Hypertrophic pachymeningitis in ANCA-associated vasculitis: a cross-sectional and multi-institutional study in Japan (J-CANVAS)

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Abstract

Background: This study investigated the characteristics of hypertrophic pachymeningitis (HP) in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), using information from a multicenter study in Japan.

Methods: We analyzed the clinical information of 663 Asian patients with AAV (total AAV), including 558 patients with newly diagnosed AAV and 105 with relapsed AAV. Clinical findings were compared between patients with and without HP. To elucidate the relevant manifestations for HP development, multivariable logistic regression analyses were additionally performed.

Results: Of the patients with AAV (mean age, 70.2 ± 13.5 years), HP was noted in 30 (4.52%), including 20 (3.58%) with newly diagnosed AAV and 10 (9.52%) with relapsed AAV. Granulomatosis with polyangiitis (GPA) was classified in 50% of patients with HP. A higher prevalence of GPA was significantly observed in patients with HP than in those without HP in total AAV and newly diagnosed AAV (p < 0.001). In newly diagnosed AAV, serum proteinase 3 (PR3)-ANCA positivity was significantly higher in patients with HP than in those without HP (p = 0.030). Patients with HP significantly had ear, nose, and throat (ENT) (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.03–2.14, p = 0.033) and mucous membrane/eye manifestations (OR 5.99, 95% CI 2.59–13.86, p < 0.0001) in total AAV. Moreover, they significantly had conductive hearing loss (OR 11.6, 95% CI 4.51–29.57, p < 0.0001) and sudden visual loss (OR 20.9, 95% CI 5.24–85.03, p < 0.0001).

Conclusion: GPA was predominantly observed in patients with HP. Furthermore, in newly diagnosed AAV, patients with HP showed significantly higher PR3-ANCA positivity than those without HP. The ear and eye manifestations may be implicated in HP development.
Introduction
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which systemically affects small- and medium-sized vessels, involves visceral impairments that can lead to life-threatening complications. AAV can be categorized into two different types based on the target antigen for ANCA, which is implicated in the pathogenesis of AAV, including myeloperoxidase (MPO) and proteinase 3 (PR3) [1]. Furthermore, microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) are common classifications of AAV [1–3]. All categories of AAV generally involve neurological manifestations, although those in the peripheral nervous system are more common than those in the central nervous system (CNS) [4, 5]. However, CNS manifestations, such as intracranial ischemia or hemorrhage attributed to vasculitis, parenchymal lesions, and encephalopathy [6, 7], are broadly involved in < 15 to > 50% of patients with AAV [4–6]. Notably, hypertrophic pachymeningitis (HP) can also develop as a CNS manifestation in AAV [6–8]. HP is characterized as an inflammatory disorder indicating intracranial or spinal thickening of the dura mater, and its pathology includes inflammatory cell infiltration and interstitial tissue fibrosis [9, 10]. HP development is secondarily ascribable to CNS infections, neoplasms, or autoinflammatory disorders; meanwhile, ANCA is more frequently implicated in the pathogenesis of immune-mediated HP [9–12]. HP could develop as the first clinical episode of AAV, whereas approximately 15% of patients with HP, even with serum positivity for ANCA, cannot be classified as having definite AAV [10, 12], suggesting that HP could be a CNS-limited type of AAV [8, 10]. Moreover, patients with ANCA- and medium-sized vessel involvement have been comprehensively categorized as ANCA-associated HP [10–16]. Given these unclassifiable categories of immune-mediated HP with ANCA positivity, it is necessary to specifically understand the clinical characteristics of HP developing in AAV. Several studies focusing on HP in AAV have been reported to date [8, 17–20].

Methods
Patients and database
This study was performed using the clinical information of 663 Asian patients with AAV who were enrolled in the J-CANVAS from 26 divisions in 24 Japanese institutions. The enrolled patients had newly diagnosed AAV or relapsed AAV between January 2017 and June 2020. All patients were aged > 20 years and classified as having MPA, GPA, or EGPA based on the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides [2] and the European Medicines Agency algorithm [3]. The information regarding the diagnosis or relapse of AAV, including epidemiological, laboratory, and radiological findings and clinical manifestations related to AAV based on the Birmingham Vasculitis Activity Score version 3 (BVAS) [21], was retrospectively extracted from the medical records of each institution. All extracted data were collected using an electric data capture system, Viedoc (PCG Solutions, Uppsala, Sweden). HP was defined as radiological findings showing thickening of the cranial or spinal dura mater on magnetic resonance imaging (MRI).

