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RESEARCH PAPER

A nationwide survey of hypertrophic pachymeningitis in Japan

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ABSTRACT

Objectives To clarify the prevalence, frequent causes and distinct features of hypertrophic pachymeningitis (HP) according to background conditions in a nationwide survey in Japan.

Methods The study began with a preliminary survey to determine the approximate number of HP patients diagnosed from 1 January 2005 to 31 December 2009, and was followed by a questionnaire survey for clinical and laboratory findings. HP was defined as a condition with thickening of the cranial or spinal dura mater with inflammation, evidenced by MRI or histology.

Results Crude HP prevalence was 0.949/100 000 population. The mean age at onset was 58.3±15.8 years. Among 159 cases for whom detailed data were collated, antineutrophil cytoplasmic antibody (ANCA)-related HP was found in 54 cases (34.0%) and IgG4/multifocal fibrosclerosis (MFS)-related HP in 14 cases (8.8%). Seventy cases (44.0%) were classified as 'idiopathic' and 21 (13.2%) as 'others'. ANCA-related HP cases showed a female preponderance, a higher age of onset, and higher frequencies of otological symptoms and elevated systemic inflammatory biomarkers, but lower frequencies of diplopia compared with idiopathic HP. IgG4/MFS-related HP cases showed a marked male predominance; all had cranial HP while none had isolated spinal HP or decreased sensation.

Conclusions HP is not extremely rare. ANCA-related HP is the most frequent form, followed by IgG4/MFS-related HP. Both forms have unique features, which may help to differentiate background causes.

INTRODUCTION

Cranial and spinal hypertrophic pachymeningitis (HP) is a rare inflammatory disorder demonstrating local or diffuse thickening of the intracranial or spinal dura mater. Thickening of the dura mater causes intracranial hypertension, cranial nerve palsy and spinal cord dysfunction. MRI findings show thickening and contrast enhancement of the affected dura mater. HP pathology shows interstitial fibrosis and inflammatory cell infiltration consisting mainly of lymphocytes. HP is aetiologically heterogeneous, secondarily developing in association with a variety of conditions, such as infection, autoimmune disease, trauma and tumours, or being labelled idiopathic in the absence of an identifiable cause.[1 2] The mechanisms underlying idiopathic HP are thus ill defined, and unidentified causes might exist. Because there have been no epidemiological or large-scale clinical studies of HP, its prevalence, frequent causes and distinct features according to background conditions are totally unknown. Therefore, we aimed to clarify these issues in a nationwide survey of HP in Japan.

METHODS

Procedures

The nationwide survey was conducted by the Research Committee of HP, sponsored by the Ministry of Health, Labour and Welfare, Japan. This study was approved by the Kyushu University Ethics Committee. The survey was undertaken in two steps: first, a preliminary survey to ascertain the approximate number of HP patients in Japan, and second, a survey using a questionnaire sheet for each patient. The hospitals studied were randomly selected from the directory of all registered hospitals in Japan. Selection was made according to stratification based on the number of beds in each hospital; the more beds a hospital had, the higher its probability of being selected.[3] 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. We excluded cases associated with malignancy and intracranial hypotension.

The questionnaire for the preliminary survey on HP patients who, because of the disease, visited hospitals from 1 January 2005 to 31 December 2009 was mailed to 5477 hospital departments (446 neurology, 731 neurosurgery, 994 internal medicine, 951 orthopaedics, 770 otorhinolaryngology, 800 paediatrics and 785 ophthalmology departments) together with the inclusion criteria. Following the collection and collation of the results of the first questionnaire, the second questionnaire was forwarded to those reporting patients in the first survey. It requested detailed clinical information on individual patients including age at onset and examination, sex, symptoms based on history and signs based on neurological examination, coexisting diseases, laboratory findings, MRI findings of brain and spinal cords, pathological findings, clinical course, treatment and prognosis. Patients reported by more than one hospital or department were treated as duplicate.

