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Cerebrospinal fluid cytokine/chemokine/growth factor profiles in idiopathic hypertrophic pachymeningitis

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ABSTRACT

Hypertrophic pachymeningitis (HP) is a rare neurologic disease causing inflammatory fibrous thickening of the brain and spinal dura mater. We investigated the cerebrospinal fluid cytokine profile of HP by measuring 28 cytokines/chemokines/growth factors with a multiplexed fluorescent immunoassay in 8 patients with HP (6 idiopathic, 1 IgG4-related, 1 anti-neutrophil cytoplasmic antibody-related), and 11 with other non-inflammatory neurologic diseases (OND). Interleukin (IL)-4, IL-5, IL-9, IL-10, TNF-α, and CXCL8/IL-8 levels were significantly higher in idiopathic HP (IHP) than OND. Cluster analyses disclosed two major clusters: one mainly consisted of IHP and the other of OND, suggesting a unique cytokine profile in IHP.

1. Introduction

Hypertrophic pachymeningitis (HP) is a neurologic disorder characterized by diffuse or focal thickening of the intracranial or spinal dura mater, presenting with intracranial hypertension, cranial nerve palsy and spinal cord dysfunction (Kupersmith et al., 2004; Lu et al., 2014). The only nationwide survey on HP conducted in Japan reported the crude prevalence rate of HP as 0.949/100,000 individuals (Yonekawa et al., 2014). Although HP occurs secondary to a variety of conditions, such as autoimmune disease, infectious disease, and granulomatous disorders (Shimojima et al., 2017; Bureta et al., 2018), our previous nationwide survey in Japan disclosed two major causes of HP: immunoglobulin (IgG)4- (8.8%), and anti-neutrophil cytoplasmic antibody (ANCA)-related diseases (34%) (Yonekawa et al., 2014). Among ANCA-associated vasculitis, myeloperoxidase (MPO)-ANCA is preferentially found in microscopic polyangiitis while granulomatosis with polyangiitis is predominantly leukocyte proteinase 3 (PR3)-ANCA-positive (Cornec et al., 2016). In ANCA-related HP, MPO-ANCA was more commonly found compared with PR3-ANCA (33 cases vs 14 cases (Yonekawa et al., 2014) and 17 cases vs 4 cases (Yokoseki et al., 2014)). However, it is often difficult to determine the cause of HP even by dural biopsy, and these cases of unknown etiology are termed "idiopathic HP (IHP)", which account for most HP cases (44%) (Yonekawa et al., 2014).

The mechanism of HP remains to be elucidated, irrespective of idiopathic or secondary type. The HP dura shows infiltration of a variety of inflammatory cells and interstitial fibrosis (Bosman et al., 2008; Hassan et al., 2011). Because components of the inflammatory process facilitate or attenuate fibroblast growth (Atamas and White, 2003; Wynn, 2008; Chen and Frangogiannis, 2013), cerebrospinal fluid (CSF) cytokine/chemokine and growth factor studies may provide insights into the mechanism of HP. However, because of the extreme rarity of HP, only one report has described the CSF cytokine/chemokine profile in MPO-ANCA-related HP (Yokoseki et al., 2014). They found an increase in interleukin (IL)-6, C-X-C motif ligand (CXCL)8/IL-8, and CXCL10/interferon (IFN)-γ-inducible protein-10 (IP-10). Because IP-10 is a downstream cytokine of IFN-γ (Luster and Ravetch, 1987), type 1 helper T cell (Th1) involvement is assumed in MPO-ANCA-related HP. Indeed, Th1 cells induce transforming growth factor β (TGF-β) production in fibroblasts by an IFN-γ-dependent mechanism and play a critical role in Th1-driven fibrosis (Sumida et al., 2008; Bouros et al., 2006), such as cardiac fibrosis (Nevers et al., 2017), and lung and

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kidney fibrosis in systemic sclerosis (Corrado, 2014).

