histological data were collected from medical records, using a structured protocol.

Demographic data included the date of birth and gender, while clinical data was divided in neurological and systemic features. Neurological characterization comprised age at presentation, onset pattern (acute, \leq seven days; subacute, $>$ seven days and \leq three months; and chronic, $>$ three months), and description of symptoms and signs (based on interview and neurological examination at first observa-

tion). Patients were further divided as having a common or uncommon neurological IgG4-RD syndrome, according to the predominant neurological features. Regarding systemic features, all patients were assessed by a specialist in autoimmune disorders.

Analytical measurements (obtained during active disease or during the first neurological evaluation) comprised serum IgG4, and other Ig populations, presence of hypocomplementemia, eosinophilia and other paraclinical autoantibodies (autoimmune and/or paraneoplastic autoantibodies depending on the clinical presentation). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were analyzed according to the reference values of 0 - 19 mm and 0 - 5 mg/L, respectively. Cerebrospinal fluid (CSF) characteristics of interest included pleocytosis, cell differentiation, protein, presence of CSF specific oligoclonal bands, and IgG and IgG4 measurements from the first lumbar puncture (LP). Serum IgG4 concentration was also re-assessed after treatment, and during a relapse. Spinal cord and brain magnetic resonance imaging (MRI) were reviewed by a neuroradiologist blinded to the clinic, with a focus placed on T1, T2, FLAIR and T1 with gadolinium enhancement sequences at first hospital admission, after treatment and during a relapse. Neurophysiological study results were also retrospectively collected. Histological features were retrieved from written pathology reports, when available.

Data on pharmacological treatments (oral and intravenous corticosteroids, corticosteroid-sparing agents, and respective response) was additionally detailed. Time to treatment was defined as time (months) from initial neurological manifestations to initiation of corticosteroids. Response to treatment included an unequivocal improvement of neurological symptoms and/or radiological findings.

Lastly, outcome information involved follow-up duration, disease progression and number of relapses (defined as new IgG4-related clinical or imaging manifestations).

Descriptive statistics

Qualitative variables were studied using absolute and relative frequencies. For quantitative variables, the median and interquartile range (p25 - p75) (IQR) were used.

Ethics

This study was approved by Centro Hospitalar Universitário de Santo António Ethics Committee. Written informed consent was obtained from each patient.

RESULTS

Fifteen patients (60% women), with a median age of 53 years (48.5 - 65.0) were included in this study. Thirteen patients were classified as possible IgG4-RD, one as

Table 1 – Histological features in biopsy specimens

Pt	Organ	Findings
3	Lacrimal gland	Lymphoplasmocytic infiltration, IgG4/IgG cell > 40% and IgG4 cell/HPF > 10 and < 100.
4	Skin nodule	Plexiform neurofibroma, no IgG4 staining.
8	Pulmonary nodule, parotid gland, pancreatic cyst, sural nerve	Pulmonary nodule – lymphoplasmocytic infiltration, IgG4/IgG cell > 40% and IgG4 cell/HPF > 10; Parotid gland – few plasmocytes, no IgG4 staining; Pancreas cyst – few plasmocytes, IH NP; Sural nerve – chronic neuropathy, no plasmocytes, no IgG4 staining.
10	Skin	Lymphoplasmocytic infiltration, epidermal necrosis, hypodermal proliferation of myofibroblasts, no IgG4 staining.
11	Conjunctiva	No lymphoplasmocytic infiltration nor IgG4 staining.
12	Liver	Cirrhotic steatohepatitis, lymphoplasmocytic infiltration, biliary duct lesions, Mallory bodies, IH NP.
13	Nasopharynx	Lymphoplasmocytic infiltration, IgG4/IgG cell < 20%.
14	Thyroid	Adenomatous hyperplasia, IH NP.

probable and one as definitive. The Appendix 1 (Appendix 1: <https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20767/15397>) summarizes the clinical and paraclinical findings from our cohort. Elevated serum IgG4 was present in all patients except for Patient 8, which was diagnosed based on supporting histological features (Table 1). Median serum IgG4 concentration was 191.5 (145.0 - 212.0) mg/dL. Serum IgG4 measurement was performed during active disease in seven patients (46.7%).