Laboratory findings included myeloperoxidase (MPO)- and proteinase-3 (PR3)-antineutrophil cytoplasmic antibody (ANCA) positivity, and elevation of

IgG4. We further classified cases into several categories according to positive findings for ANCA, IgG4 elevation and coexisting diseases. Patients were regarded as having ANCA-related HP if either MPO-ANCA or PR3-ANCA was detected, or ANCA-related diseases (ANCA-related angiitis or Wegener's granulomatosis) coexisted. Diagnosis of IgG4/multifocal fibrosclerosis (MFS)-related HP was based on the established criteria for IgG4-related disease[4] (clinical examination showing characteristic diffuse/local swelling or mass in single or multiple organs, elevated serum IgG4 levels >135 mg/dL, and IgG4-positive plasma cells in the biopsied dura with a IgG4-positive/IgG-positive cell ratio >40% and more than 10 IgG4+ plasma cells per high-power field), or the presence of MFS, such as retroperitoneal fibrosis, mediastinal fibrosis, sclerosing pancreatitis, Riedel's thyroiditis and pseudotumour of the orbit. Idiopathic HP comprised cases with no evidence of ANCA- or IgG4/MFS-related conditions, or without other causes including relevant infections asked about in the second survey, such as syphilis, tuberculosis, fungal infections (candidiasis, aspergillosis), bacterial infections (*Pseudomonas aeruginosa*, *Propionibacterium acnes*), borreliosis and cysticercosis.

Statistical analysis

The estimated total number of HP patients in Japan was extrapolated from our data using formulae derived by the epidemiology committee,[3 5] taking response rates into account. First, for each stratum, the total reported number of patients was divided by the ratio of responding institutions to the number of surveyed institutions. The results for all strata were then added to estimate the total number of HP patients.[5] Statistical analyses of numerical variables were initially performed using the Pearson's χ^2 test and Kruskal–Wallis test. When statistical significance was found, Pearson's χ^2 test or Fisher's exact test was used to determine the statistical significance of differences between groups. Uncorrelated p values were corrected by multiplying them by the number of comparisons (Bonferroni–Dunn's correction) to calculate corrected p values. Differences in ratios between two groups were tested for significance by the χ^2 test or Fisher's exact test when the criteria for the χ^2 tests were not fulfilled. In all assays, p values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

In the preliminary survey, 1904 departments (34.8%) responded, reporting 324 HP patients. In the second questionnaire, detailed clinical data on 159 patients (49.1% of those reported in the preliminary survey) were collected. The estimated crude prevalence was 0.949/100 000 population (95% CI 0.833 to 1.065). The male to female ratio was 1:0.91 (table 1). The mean age at onset was 58.3±15.8 years, and mean age at first visit to the physician was 59.7±15.2 years. HP diagnosis was made by MRI alone in 106 cases, MRI and pathology in 49 cases, and pathology alone in four cases.

Table 1 Demographic features of the 159 patients with hypertrophic pachymeningitis

Basic demographics		Initial symptoms	Number (%)
Number of cases analysed	159	Headache	56 (35.2)
Sex ratio (male:female)	1:0.91	Visual loss	21 (13.2)
Age at onset (mean±SD, years)	58.3±15.8	Double vision	20 (12.6)
Age at first visit to physician (mean±SD, years)	59.7±15.2	Otological symptoms	15 (9.4)
Disease duration (mean±SD, months)	48.3±50.9	Symptoms during entire course	Number (%)
Underlying diseases	Number	Headache	113 (71.1)
ANCA-related angiitis	21	Back pain	6 (3.8)
Wegener's granulomatosis	19	Fever	42 (26.4)
Multifocal fibrosclerosis	6*	Consciousness disturbance	21 (13.2)
IgG4-related disease	9	Convulsion	14 (8.8)
Otitis media	3	Memory disturbance and other higher brain dysfunction	11 (6.9)
Cholesteatoma of the middle ear	1	Visual loss	52 (32.7)
Sinusitis	1	Double vision	46 (28.9)
Sjögren syndrome	2	Dysphagia	13 (8.2)
Tuberculosis	2	Dysarthria	11 (6.9)
Aspergillosis	2	Weakness (facial and/or extremities)	38 (23.9)
Site of dural hypertrophy	Number (%)	Sensory disturbance	45 (28.3)
Cranial	135 (84.9)	Bladder disturbance	10 (6.3)
Spinal	14 (8.8)	Bowel disturbance	7 (4.4)
Cranial and spinal	7 (4.4)	Neurological findings	Number (%)
Mode of onset	Number (%)	Cranial nerve palsy	99 (62.3)
Acute	41 (25.8)	Neck stiffness	7 (4.4)
Subacute	75 (47.2)	Motor impairment	26 (16.4)
Chronic	27 (17.0)	Abnormal tendon reflexes	44 (27.7)
Clinical course	Number (%)	Pathological reflexes	15 (9.4)
Monophasic	51 (32.1)	Limb and/or truncal ataxia	6 (3.8)
Progressive	28 (17.6)	Decreased sensation	31 (19.5)
Relapsing-remitting	62 (39.0)	Sphincter dysfunction	5 (3.1)
Unknown	18 (11.3)		

*Includes five cases of MFS-related HP and one case assigned to ANCA-related HP.
ANCA, antineutrophil cytoplasmic antibody; HP, hypertrophic pachymeningitis; MFS, multifocal fibrosclerosis.