However, Th2 cytokines, such as IL-4 and IL-13, also exert pro-fibrotic functions related to the excessive migration and proliferation of fibroblasts in pulmonary fibrosis (Jakubzick et al., 2003; Singh et al., 2017), and renal fibrosis (Xing et al., 2011; Liang et al., 2017) under conditions of Th2-driven fibrosis (Chizzolini et al., 2011; Gieseck 3rd et al., 2018; Sciurba et al., 2018). In HP, plasma cells induced to differentiate by Th2 cytokines such as IL-4, IL-10, and IL-13 (Lu et al., 2014; Vazquez et al., 2015; De Virgilio et al., 2017), often heavily infiltrate the IgG4-related HP and IHP dura mater (Kupersmith et al., 2004; Wallace et al., 2013). Recently, we reported the first animal model of IgG4-related HP, in which mice with a mutation (Y136F) in the linker for activation of T cells (LAT) that induces Th2 cell proliferation and IgG1 (IgG4 human equivalent) overexpression showed a massive infiltration of IgG1 (equivalent to human IgG4)-positive plasma cells together with marked storiform fibrosis in the dura mater (Cui et al., 2018). Accordingly, Th2 cytokines also seem to play a crucial role in the pathomechanism of HP; however, the contribution of Th2 cytokines remains to be elucidated in human HP. Yokoseki et al. reported the occurrence of Th1-dominant granulomatous lesions in the dura mater as well as an increase in CXCL10 in the CSF of ANCA-related HP, suggesting CSF cytokine profiles reflect dominant dural pathology in inflammatory dural diseases (Yokoseki et al., 2014). Therefore, in the present study, we aimed to clarify the CSF cytokine/chemokine/growth factor profiles in patients mainly with IHP.

2. Subjects and methods

2.1. Subjects

All patients were thoroughly examined at the Department of Neurology, Kyushu University Hospital, Japan, between 1st January 2008 and 31st May 2017. CSF samples were obtained from eight patients with HP (six with IHP and one each with IgG4-related and ANCA-related HP), and eleven with other non-inflammatory neurologic diseases (OND) (Table 1). For diagnosis, HP was defined as a thickening of the cranial or spinal dura mater with inflammation, and cases in whom either thickening of the dura mater was detected by MRI, or fibrotic thickening with inflammatory cell infiltration was observed in biopsied dura mater, were included (Yonekawa et al., 2014). Patients were regarded as having ANCA or IgG4-related HP if MPO-ANCA or PR3-ANCA was detected, or ANCA-related diseases coexisted. A diagnosis of IgG4-related HP was based on the established criteria for IgG4-related disease (Umehara et al., 2012). IHP comprised cases with no evidence of ANCA or IgG4-related conditions, or without other causes including relevant infections. We also excluded cases associated with malignancy and intracranial hypotension (Yonekawa et al., 2014). The clinical features of the HP patients are summarized in Table S1. The present study was approved by The Kyushu University Institutional Review Board.

2.2. Multiplexed fluorescent immunoassay

CSF samples were obtained by non-traumatic lumber puncture. Then samples were immediately centrifuged at 800 rpm (100 × *g*)/minute (min) at 4 °C for 5 min, and the supernatants were stored at −80 °C until analysis. The concentrations of 28 cytokines/chemokines and growth factors (Tables S2 and S3) in the supernatants of the CSF were measured by multiplexed fluorescence immunoassay, as previously described (Yamasaki et al., 2017). As shown in Tables S2 and S3, the cytokines/chemokines and growth factors measured in the present study were IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17A, IFN-γ, tumor necrosis factor (TNF)-α, CXCL8/IL-8, CXCL10/IP-10, C−C motif ligand (CCL)2/monocyte chemoattractant protein-1 (MCP-1), CCL3/macrophage inflammatory protein (MIP)-1α, CCL4/MIP-1β, CCL5/regulated upon activation, normal T cell expressed and secreted (RANTES), CCL11/eotaxin, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), platelet-derived growth factor (PDGF)-BB, basic fibroblast growth factor (bFGF), vascular endothelial growth factor-A (VEGF-A), and IL-1 receptor antagonist (IL-1ra). The Bio-Plex Cytokine Assay System (Bio-Rad, Hercules, CA) was used according to the manufacturer's instructions. All the samples were diluted four-fold and analyzed in duplicate. Cytokine/chemokine and growth factor concentrations were calculated by reference to a standard curve for each molecule derived using various concentrations of the standards assayed in the same manner as the CSF samples. The detection limit for each molecule was determined by the recovery of the corresponding standard (calculated by: (observed concentration)/(expected concentration) × 100), and the lowest values with > 70% recovery were set as the lower detection limits (Tateishi et al., 2010; Matsushita et al., 2013; Yamasaki et al., 2017). Detection rates of each cytokine/chemokine and growth factor are shown in Tables S2 and S3.