Neurological manifestations were the presenting symptom of the disease in 80% of our cohort (n = 12/15). The median age at first neurological manifestation was 49.0 (34.5 - 57.5) years. Median time to diagnosis was three years (0.0 - 4.5). Onset was subacute in seven (46.7%), acute in five (33.3%) and chronic in two (13.3%). The most common neurological phenotypes were meningoencephalitis in four patients (26.7%) (two with classical features of hypertrophic pachymeningitis), orbital pseudotumor in two (13.3%), and cranial neuropathies in two (13.3%, multiple in one). Peripheral nerve involvement was present in two individuals (13.3%), in the form of radiculopathy in one (which also presented a tonically dilated pupil – Adie's Pupil) and sensitive polyneuropathy in one. One patient (6.7%) presented with cavernous sinus syndrome and one (6.7%) with brain parenchymal lesions. Two patients (13.3%) presented with longitudinally extensive transverse myelitis (LETM); extensive investigation ruled out other potential causes for myelitis. Additionally, in one patient with asymmetrical parkinsonism, a brain MRI was performed due to initial poor levodopa response, disclosing mild pachymeningitis (Fig. 1C). For this reason, this patient was considered asymptomatic for IgG4-RD. Three patients presented extra-neurological symptoms: xerostomia (Patient 8, with unilateral parotid enlargement), dacryoadenitis (Patient 3, with unilateral lacrimal gland enlargement) and panniculitis and orchiepididymitis (Patient 10). All patients performed thoracic-abdominal-pelvic CT, of which only one was deemed as normal. Mediastinal-hilar-axillary lymphadenopathies were the most common finding, being present in seven patients (46.7%). Other features are

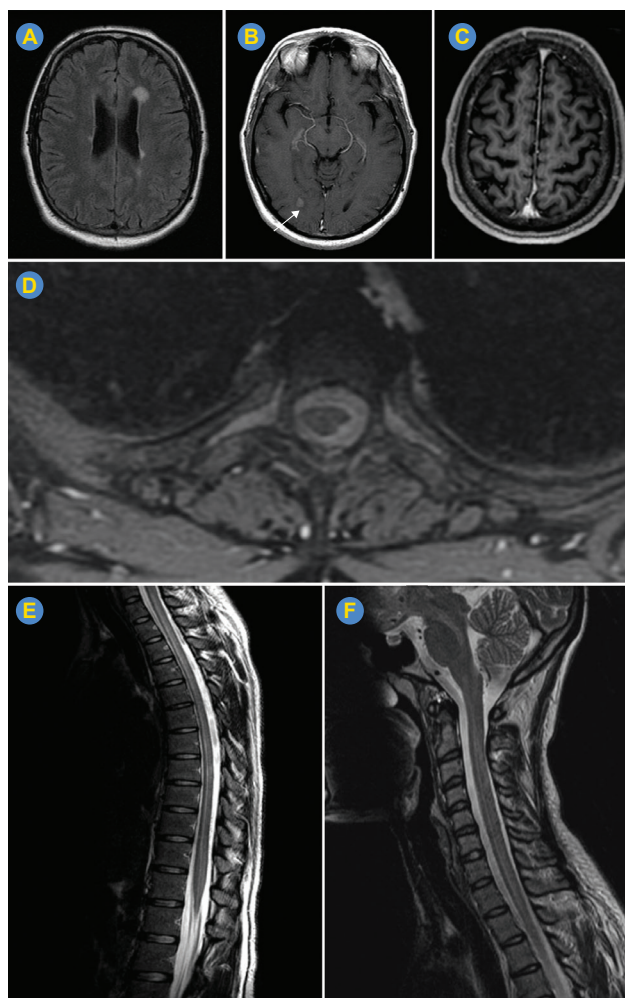


Figure 1 – MRI at disease onset. Oval, periventricular white matter lesions in FLAIR-WI, and one gadolinium-enhancing lesion (arrow) (A, B, Patient 15). Sagittal T1-WI after gadolinium administration displays mild pachymeningitis at left parasagittal parietal dura (C, Patient 14). Patient 7 features circumferential thickening of the dura (hypertrophic pachymeningitis), from C6-D12, with marked gadolinium-enhancement as shown in axial T1-WI at lower dorsal level (D). Extensive hyperintensity of spinal cord on T2-WI between T2 and conus medullaris (LETM) (E, F, Patient 13).

summarized in the Appendix.

In fourteen patients a CSF analysis was performed. Seven patients had pleocytosis (50.0%), with a median cell count of 8.5 (1.0 - 180.0) cells/mm³, all lymphocytic-predominant. Elevated CSF proteins were present in 64.3%, with a median protein count of 74.0 (32.0 - 104.0) mg/dL. Oligoclonal bands restricted to the intrathecal compartment were present in seven patients (50.0%). One case had hypereosinophilia and none had hypocomplementemia. Erythrocyte sedimentation rate was above reference level in 33.3% (range 25.0 - 94.0 mm/h) and elevated CRP in 20.0% (range 11.1 - 63.3 mg/L, respectively). Other autoantibodies found included ANA in four patients, and peroxidase and thyroglobulin in one. Four patients had elevated total IgG and two had hyper-IgE, while another two cases had IgA and IgM deficiencies. Anti-aquaporin 4 (anti-AQP4) and anti-myelin oligodendrocyte glycoprotein (anti-MOG) were negative in the patients with LETM.