Table 2 Cranial nerve involvement in hypertrophic pachymeningitis patients

	n/N (%)
Cranial nerve involvement	99/159 (62.3)
Single	40/99 (40.4)
Multiple	59/99 (59.6)
Cranial nerves	n/N (%)
I	2/99 (2.0)
II	41/99 (41.4)
III	30/99 (30.3)
IV	25/99 (25.3)
V	19/99 (19.2)
VI	35/99 (35.4)
VII	19/99 (19.2)
VIII	27/99 (27.3)
IX	13/99 (13.1)
X	10/99 (10.1)
XI	5/99 (5.1)
XII	8/99 (8.1)

n, number of involved cases, N, number of cases collated, or total number of involved cases.

The diseases underlying HP were heterogeneous. ANCA-related angiitis and Wegener's granulomatosis were the most common coexisting diseases. IgG4/MFS-related diseases followed. Among 14 cases diagnosed as having IgG4/MFS-related HP, four cases had retroperitoneal fibrosis and were thus regarded as having MFS-related HP. The remaining 10 cases were diagnosed as having IgG4-related HP based on the IgG4-related disease criteria[4]; one had definite IgG4-related disease (IgG4+ cells in biopsied dura, elevated serum IgG4 concentrations and diffuse/local organ swelling or mass), six of these had probable IgG4-related HP (IgG4+ cells in biopsied dura and diffuse/local organ swelling or mass), and three had possible IgG4-related HP (elevated serum IgG4 concentrations and diffuse/local organ swelling or mass). Otorhinolaryngological disorders, such as otitis media and sinusitis, occasionally accompanied. Infectious causes were rarely identified, with only two cases with tuberculosis and two cases of aspergillosis. HP was confined to the cranial dura in 137 cases (86.2%), the spinal dura in 15 (9.4%), and both in 7 (4.4%) (demographic features according to the sites of HP are shown in online supplementary table S1). Approximately half the HP cases had subacute onset, whereas, the rest showed either an acute or chronic pattern. More than 50% of HP patients showed either a relapsing-remitting or progressive course.

Symptoms and neurological findings

Headache was the most common initial symptom of HP (35.2%), followed by ophthalmological symptoms, such as visual loss and double vision (each 13.2% and 12.6%, respectively) (table 1). Some patients (9.4%) had otological symptoms including deafness and tinnitus. During the entire course, the frequency of headache rose to 71.1%. Fever was seen in one-quarter of HP patients. Visual loss and double vision were observed in approximately one-third of HP patients, compared with <10% for dysphagia and dysarthria. Neurological findings revealed frequent involvement of the cranial nerves (62.3%). Multiple involvements were more common than isolated involvement, and cranial nerves II–VIII were more frequently affected than IX–XII (table 2). Although headache was the most frequent symptom, neck stiffness was uncommon (4.4%). Abnormal tendon reflex and decreased sensation were seen in approximately one-quarter of HP patients. Ataxia and sphincter dysfunction were relatively rare.

Laboratory findings in peripheral blood and CSF

Non-specific inflammation was seen in a half to three-quarters of HP cases, such as increased erythrocyte sedimentation rate (ESR), white blood cells (WBC) or C-reactive protein (CRP) (table 3). Antinuclear antibody was detected in 16.9% of cases

Table 3 Laboratory, neuroimaging, and pathological findings in 159 hypertrophic pachymeningitis cases

Laboratory findings	n/N (%)	Neuroimaging	n/N (%)
Blood		MRI	
ESR elevation	78/104 (75.0)	Thickening of the cranial dura mater	141/156 (90.4)
WBC increase	63/146 (43.2)	Gd enhancement of cranial dura	124/139 (89.2)
CRP elevation	110/149 (73.8)	Thickening of the spinal dura mater	21/54 (38.9)
ANA elevation	20/118 (16.9)	Gd enhancement of spinal dura	17/20 (85.0)
MPO-ANCA positivity	33/119 (27.7)	Gallium scintigraphy	
PR3-ANCA positivity	14/111 (12.6)	Increased uptake	22/50 (44.0)
IgG4 elevation	7/27 (25.9)	SPECT	
STS	2/122 (1.6)	Hypoperfusion	7/29 (24.1)
Anti-HTLV-1 Ab	1/50 (2.0)	Hyperperfusion	3/29 (10.3)
ADA elevation	3/28 (10.7)	PET	
ACE elevation	1/56 (1.8)	Positive accumulation	2/17 (11.8)
CSF		Pathological findings of dura mater	n/N (%)
Pleocytosis	71/116 (61.2)	Fibrosis	43/52 (82.7)
Protein elevation	115/119 (99.6)	Infiltration of inflammatory cells	47/52 (90.4)
TPLA positivity	0/7 (0.0)	Angiitis	4/52 (7.7)
ADA elevation	2/22 (9.1)	Granuloma	15/52 (28.8)
		Necrosis	8/52 (15.4)
		Oedema	5/52 (9.6)
		IgG4-positive plasma cells	11/42 (26.2)