Study design
In this cross-sectional study, epidemiological, clinical, and laboratory findings, including MPO- and PR3-ANCA, were compared between patients with and without HP. These parameters were evaluated separately in all enrolled patients with newly diagnosed AAV, and those with relapsed AAV. The overall disease activity, whose scale is determined to be between 0 and 63, and the incidence of manifestations related to AAV were evaluated according to the BVAS [21]. In addition,
Epidemiologic and laboratory findings in patients with HP

The mean age and male-to-female ratio were 70.2 ± 13.5 years and 1:1.22, respectively, in 663 patients (total AAV), including 558 with newly diagnosed AAV (mean age, 70.8 ± 13.2 years; male-to-female ratio, 1:1.20) and 105 with relapsed AAV (66.8 ± 14.5 years; male-to-female ratio, 1:1.22, respectively, in 663 patients (total AAV), respectively) in patients with HP, whereas higher serum creatinine (Cre) levels and lower estimated glomerular filtration rate (eGFR) were significantly more frequent in those without HP (p = 0.005, p = 0.0005, respectively).

Statistical analyses

All data are presented as the mean ± standard deviation (SD), and two-sided p-values < 0.05 were considered statistically significant. The Mann-Whitney U test and Fisher’s exact probability test were used to compare the patients with and without HP. Multivariable logistic regression analyses were used to evaluate the relationships between relevant manifestations, including mucous membrane/eye and ENT manifestations which were determined based on previous studies [8, 10, 17–19], and HP development by estimating a regression coefficient with a two-sided 95% confidence interval (CI). They were adjusted for age, sex, and lung and renal manifestations as potential confounding variables based on previous studies and clinical perspectives. Statistical analyses were performed using the JMP 14.3.0 software (SAS Institute Inc., Cary, NC).

Results

Epidemiologic and laboratory findings in patients with HP

The mean age and male-to-female ratio were 70.2 ± 13.5 years and 1:1.22, respectively, in 663 patients (total AAV), including 558 with newly diagnosed AAV (mean age, 70.8 ± 13.2 years; male-to-female ratio, 1:1.20) and 105 with relapsed AAV (66.8 ± 14.5 years; 1:1.39). The mean disease duration of patients with relapsed AAV was 5.7 ± 5.6 years. Of total AAV, HP was observed in 30 (4.52%) patients (Table 1). They were equally classified as having GPA or MPA (n = 15 [50%] each). A significantly higher classification of GPA was shown in patients with HP than in those without HP (p = 0.0003), although that
Table 1  Demographic and laboratory findings between AAV patients with and without HP