2.3. Statistical analysis

Prism software (GraphPad 6.0, La Jolla, CA) was used to conduct statistical analysis. All data are expressed as the mean ± standard deviation. The Mann–Whitney *U* test was used to compare continuous variables and the chi-square test or Fisher's exact probability test (when criteria for the chi-square test were not fulfilled) were used to compare categorical variables between patients with HP and OND. Heatmap and clustering analysis were generated by the package 'gplots' in R on the basis of Spearman's rank correlation coefficient analysis. K-means clustering, principal component analysis (PCA), and canonical discriminant analysis (CDA) were generated by JMP Pro software (ver.13.0.0; SAS Institute, Cary, NC).

Table 1
Demographic features of patients with HP and OND at time of CSF collection.

	HP patients (n = 8)	OND patients (n = 11)	p-Value*
Male/female (ratio)	2/6 (1.0:3.0)	6/5 (1.0:0.8)	NS
Age at examination (years)[a]	59.5 (46.3–67.5)	65.0 (60.0–72.0)	NS
Underlying diseases	6 with idiopathic HP, 1 with IgG4-related HP, and 1 with MPO-ANCA-related HP	4 with NPH, 3 with ALS, 2 with hereditary spinocerebellar degeneration, 1 each with alcoholic neuropathy or cervical spondylosis	

The Mann–Whitney *U* test was used to compare continuous variables and the chi-square test or Fisher's exact probability test (when criteria for the chi-square test were not fulfilled) were used to compare categorical variables between patients with HP and OND.
ALS = amyotrophic lateral sclerosis; ANCA = anti-neutrophil cytoplasmic antibodies; CSF = cerebrospinal fluid; HP = hypertrophic pachymeningitis; IgG = immunoglobulin; MPO = myeloperoxidase; NPH = normal pressure hydrocephalus; NS = not significant; OND = other non-inflammatory neurologic diseases.
[a] Median (interquartile range).
* p-Value < .05 is regarded as statistically significant.

