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Diagnostic value of *IgG4 Indices* in IgG4-Related Hypertrophic Pachymeningitis ☆,☆☆,★

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ABSTRACT

Diagnosis of IgG4-Related Hypertrophic Pachymeningitis (IgG4-HP) relies on meningeal biopsies, because cerebrospinal fluid (CSF) diagnostic biomarkers are lacking. Here, we determined whether IgG4 intrathecal production could distinguish IgG4-HP from other disorders presenting with HP (OHP). In patients with IgG4-HP, the median CSF IgG4 concentration, IgG4 Index and $IgG4_{Loc}$ were significantly higher than in both controls and OHP. CSF IgG4 levels higher than 2.27 mg/dL identified 100% of IgG4-HP and 5% of OHP. An $IgG4_{Loc}$ cut-off of 0.47 identified 100% of IgG4-HP and no cases of OHP. Our results support CSF IgG4 quantification and *IgG4 Indices* as alternatives to meningeal biopsy for the diagnosis of IgG4-HP when this procedure is contraindicated or uninformative.

1. Introduction

IgG4-related disease (IgG4-RD) is a fibrotic disorder characterized by often elevated serum IgG4 and responsiveness to glucocorticoid treatment (Cheuk and Chan, 2010). The disease was first defined in relation to the pancreas but many other sites of involvement have been progressively recognized on the basis of striking similar histopathological features (Hamano et al., 2001; Zen and Nakanuma, 2011): namely, diffuse lymphoplasmacytic infiltration by IgG4-positive plasma cells, occasional eosinophils, storiform fibrosis and obliterative phlebitis (Deshpande, 2012).

Central nervous system (CNS) involvement has been initially demonstrated in the form of hypophysitis and subsequently described in a subset of patients with idiopathic hypertrophic pachymeningitis (IHP) (Wallace et al., 2013). We recently described three patients affected by IgG4-related hypertrophic pachymeningitis (IgG4-HP) and demonstrated an intrathecal IgG synthesis with oligoclonal pattern. We also evidenced cerebrospinal fluid (CSF) IgG4 production and suggested that an IgG4 Index would be a relatively non-invasive test as an adjunct to the diagnosis of IgG4-HP (Della-Torre et al., 2012, 2013). In effect, due both to the rarity of this condition and the extensive differential diagnosis, the evaluation of IHP might be extremely challenging and often requires an invasive bioptic procedure. For these reasons, a comprehensive definition of CSF findings in IgG4-HP could be crucial for diagnostic, prognostic, and therapeutic purposes, mainly in those patients with exclusive pachymeningeal involvement and/or normal serum IgG4 levels.

In the present work we sought to determine whether IgG4 intrathecal production, as assessed by the measurement of IgG4 concentrations within the CSF, and *IgG4 Indices* could distinguish IgG4-HP from other

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★ *APPROVAL of ETHIC COMMITTEE:* All subjects provided written informed consent for invasive tests such as meningeal biopsy and lumbar puncture that were performed for diagnostic purposes. Therefore, this retrospective analysis was not reviewed by an institutional ethics committee, but all tests were performed in accordance with institutional guidelines as well as with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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inflammatory, infectious, and neoplastic disorders that occasionally present with HP, namely, other HP (OHP).

2. Material and methods

2.1. Patients

The retrospective case–control study is based on 30 patients (22 men, 8 women) who were referred to our tertiary care centres (San Raffaele Hospital, Milan, Italy and Department of Neuroscience, Padua, Italy) between November 2007 and November 2012 with evidence of HP on magnetic resonance imaging (MRI). Three patients, reported in detail elsewhere (Della-Torre et al., 2012, 2013) (median age, 62 years; interquartile range (IQR) 52–67) were diagnosed with definite IgG4-HP based on comprehensive diagnostic criteria: compatible organ involvement, serum IgG4 levels > 135 mg/dL, pathological findings on meningeal biopsies showing lymphoplasmacytic infiltration of IgG4 bearing plasma cells with an absolute number > 50/HPF and a percentage of $IgG4^+/IgG^+$ cells > 40%, surrounded by storiform fibrosis (Deshpande, 2012). Their demographic characteristics and pathology features are shown in Table 1.

Cerebrospinal fluid IgG subclasses concentration and related intrathecal production Indices from patients with IgG4-HP were compared to those of nine control subjects and those of 21 patients with OHP, matched in a 1:3 and 1:7 ratio respectively, by age (±3 year) and sex.

The group of control subjects was used to determine normal ranges for all the measures considered and included patients undergoing elective trans-sphenoidal surgery for pituitary non-secreting adenomas without elevation of serum inflammatory markers or IgE levels, peripheral blood eosinophilia, allergies to foods or air pollens, blood–CSF barrier damage or oligoclonal bands on CSF analysis, nor evidence of meningitis on MRI.