Ab, antibody; ADA, adenosine deaminase; ANA, antinuclear antibody; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; Gd, gadolinium; HTLV-1, human T-lymphotrophic virus type I; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibodies; PET, positron emission tomography; PR3-ANCA, proteinase-3-antineutrophil cytoplasmic antibodies; SPECT, single photon emission CT; STS, serologic test for syphilis; TPLA, treponema pallidum latex agglutination; WBC, white blood cells.

assessed, and adenosine deaminase (ADA) was elevated in 10.7%. Serologic tests for syphilis and human T-lymphotrophic virus type 1 antibody were rarely positive (1.6% and 2.0%, respectively). The most noticeable finding was that MPO-ANCA and PR3-ANCA were positive in 33/119 (27.7%) and 14/111 (12.6%) cases assessed, respectively. In four cases, MPO-ANCA and PR3-ANCA were detected. As a result, 43 cases were ANCA-positive. Furthermore, hyper-IgG4aemia was observed in 7/27 (25.9%) cases examined. Cerebrospinal fluid (CSF) pleocytosis was detected in 71/116 (61.2%) cases, while variable degrees of protein elevation were found in 115/116 (96.6%) cases. ADA elevation in the CSF was found in 2/22 (9.1%) cases.

Neuroimaging

On brain MRI, hypertrophic change of the cranial dura mater was found in 141/156 (90.4%) cases examined (table 3). Gadolinium (Gd) enhancement was observed in 124/139 (89.2%). Hypertrophic changes of the spinal dura mater were found in 21/54 (38.9%) cases examined, while Gd-enhancement was seen in 17/20 (85.0%). Thickening of the cranial dura mater was diffuse in 33/141 (23.4%) cases and partial in 108/141 (76.6%). Increased uptake in gallium scintigraphy was found in 22/50 (44.0%). Abnormalities in single photon emission CT (SPECT) and positron emission tomography (PET) findings were observed in 10/29 (34.5%) cases and 2/17 (11.8%) cases, respectively.

Pathological findings

Fifty-two patients underwent biopsy of the dura mater (table 3). The main pathological findings were fibrosis (82.7%), inflammatory cell infiltration (monocytes, plasma cells, eosinophils and polymorphonuclear leucocytes) (90.4%) and granuloma (28.8%). Necrosis and oedema were found in some cases. Importantly, IgG4-positive cells were found in 11/42 (26.2%) cases assessed; seven in IgG4/MFS-related HP and four in ANCA-related HP. Importantly, IgG4-positive cells were found in 11/42 (26.2%) cases assessed. Angiitis was detected in 4/52 cases (7.7%). Culture of the biopsied dura mater in 27 patients identified tuberculosis in one while the rest were negative. The brain adjacent to thickened dura mater was biopsied in eight cases, revealing infiltration of inflammatory cells in seven, while granuloma and necrosis were each observed in four cases, and IgG4-positive cells in one.

Treatment

Selected treatment options in our HP series are listed in online supplementary table S2. In 12 cases of infectious HP, antibiotic, antifungal, and antituberculosis drugs were used as the first-line therapy for relevant pathogens. Corticosteroids, mostly methylprednisolone pulse therapy followed by oral administration, were administered as the first choice for HP when infectious cases were excluded. A total of 94 cases received corticosteroids as immunotherapy at first, resulting in an 87.2% improvement. In 54 cases with insufficient response to corticosteroids, immunosuppressants were added and 92.6% improved. Only 24 cases (15.1%) required surgery.

Comparison of idiopathic, ANCA-related and IgG4/MFS-related HP

According to the classification stated in the section on Methods, ANCA-related and IgG4/MFS-related diseases are the two major causes of HP in Japan (figure 1A,B). There were 48 (30.2%) and 14 (8.8%) cases of ANCA-related and IgG4/MFS-related HP, respectively. Six patients (3.8%) with ANCA-related HP also had either hyper-IgG4aemia or IgG4-positive plasma cells in the biopsied dura (combined cases in figure 1A,B). Such cases were included in the ANCA-related HP group in the following analyses because they showed similar features to ANCA-related HP and ANCA-related disease could show hyper-IgG4aemia. Idiopathic HP comprised 44.0% (70/159) of cases while various other causes were responsible for 13.2% (21/159).