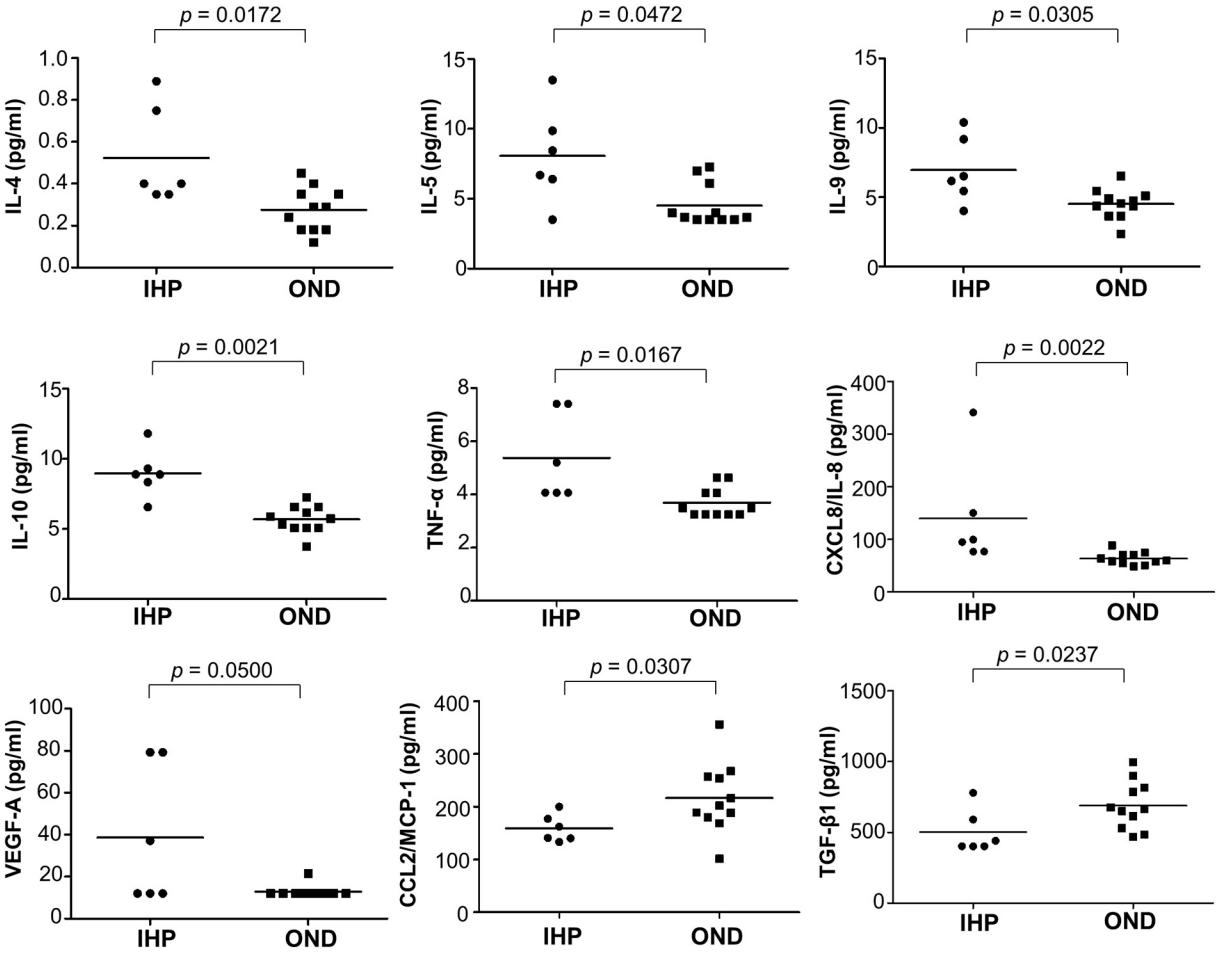

Fig. 1. CSF cytokine levels in patients with IHP and OND.
Six IHP patients and 11 OND patients were analyzed. CCL = C-C motif ligand; CXCL = C-X-C motif ligand; IHP = idiopathic hypertrophic pachymeningitis; IFN = interferon; IL = interleukin; MCP-1 = macrophage chemoattractant protein-1; OND = non-inflammatory neurologic diseases; TGF-β1 = transforming growth factor-β; TNF-α = tumor necrosis factor-α; VEGF-A = vascular endothelial growth factor-A.

3. Results

3.1. Detection rate of CSF cytokines/chemokines and growth factors in IHP

Detection rates of cytokines/chemokines and growth factors in CSF are shown in Tables S2 and S3.The detection rates of IL-6, GM-CSF, PDGF-BB and IL-1ra were significantly higher in IHP patients than in OND patients (IL-6: $p = .0010$, GM-CSF: $p = .0294$, PDGF-BB: $p = .0063$, and IL-1ra: $p = .0294$, respectively) (Table S2). Furthermore, even in total HP patients, the detection rates of IL-6, GM-CSF, PDGF-BB and IL-1ra were significantly higher than those in OND patients (IL-6: $p = .0007$, GM-CSF: $p = .0144$, PDGF-BB: $p = .0036$, and IL-1ra: $p = .0144$, respectively) (Table S3).

3.2. CSF cytokine levels

Compared with OND patients, IHP patients showed significantly increased levels of IL-4 ($p = .0172$), IL-5 ($p = .0472$), IL-9 ($p = .0305$), IL-10 ($p = .0021$), TNF-α ($p = .0167$), CXCL8/IL-8 ($p = .0022$), and VEGF-A ($p = .0500$), and significantly decreased levels of CCL2/MCP-1 ($p = .0307$) and TGF-β1 ($p = .0237$) (Fig. 1). In addition, these cytokines also showed similar significant changes even when total HP (including IgG4-related and ANCA-related HP) patients were used (Fig. S1).