The group of subjects with OHP included patients with granulomatosis with polyangiitis (GPA, formerly Wegener's) ($n = 3$); sarcoidosis ($n = 3$) (Della Torre et al., 2013); Behcet's disease ($n = 1$); diffuse large B-cell lymphoma (DLBCL)($n = 2$); POEMS syndrome ($n = 2$); meningeal carcinomatosis related to metastatic lung adenocarcinoma, melanoma, and breast cancer ($n = 1$ each); tuberculosis, cysticercosis, nocardiosis, and syphilis ($n = 1$ each); and IHP ($n = 3$). Behcet's disease and GPA were diagnosed according to internationally recognized classification criteria (Watts et al., 2007; Davatchi, 2012); the diagnoses of sarcoidosis, DLBCL, and metastatic cancer were confirmed by histological evaluation of meningeal biopsies. Tuberculosis, cysticercosis, nocardiosis, and syphilis were diagnosed according to CSF microbiological and immunological results. POEMS syndrome was diagnosed according to the current criteria (Dispenzieri, 2012). The diagnosis of IHP was made when a thorough clinical, microbiological, serological, radiological, and histological work out was unrevealing.

All subjects provided written informed consent for invasive tests such as meningeal biopsy and lumbar puncture that were performed for diagnostic purposes.

2.2. Laboratory tests

Paired CSF and serum samples were collected before the administration of any specific therapy, centrifuged within 30 min and stored at −20 °C. Albumin and total IgG concentrations were

Table 1
Cerebrospinal fluid, serological and microbiological findings in the three patients with IgG4-HP, and comparison with Control subjects and patients with Other forms of Hypertrophic Pachymeningits (OHP). (*) Normal values for serum IgG subclasses correspond to reference ranges used at San Raffaele Institute. (§) Rheumatoid factor, anti-nuclear, anti-cyclic citrullinated peptide, and anti-neutrophil cytoplasmic antibodies. **(°)** PCR for Herpes simplex virus types 1 and 2, Varicella-Zoster virus, Cytomegalovirus, Epstein-Barr virus, Enterovirus, Mycobacterium tuberculosis; Gram, acid-fast stain and microbiological cultures; search for Aspergillus fumigatus and Cryptococcus neoformans antigens; serology for Lyme disease, brucellosis, syphilis. **(^)** Albumin Quotient measures the blood–CSF barrier permeability. ($^{\#}$) Calculated vs 5 patients with OHP who exhibited positive IgG_{Loc}. **(a)** IgG4-HP vs Controls subjects vs OHP patients by use of the Kruskal–Wallis test. **(b)** IgG4-HP vs Controls subjects by use of the Wilcoxon rank sum test. **(c)** IgG4-HP vs OHP patients by use of the Wilcoxon rank sum test.

	Normal values*	IgG4 Related Hypertrophic Pachymeningitis ($n = 3$)				Control subjects ($n = 9$)	Other forms of Hypertrophic Pachymeningits ($n = 21$)	*P*-value[a]	*P*-value[b]	*P*-value[c]
		Patient 1	Patient 2	Patient 3	Median (Q1–Q3)	Median (Q1–Q3)	Median (Q1–Q3)			
Age, years		52	62	67	62 (52–67)	58 (55–63)	60 (50–70)	0•918	0•999	0•861
Sex, males, *n* (%)		Female	Male	Male	2 (67%)	6 (67%)	14 (67%)	0•999	0•999	0•999
Organ involvement		Dura mater, Periorbital tissue	Dura mater	Dura mater, Retroperitoneal fibrosis						
Serum analysis										
Albumin (mg/dL)	(3500–5000)	3350	2370	3430	3350 (2370-–3430)	3540 (3450–3890)	3610 (3015–3770)	0•187	0•065	0•221
IgG (mg/dL)	(840–1600)	651	607	930	907 (652–930)	1130 (1081–1295)	876 (712–1173)	0•195	0•096	0•663
Autoimmunity[§]	Negative	Negative	Negative	Negative						
ACE (U/l)	(37–137)	29	41	68						
CSF analysis										
Appearance	Colorless, clear	Colorless, clear	Colorless, clear	Colorless, clear						
Total protein (mg/dL)	(12–60)	44	76	82	76 (44–82)					
Glucose (mg/dL)	(40–80)	59	42	73	42 (59–73)					
Cells (μL)	(0–1)	2 (lymphocytes)	32 (lymphocytes)	1 (lymphocytes)	2 (1–32)					
Cytology		No atypical cells	No atypical cells	No atypical cells						
Microbiology°	Negative	Negative	Negative	Negative						
Oligoclonal bands	Absent	Present	Present	Present						
Albumin (mg/dL)	(10–30)	25	85	38	38 (25–85)	17 (12–32)	41 (27–83)	0•011	0•096	0•793
Albumin Quotient^	(<0•7)	0•8	3•6	1•1	1•1 (0•8–3•6)	0 (0–1)	1 (1–3)	0•007	0•065	0•998
IgG (mg/dL)	(0•8–3•8)	8•7	17•4	18•8	18•8 (8•7–17•4)	2•5 (2–4•5)	9•0 (3•7–26•5)	0•003	0•016	0•257
IgG Index	(<0•70)	1•8	0•8	1•8	1•8 (0.8–1•8)	0•5 (0•4–0•5)	0•6 (0•5–1)	0•008	0•016	0•015
IgG_{Loc}	(0)	5•5	1•0	12•4	5•5 (1•0–12•4)	0	5•7 (0•4–20)	N/A	N/A	0•686[#]