Comparisons of demographic features among idiopathic, ANCA-related and IgG4/MFS-related HP revealed a male predominance for idiopathic HP (male:female=1:0.75) and a female preponderance for ANCA-related HP (1:1.34) (table 4). Interestingly, IgG4/MFS-related HP showed a marked male predominance (1:0.17). Thus, sex ratios were significantly different among the three groups. All IgG4/MFS-related HP cases exhibited cranial HP; none showed isolated spinal HP, while isolated spinal HP was occasionally seen in idiopathic and ANCA-related HP (12.9% and 5.6%, respectively). Age of onset was significantly older in ANCA-related HP cases than in idiopathic HP cases. There was no significant difference in the mode of onset and clinical course among the three groups; however, ANCA-related HP cases less frequently developed acute onset while IgG4/MFS-related HP cases tended to show a monophasic course more frequently than did the others ($p=0.0553$).

As initial symptoms, ANCA-related HP cases showed a higher frequency of otological symptoms but lower frequency of double vision, compared with idiopathic HP cases (see table 4 and online supplementary figure S1). Regarding symptoms and signs during the entire course, ANCA-related HP cases had significantly greater frequency of fever compared with idiopathic HP, and lower frequency of double vision compared with idiopathic and IgG4/MFS-related HP cases. Sensory disturbance was more common in idiopathic HP cases than ANCA-related and IgG4/MFS-related HP cases. Systemic inflammatory responses, such as elevated ESR and CRP, and increased WBC, were more frequently found in ANCA-related HP compared with idiopathic HP.

DISCUSSION

This nationwide epidemiological survey of HP in Japan enabled us to elucidate the prevalence and clinical characteristics of HP. This is epoch-making because there has been no previous epidemiological survey of HP, with a series of approximately 10 patients being the largest.[1 6] The main new findings of the present study are as follows: (1) crude HP prevalence was determined to be 0.949/100 000; (2) among all HP cases, the most common cause is ANCA-related HP, making up as much as 34.0% of all cases, and the second most common cause is IgG4/MFS-related HP, making up 8.8% (12.6%, if including ANCA-related HP cases with hyper-IgG4aemia); (3) ANCA-related HP showed a female preponderance, a higher age at onset, and higher frequencies of otological symptoms and elevated systemic inflammatory markers compared with idiopathic HP, but lower frequencies of diplopia compared with idiopathic and IgG4/MFS-related HP; (4) IgG4/MFS-related HP showed a marked male predominance, and all IgG4/MFS-related HP patients had cranial HP while none had isolated spinal HP, resulting in a lower frequency of decreased sensation compared with idiopathic HP patients who occasionally had spinal HP.

However, our study has some limitations. First, the rate of response to the preliminary survey was not very high; however, the estimated number of HP patients in Japan was calculated by taking the response rate in each stratum into account.[5] The response rate in the secondary survey was reasonably high