3.3. Cluster analysis of CSF cytokines/chemokines and growth factors

We performed dual cluster analysis to elucidate differences in cytokine/chemokine expression profiles between eight HP patients (HP1 was IgG4-related HP, HP2–7 were IHP, and HP8 was MPO-ANCA-related HP) and eleven OND patients. The resultant heatmap showed two major clusters of patients (Fig. 2A). Cluster 1 consisted of HP patients (five IHP (HP2–6) and one IgG4-related HP patient (HP1)), except for one OND patient in the most distant position. Cluster 2 mainly consisted of OND patients while two HP patients (one IHP (HP7) and one MPO-ANCA-related HP (HP8)), were also included in the distant positions. Cluster 1 was composed of cases with higher levels of Th2 cytokines/chemokines (Cluster B1 on the vertical label) compared with Cluster 2. The results of PCA also indicated distinct expression patterns of cytokines/chemokines between the HP and OND groups (Fig. 2B): the right side of component 1 included HP patients exclusively (five IHP (HP2–6) and one IgG4-related HP patient (HP1)), whereas the left side included all OND patients and two HP patients (one IHP (HP7) and one MPO-ANCA-related HP patient (HP8)). According to k-means clustering, three clusters were identified (Fig. S3): most OND patients and two HP patients (one IHP (HP7) and one MPO-ANCA-related HP patient (HP8)), were again shown in the center of Cluster 2 while the other five IHP patients (HP2–6) and one IgG4-related HP patient (HP1) were distributed in the distant positions or in Clusters 1 and 3. Canonical discriminant analysis based on 28 cytokine levels were conducted to explore cytokines that could best discriminate HP from OND patients