Concerning brain and/or spinal cord MRI at first hospital admission (Fig. 1), the observed abnormalities were the following: white matter lesions (n = 4), hypertrophic pachymeningitis (n = 3), myelitis (n = 3, two LETM), orbital pseu-

dotumor (n = 1), multiple cranial nerve hyperintensity (n = 1), middle cerebellar peduncle hyperintensity (n = 1), and diffuse leptomeningeal enhancement (n = 1). Three patients had normal brain and spinal MRI (Patients 6, 9, 10).

Histopathological data was available in seven (46.7%) patients (Table 1). Two patients fulfilled the histopathological criteria for IgG4-RD with specimens taken from a lung nodule (Patient 8) and lacrimal gland (Patient 3). A peripheral nerve biopsy from patient 8 showed no specific features suggestive of IgG4-RD (Fig. 2.) In the remaining five patients, two skin biopsies (corresponding to one case of panniculitis and one of hypermetabolic subcutaneous lesion on PET scan), one conjunctival biopsy (asymptomatic), one liver biopsy (cytocholelasis) and one nasopharynx biopsy (nasopharyngeal thickening) did not find IgG4-related pathological features.

Ten patients (66.7%) received high-dose IV methylprednisolone pulse therapy during active disease, six later switched to oral prednisolone taper. The median time from diagnosis to treatment was 1.5 (0.0 - 72.0) months. Steroid-sparing immunosuppressors were also used, most frequently azathioprine (40.0%) and rituximab (13.3%) (Appendix 1:

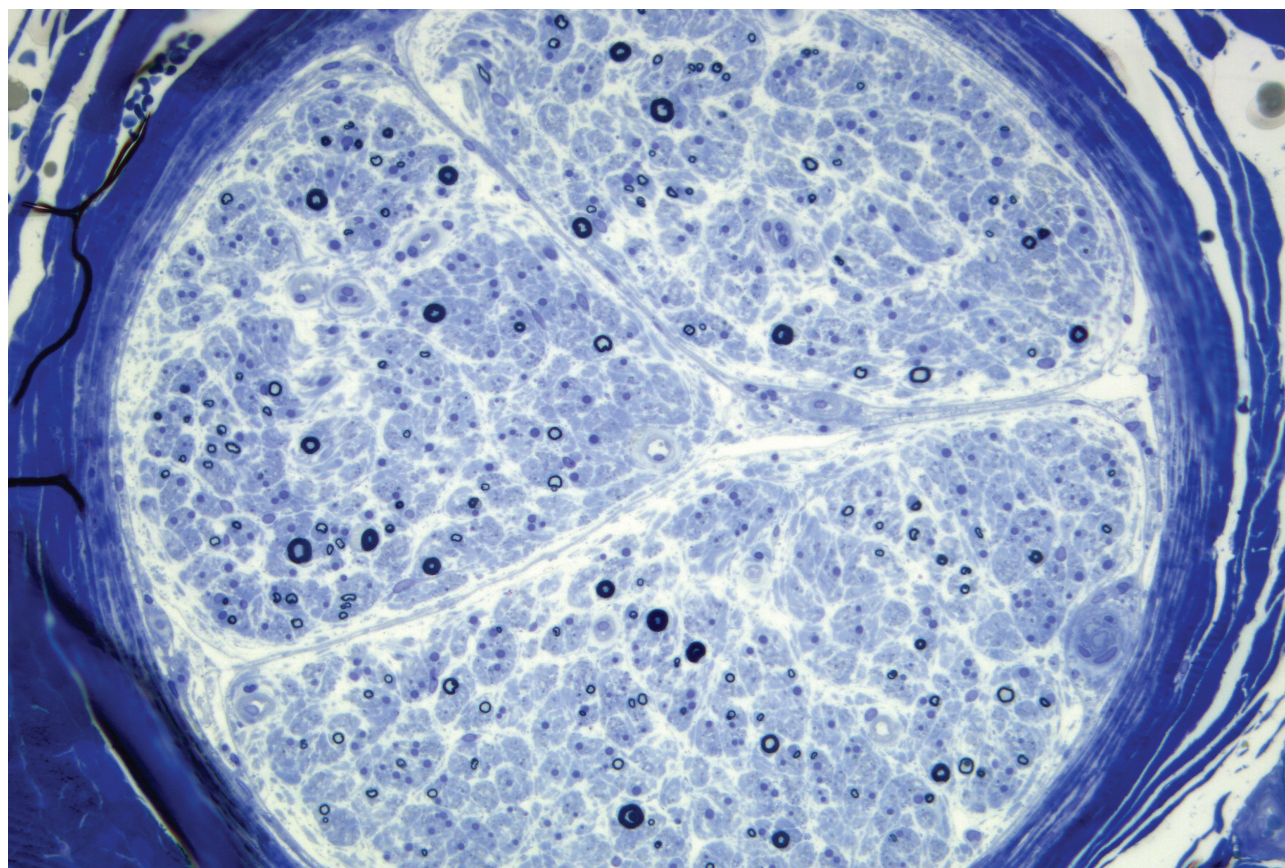


Figure 2 – Sural nerve biopsy of Patient 8. Chronic and severe neuropathy, with loss of large and small myelinated fibres, and moderate endoneurial fibrosis. There are no regeneration clusters, or onion bulbs. Absence of lymphoplasmacytic infiltration or deposition of abnormal substances precludes immunohistochemistry performance. Toluidine blue, scale bar: 100 µm.

<https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20767/15397>). All treated patients had improvement under corticosteroids (oral and/or IV), and neuroimaging improvement was documented in five (Fig. 3.). Serum IgG4 concentration decreased after corticotherapy in 80.0% (Appendix 1: <https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20767/15397>). Two patients remained free from neurological manifestations after treatment (Patients 2 and 4). Relapses were identified in four patients (cranial nerve neuropathy, paroxysmal vertigo, and meningoencephalitis in two), albeit new brain MRIs did not show additional lesions. Serum IgG4 concentration upon relapse increased in 75.0%, and two relapses were temporally related to steroid tapering. After a median follow-up time of 45.5 (1.0 - 143.0) months, four patients (26.7%) were asymptomatic and had a normal neurological examination.

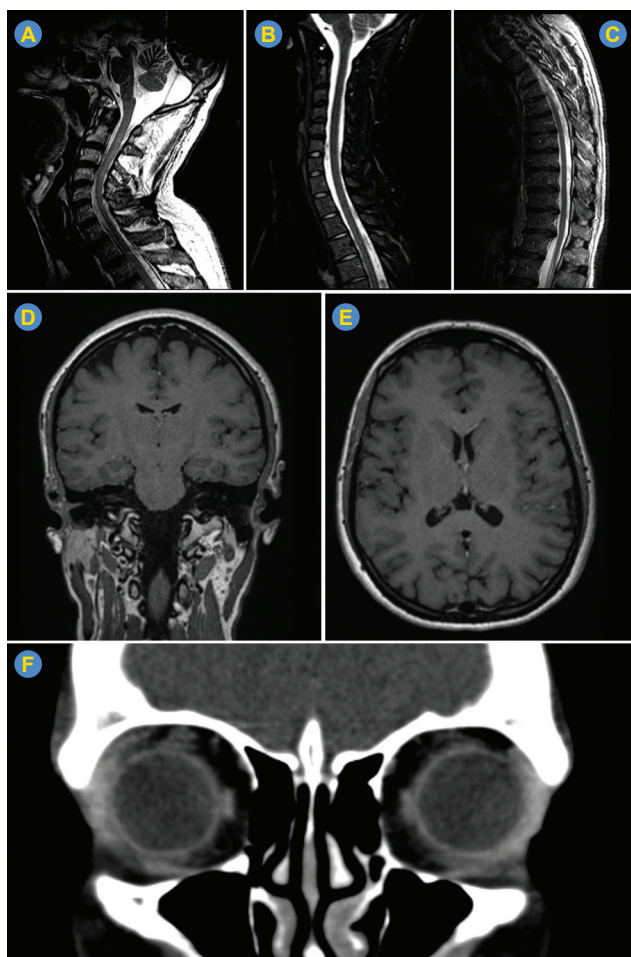


Figure 3 – MRI after corticosteroids. Regression of the extensive spinal cord T2 hyperintensity (A, B, C, Patients 11 and 13). Regression of leptomeningeal and pachymeningeal enhancement (D, E, Patient 13). Orbital CT in Patient 3 showing reduction of right lacrimal gland enlargement (F).