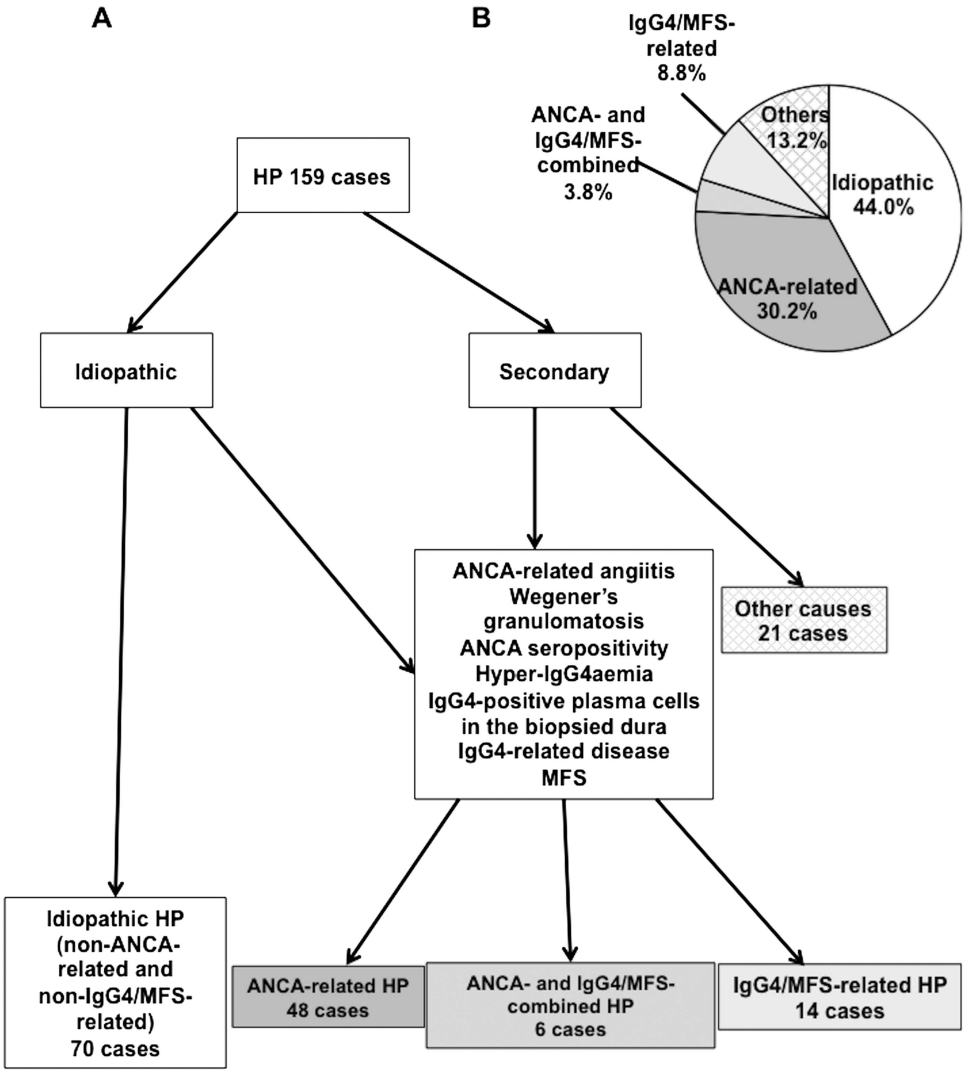

Figure 1 Classification of hypertrophic pachymeningitis (HP) in the present nationwide survey in Japan. (A) Flow chart showing the classification of the 159 HP patients. Causes of HP, idiopathic or secondary, were initially judged by the physician in charge. We classified 70 cases as having idiopathic HP because neither antineutrophil cytoplasmic antibody (ANCA)-related nor IgG4/multifocal fibrosclerosis (MFS)-related systemic diseases was present. We extracted 68 cases with ANCA-related angiitis, Wegener's granulomatosis, ANCA-seropositivity, hyper-IgG4aemia, IgG4-positive plasma cells in the biopsied dura mater, IgG4-related disease, and MFS from cases with secondary HP and those initially judged as 'idiopathic HP' by the physician in charge. We further divided them into 48 cases with ANCA-related HP, 14 cases with IgG4/MFS-related HP, and six cases with combined ANCA-related and IgG4/MFS-related HP. (B) Proportions of idiopathic and secondary HP according to the major underlying diseases. Idiopathic HP accounts for 44.0% of all cases while ANCA-related and IgG4/MFS-related cases make up 30.2% and 8.8%, respectively. When ANCA- and IgG4/MFS-combined cases (3.8%) are included, the percentages rise to 34.0% in ANCA-related HP and 12.6% in IgG4/MFS-related HP.

compared with the response rates of the secondary surveys in recent nationwide epidemiological surveys of multiple sclerosis and myasthenia gravis conducted in Japan (39.3% and 36.9%, respectively).[3 7] We thus believe that the response rates did not impair the quality of the present study. Second, the diagnosis of HP depended on a decision by a doctor in charge, and we cannot completely neglect the possibility that the doctors in charge did not have an opportunity to thoroughly review the medical charts and radiological reports. ANCA and serum IgG4 were not examined in all patients, generating a possibility that the idiopathic HP group may contain some secondary HP cases. Third, therapeutic efficacy was based on the judgement of each doctor, yielding some uncertainty. Fourth, performance of Gd-enhanced MRI was not an inclusion criterion, which may have caused some diagnostic inaccuracy in 11 patients (6.9%) diagnosed with non-enhanced MRI alone in the second survey. With these reservations in mind, the prevalence of HP in Japan (0.949/100 000) is much higher than those of rare neurological diseases, such as Creutzfeldt–Jakob disease (0.1/100 000).[8] Given the relapsing and progressive nature of HP without adequate medication, it casts a non-negligible healthcare burden on our society.