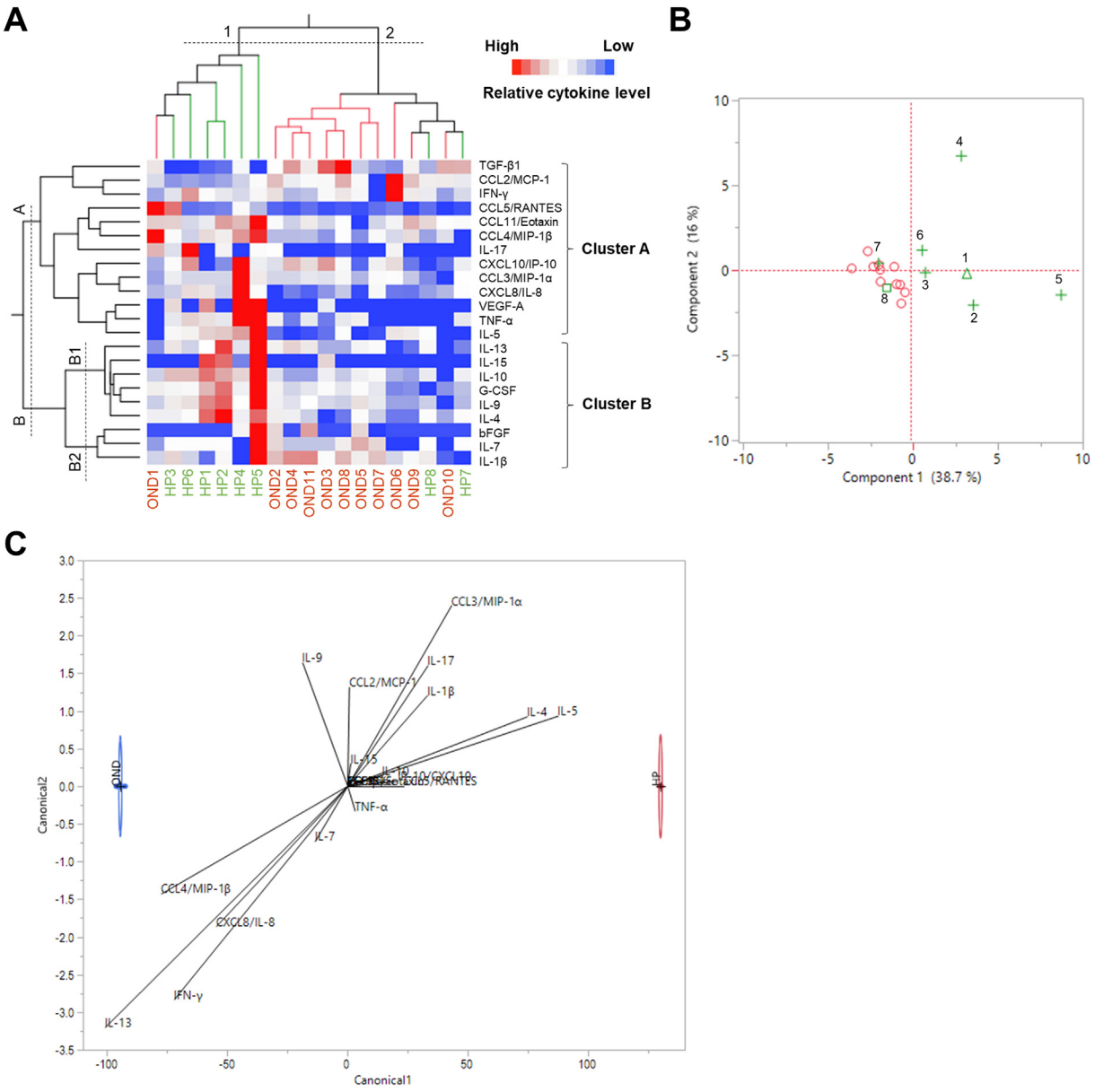

Fig. 2. Two-way cluster analysis, principal component analysis and canonical discriminant analysis of CSF cytokines/chemokines and growth factors in HP and OND patients.

(A) Heatmap for two-way cluster analysis including eight HP patients (HP1 was IgG4-related HP, HP2–7 were IHP, and HP8 was MPO-ANCA-related HP) and 11 OND patients. Horizontal labels indicate each patient. HP patients are indicated in green characters while OND patients are indicated in red characters. There are two major clusters of patients: Cluster 1 mainly including HP patients and Cluster 2 mainly including OND patients. Vertical label indicates each cytokine. Clusters mainly consisting of Th2 chemokines (Cluster B1) and others (Cluster A) were observed. The orders (1, 2, B1 and B2) indicate the cut-off position for each cluster (Cluster 1, Cluster 2, Cluster B1 and Cluster B2, respectively). Dotted line: cut-off level. (B) Principal component analysis of CSF cytokine data in HP and OND patients. This analysis included 8 HP patients (HP1 was IgG4-related HP, HP2–7 were IHP, and HP8 was MPO-ANCA-related HP) and 11 OND patients. The first two principal components contributed to 54.7% of the total variance, with the first and second components accounting for 38.7% and 16.0%, respectively. The OND group is clustered in the left part, while the HP group is mainly clustered in the right part. 1–8: HP1-HP8; Open circle: OND patients; Cross: idiopathic HP patient; Open square: MPO-ANCA-related HP; Open triangle: IgG4-related HP. (C) Canonical plot for HP and OND patients. Canonical discriminant analysis using the levels of 28 cytokines was performed in eight patients with HP (red) and 11 patients with OND (blue). bFGF = basic fibroblast growth factor; CSF = cerebrospinal fluid; CCL = C-C motif ligand; CXCL = C-X-C motif ligand; G-CSF: granulocyte colony-stimulating factor; IHP = idiopathic hypertrophic pachymeningitis; HP = hypertrophic pachymeningitis; IFN = interferon; IL = interleukin; IP-10 = interferon (IFN)-γ-inducible protein-10; MCP-1 = monocyte chemoattractant protein-1; MIP = macrophage inflammatory protein; OND = other non-inflammatory neurologic diseases; RANTES: regulated on activation, normal T cell expressed and secreted; TNF-α = tumor necrosis factor-α; TGF-β1 = transforming growth factor-β; VEGF-A = vascular endothelial growth factor-A. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(Fig. 2C). As a result, HP and OND patient groups were well separated by the measured cytokine levels on Canonical 1 axis, and the HP patient group was highly and positively associated with IL-4 and IL-5, suggesting that among cytokines the levels of IL-4 and IL-5 are major discriminants between HP and OND patient groups.