DISCUSSION

We describe a cohort of patients with IgG4-RD that illustrates the high variability in clinical expression associated with this disorder, with both central and peripheral nerve involvement.¹

Meningoencephalitis with or without associated hypertrophic pachymeningitis is a classical manifestation of IgG4-RD and was the most common presentation in our cohort.¹¹ The variety in clinical features at presentation reflects mechanical compression of vascular or nerve structures in these cases.^{9,13} Gait instability has previously been described in cases of IgG4-RD with meningeal involvement, in agreement with our findings.¹⁴ Interestingly, we described one case with asymptomatic hypertrophic pachymeningitis and two cases with meningoencephalitis lacking meningeal enhancement on brain MRI. These findings suggest that a continuous inflammatory process in IgG4-RD may go unnoticed on routine imaging studies and may even be subclinical.¹⁵

Brain parenchyma involvement was present in four patients. While being considered non-specific in three, one patient had a clear inflammatory periventricular lesion. This was considered a clinically isolated syndrome for many years, but persistently elevated IgG4 serum concentration together with radio-labelling of thyroid, lung and lymph node tissue in PET-scan favored the diagnosis of IgG4-RD. Brain parenchyma involvement is considered a rare finding in IgG4-RD.¹⁶

Classical IgG4-related neurological manifestations were less frequently found in our cohort and included orbital pseudotumor and cranial neuropathies. Most of the cohort had isolated neurological IgG4-RD, and this is in line with the literature.¹ Investigation directed at systemic involvement revealed minor abnormalities in different organs, in spite of not fulfilling the organ-specific diagnosis criteria for the disorder.

Interestingly, we identified two patients presenting with involvement of the spinal cord parenchyma, which is atypical for IgG4-RD.^{1,3} To the best of our knowledge, there are only two previous descriptions of parenchymal spinal cord involvement.^{17,18} Patient 11 has previously been described as a case report by our group.¹⁹

Other atypical findings were present in our cohort, including a patient with sensory ganglionopathy (Patient 8). This patient had parotid gland obstruction and lung biopsy-proven IgG4-RD. K. Ohyama *et al* (2015)²⁰ found IgG4-positive plasma cells in sural nerve biopsies of patients with idiopathic peripheral neuropathies, although dorsal root ganglion involvement has never previously been described. The finding of bilateral Adie pupil in Patient 9 further raises the possibility of lymph node involvement.

Overall, IgG4 concentration appeared to decrease after

treatment with corticosteroids. CSF analysis showed elevated protein levels and intrathecal production of oligoclonal bands in most cases, which is consistent with previous studies.¹ The brain MRI evaluation showed that, although the pachymeninges are the most common meningeal component involved, the inflammation may extend diffusely to the leptomeninges, which has been previously reported in four cases.^{10,21-23} Three of the cases that presented pachymeningeal involvement have previously been described.⁸

The main strength of this work is the well-documented patient history and the descriptive imaging findings that it provides. However, this study has several limitations that should be accounted for. A relevant limitation of this study is the limited number of IgG4-RD histopathological confirmations. Possible explanations for the some of the biopsies being negative include: (1) performance of biopsies in anatomical locations normally associated with findings of poor specificity (lymph nodes, skin, conjunctiva), (2) use of needle aspiration biopsy, in the case of pancreatic lesion, (3) absence of immunohistochemistry in five biopsy samples, and (4) histological evaluation not being directed towards the organ of disease activity, with only one patient having a biopsy sample of the nervous system (sural nerve).^{5,7} The two biopsy-proven IgG4-RD did not show a swirling, 'cart-wheel' pattern of fibrosis (storiform fibrosis) or obliterative phlebitis. However, the consensus pathologic criteria contemplate the absence of these features in the specific cases of lacrimal and lung specimens. Second, the upper limit cutoff for the serum IgG4 concentration was different from the one set by the Japanese College,⁶ even if in the three patients presenting values below 135 mg/dL they were consistently above 100 mg/dL in further measurements and other mimics were extensively searched for and excluded. Third, this is a retrospective study from a single centre, with a relatively small sample size, which limits generalizability.

CONCLUSION

This study highlights the phenotypical variability of the neurological IgG4-RD and underscores the importance of

considering IgG4-RD in the differential diagnosis of recurrent aseptic meningitis, cranial neuropathies with atypical features, sensory ganglionopathies, and longitudinally extensive myelitis. The absence of non-neurological manifestations and biopsy inaccessibility hampers the diagnosis of neurological IgG4-RD. In the future, additional neurological and neuroimaging descriptions as well as nervous system-specific criteria are needed.

AUTHOR CONTRIBUTIONS

JM, MJM: Study design, data collection and analysis, drafting of the manuscript.

FJ, EP, AS, IL, VO, APS, JD, LM, NVC, RS, RT, AMS: Data analysis, critical review of the article.

ES: Study design, data analysis, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

LM received payments from Alnylan for consulting services and giving lectures in symposia.

All other authors have declared that no competing interests exist.

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