The most important finding of the present study is that ANCA-related disease and IgG4/MFS-related disease are the two major conditions underlying HP in Japan, where infectious causes are infrequent. Both conditions may not be mutually exclusive, and indeed, occurrence of IgG4-related HP was previously reported in association with either ANCA positivity[9] or Churg–Strauss syndrome (CSS).[10] However, because CSS itself shows hyper-IgG4aemia,[11] increased serum IgG4 levels in ANCA-related HP may not be pathognomonic. Wegener's granulomatosis frequently produces mucosal thickening of the nasal

Table 4 Comparison of clinical features among idiopathic, ANCA-related, and IgG4/MFS-related hypertrophic pachymeningitis cases

	Idiopathic n=70	ANCA-related n=54	IgG4/MFS-related n=14	p Value
Sex ratio (male:female)	1:0.75	1:1.34	1:0.17	**0.0126***
Location of hypertrophic dura				
Cranial	58 (82.9)	49 (90.7)	14 (100.0)	NS
Spinal	9 (12.9)	3 (5.6)	0 (0.0)	NS
Cranial and spinal	3 (4.3)	2 (3.7)	0 (0.0)	NS
Age of onset (mean±SD, years)	54.8±16.5	62.5±14.4	56.7±12.5	**0.0183†**
Time between onset and diagnosis (mean±SD, months)	25.3±72.2	14.6±36.6	3.57±3.59	NS
Age at first visit to physician (mean±SD, years)	56.4±16.0	63.5±13.6	57.0±12.5	**0.0321†**
Disease duration (mean±SD, months)	49.8±52.7	49.3±51.8	20.3±20.7	NS
Mode of onset				
Acute	21 (30.0)	12 (22.2)	5 (35.7)	NS
Subacute	29 (41.4)	28 (51.9)	8 (57.1)	NS
Chronic	16 (22.9)	7 (13.0)	1 (7.1)	NS
Unknown	4 (5.7)	7 (13.0)	0 (0.0)	
Clinical course				
Monophasic	23 (32.9)	16 (29.6)	9 (64.3)	NS
Progressive	14 (20.0)	8 (14.8)	2 (14.3)	NS
Relapsing-remitting	27 (38.6)	22 (40.7)	3 (21.4)	NS
Unknown	6 (8.6)	8 (14.8)	0 (0.0)	
Initial symptom				
Headache	22 (31.4)	14 (25.9)	7 (50.0)	NS
Visual loss	12 (17.1)	3 (5.6)	1 (7.1)	NS
Double vision	14 (20.0)	2 (3.7)	3 (21.4)	**0.0387†**
Otological symptoms	3 (4.3)	12 (22.2)	1 (7.1)	**0.0124†**
Symptoms and signs during entire course				
Headache	44 (62.9)	43 (79.6)	11 (78.6)	NS
Back pain	6 (8.6)	0 (0.0)	0 (0.0)	NS
Fever	11 (15.7)	25 (46.3)	2 (14.3)	**<0.001†**
Consciousness disturbance	10 (14.3)	7 (13.0)	3 (21.4)	NS
Convulsion	7 (10.0)	6 (11.1)	1 (7.1)	NS
Memory disturbance /higher brain dysfunction	5 (7.1)	5 (9.3)	1 (7.1)	NS
Visual loss	21 (30.0)	14 (25.9)	3 (21.4)	NS
Double vision	26 (37.1)	8 (14.8)	7 (50.0)	**0.0236†, 0.0149***
Dysphagia	6 (8.6)	4 (7.4)	1 (7.1)	NS
Dysarthria	5 (7.1)	4 (7.4)	0 (0.0)	NS
Weakness (facial and/or extremities)	22 (31.4)	11 (20.4)	1 (7.1)	NS
Sensory disturbance	29 (41.4)	10 (18.5)	1 (7.1)	**0.0321†**
Bladder disturbance	6 (8.6)	2 (3.7)	0 (0.0)	NS
Bowel disturbance	4 (5.7)	2 (3.7)	0 (0.0)	NS
Neurological findings				
Cranial nerve palsy	39 (55.7)	34 (63.0)	10 (71.4)	NS
Neck stiffness	3 (4.3)	2 (3.7)	2 (14.3)	NS
Motor impairment	14 (20.0)	8 (14.8)	1 (7.1)	NS
Abnormal tendon reflexes	20 (28.6)	17 (31.5)	0 (0.0)	NS
Pathological reflexes	8 (11.4)	4 (7.4)	0 (0.0)	NS
Limb and/or truncal ataxia	3 (4.3)	2 (3.7)	0 (0.0)	NS
Decreased sensation	24 (34.3)	12 (22.2)	0 (0.0)	NS
Sphincter dysfunctions	6 (8.6)	2 (3.7)	0 (0.0)	NS
Laboratory data				
WBC increase	17 (24.3)	34 (63.0)	6 (42.9)	**<0.001†**
ESR elevation	27 (38.6)	34 (63.0)	8 (57.1)	**0.0219†**
CRP elevation	38 (54.3)	47 (87.0)	12 (85.7)	**<0.001†**
Reaction to immunotherapy				
Corticosteroids				
Remission	27/46 (58.7)	7/12 (58.3)	7/13 (53.8)	NS
Insufficient	15/46 (32.6)	4/12 (33.3)	4/13 (30.8)	NS
Unknown	4/46 (8.7)	1/12 (8.3)	2/13 (15.4)	