Additional clustering analysis of correlations between each CSF cytokine level in IHP and OND patient groups demonstrated distinct major clusters of cytokines/chemokines between the two groups (Fig. S2). The IHP patient group had four major clusters. Cluster 1 comprised IL-9, G-CSF, IL-10, IL-13, IL-5, CCL4/MIP-1β, bFGF, VEGF-A, TNF-α,

CCL11/eotaxin and CCL5/RANTES. Cluster 2 consisted of IL-17, IFN-γ, IL-1β, IL-7 and IL-4. Cluster 3 composed of CCL3/MIP-1α, CXCL10/IP-10 and CXCL8/IL-8. Cluster 4 composed of CCL2/MCP-1 and TGF-β1. By contrast, the OND patient group had 3 clusters, which showed a distinct pattern from those in IHP patients and a weaker correlativity between each cytokine compared with IHP patients.

4. Discussion

In the present study, we found significantly increased CSF levels of IL-4, IL-5, IL-9, IL-10, TNF-α, CXCL8/IL-8, and VEGF-A together with significantly higher detection rates of IL-6, GM-CSF, PDGF-BB and IL-1ra in IHP patients compared with OND patients. Among these, IL-4, IL-5, IL-6, IL-9 and IL-10 belong to the Th2 cytokine group (Wynn, 2015; Oliphant et al., 2011), suggesting Th2 cell involvement in IHP. The dual cluster analyses disclosed two major clusters: one mainly consisted of IHP patients and the other of OND patients. The cluster analysis of correlations between each CSF cytokine level also detected a large cluster of upregulated cytokines/chemokines comprised mainly of Th2 cytokines, including IL-9, G-CSF, IL-10, IL-13, IL-5, CCL4/MIP-1β, bFGF, VEGF-A, TNF-α, CCL11/eotaxin, and CCL5/RANTES in IHP but not OND patients, supporting the contribution of Th2 cells to dural inflammatory fibrosis observed in most IHP patients.

The results of the dual clustering analysis, the PCA, and the k-means clustering analysis consistently showed that all but one IHP patient and one IgG4-related HP patient belonged to the same cluster with the upregulation of Th2 cytokines. The results of CDA also suggested that the levels of IL-4 and IL-5, representative Th2 cytokines, were crucial discriminating factors between the HP and OND patient groups. Although mechanism of IgG4-related disease remains to be established, Th2 cytokines drive plasma cell differentiation and proliferation with class switching to IgG4 (Jeannin et al., 1998; Jelinek, 2000; Lu et al., 2014; De Virgilio et al., 2017). Thus, Th2 cells likely play a key role in this condition. In our animal model of IgG4-related HP, which is driven by overactive Th2 cells (Cui et al., 2018), the massive infiltration of B220-positive B cells, IgG1 (human equivalent of IgG4)-positive cells, and CD138-positive plasma cells in the dura mater was followed by marked fibrotic thickening. Therefore, Th2 cytokines are likely to be involved in plasma cell infiltration and following dural fibrosis of IgG4-related HP. Plasma cell infiltration is also frequently observed in the dura of IHP (Kupersmith et al., 2004; Lu et al., 2014). Plasma cells and B cells promote fibrosis through autoantibodies that activate fibroblasts and cell-cell contact with fibroblasts that induce contact-dependent fibroblast collagen production (Sakkas and Bogdanos, 2016). Accordingly, Th2 cytokines may also be contributory in not all but most patients with IHP, which could be a Th2-driven fibrosis, like IgG4-related HP.

Among the elevated cytokines/chemokines and growth factors in IHP patients, IL-4 has been shown to have chemoattractant effects and induce the proliferation of fibroblasts, leading to tissue fibrosis (Postlethwaite and Seyer, 1991; Jakubzick et al., 2003; Brown and O'Reilly, 2018). IL-10 (Sziksz et al., 2015), TNF-α (Connolly et al., 2009), CXCL8/IL-8 (Yang et al., 2018), VEGF-A (Barratt et al., 2018), and PDGF-BB (Antoniades et al., 1990) can also promote fibroblast proliferation, thereby contributing to dural fibrosis. Simultaneously upregulated growth factors are likely to cooperatively promote inflammatory fibrosis of the dura in IHP.

In our study, one ANCA-related HP patient and one IHP patient did not belong to the above-mentioned Th2 cytokine-related HP group. Because fibrosis itself is induced by heterogeneous mechanisms including Th1-, Th2-, and even Th17-mediated fibrosis (Wynn, 2004; Yoshizaki et al., 2010; Okamoto et al., 2012; Sciurba et al., 2018), IHP might also be heterogeneous. Yokoseki et al., reported an increase of CXCL10/IP-10 levels in the CSF of MPO-ANCA-related HP (Yokoseki et al., 2014). Although we could not confirm this because of the small sample size in this study, ANCA-related HP may be driven by a Th1-related mechanism, which might also have a role in the pathogenesis of IHP.

TGF-β1 and CCL2/ MCP-1 were significantly decreased in IHP patients. IL-10, which was significantly upregulated in our patients, can suppress TGF-β1 production (Nakagome et al., 2006). It might explain the decrease of TGF-β1 in our patients. TGF-β functions as a potent immune suppressor by inhibiting the proliferation, differentiation, activation, and effector functions of immune cells (Mantel and Schmidt-Weber, 2011; Wynn and Ramalingam, 2012). Thus, a decrease in the anti-inflammatory effects of TGF-β might eventually potentiate dural inflammation in IHP. Alternatively, because TGF-β1 is a potent profibrotic cytokine (Fernandez and Eickelberg, 2012; Cui et al., 2018), TGF-β1 might be consumed by highly proliferating fibroblasts in the HP dura. The profibrotic role of CCL2/ MCP-1 is controversial (Kalderén et al., 2014). Indeed, the anti-fibrotic role of CCL2/MCP-1 was previously reported (Mitchell et al., 2009), consistent with the downregulated level of this cytokine in the present study. Further studies are required to clarify the roles of these downregulated cytokines in HP.

This study had some limitations. First, a small number of HP patients were enrolled because of the extreme rarity of this disease, which may have caused some selection bias. Yokoseki et al., found no increase in Th2 cytokines, such as IL-4, in IHP patients (Yokoseki et al., 2014). The sensitivity of different detection methods used between these two studies might have led to the different results observed. Given that our study and that of Yokoseki et al. (2014) used limited numbers of IHP patients, the heterogeneity of IHP as shown in this study and selection bias might also account for this discrepancy. To solve this issue, larger samples of IHP cases are needed for future studies. Second, we did not study serum cytokine/chemokine levels in the present study. We think CSF cytokine/chemokine levels might reflect dural inflammation more than serum levels because IHP is usually a localized disease of the dura mater rather than a systemic disease. Although these limitations should be taken in mind, we found significant changes in CSF Th2 cytokine/chemokine levels in our IHP patients. Although these findings should be regarded as preliminary, we think Th2 cell involvement in HP pathogenesis is worth investigating.

In summary, we identified a Th2 cytokine shift in the CSF of IHP patients, which is relevant to plasma cell infiltration in idiopathic and IgG4-related HP. Cytokine profiles should be investigated according to HP subtype and in larger sample sizes in future studies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2019.01.010.

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Conflicts of interest

R.Y. has received honoraria from Biogen Japan and Japan Blood Products Organization; J.K. is a consultant for Biogen Japan and

Medical Review, and has received honoraria from Bayer Healthcare, Mitsubishi Tanabe Pharma, Nobelpharma, Otsuka Pharmaceutical, Sanofi K.K., Chugai Pharmaceutical Co. Ltd., Teijin Pharma, Novartis Pharma, and Medical Review; the remaining authors declare no conflicts of interest.

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