Continued

Table 4 Continued

	Idiopathic n=70	ANCA-related n=54	IgG4/MFS-related n=14	p Value
Corticosteroids+immunosuppressants				
Remission	3/14 (21.4)	12/28 (42.9)	0/1 (0.0)	NS
Insufficient	9/14 (64.3)	12/28 (42.9)	1/1 (100.0)	NS
Unknown	2/14 (14.3)	4/28 (14.3)	0/1 (0.0)	

A p value of <0.05 has been estimated as significant among the three groups because we performed Bonferroni-Dunn's correction. When we found a significant difference among the three groups, we performed a Mann–Whitney's test, Pearson's χ^2 test or Fisher's exact test to assess the significance of differences between groups.
†Between idiopathic and ANCA-related HP.
*Between ANCA-related and IgG4/MFS-related HP.
Concerning the clinical features according to the location of hypertrophic dura, see the online supplementary table S1.
ANCA, antineutrophil cytoplasmic antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HP, hypertrophic pachymeningitis; MFS, multifocal fibrosclerosis; WBC, white blood cells.

and paranasal sinuses[12]; therefore, its intracranial extension could produce HP. There are several reports of HP harbouring ANCA in the absence of clinically overt manifestations of Wegener's granulomatosis.[13–15] We included HP cases demonstrating ANCA positivity alone in the ANCA-related HP group, because demographic features are similar between those with and without clinical manifestations of Wegener's granulomatosis.

Based on the observation that HP developed in a patient with MFS,[16] a chronic fibrosing inflammation of connective tissues comprising retroperitoneal and mediastinal fibrosis, sclerosing pancreatitis and cholangitis, and Riedel's thyroiditis,[17] it was proposed that HP could be a manifestation of MFS. Later, with the finding of infiltration of IgG4-positive plasma cells and hyper-IgG4aemia in lymphoplasmacytic sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis, MFS was supposed to be an IgG4-related disease, featuring IgG4-positive plasma cell infiltration and fibrosis in many organs.[18 19] Recent case reports of IgG4-related HP, evidenced by IgG4-positive plasma cell infiltration, show a monophasic, steroid-responsive course.[20 21] Thus, ANCA-related and IgG4/MFS-related systemic diseases might be overlooked causes of HP.

Idiopathic HP showed a slight male predominance, while ANCA-related HP showed a female preponderance and IgG4/MFS-related HP had a marked male predominance, although there is no male or female preponderance in either ANCA-related[22 23] or IgG4/MFS-related systemic diseases.[24] ANCA-related HP cases had a higher age of onset than idiopathic HP cases and IgG4/MFS-related HP cases, probably reflecting the fact that age at onset of classical CSS patients among the Japanese is around 60 years, according to the results of a nationwide survey we previously conducted.[25] In terms of symptoms during the entire course, ANCA–related HP cases showed higher frequencies of fever and otological symptoms as initial symptoms, but lower frequencies of diplopia compared with idiopathic HP and IgG4/MFS-related HP cases. IgG4/MFS-related HP cases showed a higher frequency of cranial nerve involvement but less frequent sensory disturbance/decreased sensation. By contrast, idiopathic HP cases showed a higher frequency of double vision as an initial symptom and sensory disturbance/decreased sensation during the course. Thus, besides the differences in sex and age at onset, clinical manifestations are somewhat distinct among the three major groups of HP, which may be partly derived from the nature of the underlying diseases.

We conclude that ANCA-related disease and IgG4/MFS-related disease are the two major causes of HP in Japan. It is necessary to elucidate whether these findings, including an extremely high frequency of ANCA-related HP, are applicable to other races, by conducting large-scale epidemiological surveys in the future.

Contributors TY, HM and J-iK conceived the study, supervised the analyses and wrote the paper. TY and KS performed the statistical analyses. SU, TM, KM, NI, RY, MY, SK and KF participated in procedure development and collated the data.

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Notes