| Characteristics | Total AAV (n = 30) | Non-HP (n = 633) | p-values | Newly diagnosed AAV (n = 20) | Non-HP (n = 538) | p-values | Relapsed AAV (n = 10) | Non-HP (n = 95) | p-values |
|-----------------|-------------------|------------------|----------|----------------------------|------------------|----------|----------------------|----------------|----------|
| Age, years      | 71.1 ± 8.0        | 70.2 ± 13.7      | 0.509    | 70.8 ± 8.5                 | 70.9 ± 13.4      | 0.349    | 71.9 ± 7.5           | 66.3 ± 15.0    | 0.425    |
| Sex, male/female, n (%) | 18/12          | 280/353         | 0.095    | 12/8                      | 280/353          | 0.177    | 6/4                  | 38/57          | 0.315    |
| AAV classification, n (%) | GPA 15 (50) | MPA 15 (50)     | EGPA 0 | GPA 15 (50) | MPA 15 (50) | EGPA 0 | GPA 15 (50) | MPA 15 (50) | EGPA 0 |
| PR3             | 6 (20)            | 78 (12)          | 0.254    | 5 (25)                    | 47 (9)           | 0.030    | 1 (10)               | 31 (32)        | 0.277    |
| MPO             | 23 (77)           | 473 (75)         | 0.999    | 14 (70)                   | 421 (78)         | 0.409    | 9 (90)               | 52 (55)        | 0.042    |
| Seronegative    | 1 (3)             | 82 (13)          | 0.159    | 1 (5)                     | 70 (13)          | 0.494    | 0                    | 12 (13)        | 0.599    |
| Laboratory data |                   |                  |          |                           |                  |          |                      |                |          |
| White blood cells, /μL | 9618 ± 4124 | 12398 ± 6425 | 0.009    | 10510 ± 4628              | 12729 ± 6533     | 0.129    | 7834 ± 2069          | 10528 ± 5435   | 0.084    |
| Neutrophils, /μL | 8017 ± 4189 | 8456 ± 4487 | 0.586    | 8635 ± 4889               | 8569 ± 4588      | 0.936    | 6842 ± 2102          | 7830 ± 3848    | 0.523    |
| Lymphocytes, /μL | 1045 ± 630 | 1326 ± 748 | 0.020    | 1269 ± 632               | 1357 ± 756       | 0.826    | 587 ± 310            | 1153 ± 679     | 0.002    |
| C-reactive protein, mg/dL | 5.22 ± 5.59 | 7.12 ± 6.27 | 0.250    | 7.35 ± 5.70               | 7.73 ± 6.33      | 0.892    | 3.97 ± 4.86          | 3.68 ± 4.70    | 0.674    |
| Serum creatinine, mg/dL | 0.79 ± 0.36 | 1.44 ± 1.55 | 0.005    | 0.78 ± 0.33               | 1.45 ± 1.57      | 0.019    | 0.82 ± 0.44          | 1.39 ± 1.43    | 0.111    |
| eGFR            | 75.7 ± 24.8       | 57.2 ± 31.9      | 0.0005   | 75.8 ± 23.0               | 57.1 ± 32.1      | 0.004    | 76.5 ± 29.5          | 57.8 ± 31.3    | 0.077    |

Values are expressed as the mean ± SD. Statistical significance was set at p-value < 0.05.

ANCA antineutrophil cytoplasmic antibody, AAV ANCA-associated vasculitis, GPA eosinophilic granulomatosis with polyangiitis, eGFR estimated glomerular filtration rate, GPA granulomatosis with polyangiitis, HP hypertrophic pachymeningitis, MPA microscopic polyangiitis.

with HP than in those without HP (incidence: \( p = 0.007, p = 0.0002 \), respectively) (scores: \( p = 0.013, p < 0.0001 \), respectively). In relapsed AAV, the incidence and scores of mucous membrane/eye manifestation were significantly higher in patients with HP than in those without HP (\( p = 0.002, p = 0.0001 \), respectively), whereas those of ENT manifestations were not significantly different. Meanwhile, significantly higher rates of complications of “sudden visual loss” and “conductive hearing loss,” which are classified as mucous membrane/eye and ENT manifestations, respectively [21], were demonstrated in patients with HP than in those without HP in each analysis of total AAV (\( p < 0.0001, p < 0.0001 \), respectively), newly diagnosed AAV (\( p = 0.012, p < 0.0001 \), respectively), and relapsed AAV (\( p = 0.001, p = 0.044 \), respectively) (Table 3). Conversely, the incidence of cutaneous and renal manifestations was significantly lower in patients with HP than in those without HP in total AAV (\( p = 0.042, p = 0.003 \), respectively). The scores of renal manifestations were also significantly lower in patients with HP than in those without HP in the analyses of total AAV and newly diagnosed AAV (\( p = 0.0008, p = 0.002 \), respectively). In relapsed AAV, the incidence and scores of renal manifestations were not significantly different between patients with and without HP; however, those in patients without HP were significantly lower in relapsed AAV than in newly diagnosed AAV (\( p < 0.0001, p < 0.0001 \), respectively). Moreover, incidence and scores of renal manifestations were not significantly different between patients with HP in newly diagnosed AAV and those in relapsed AAV (Additional file 1: Table S1).

These results suggest that mucous membrane/eye and ENT manifestations may be implicated in the development of HP. Moreover, previous studies indicated the frequent existence of these two manifestations in patients with HP in AAV [8, 10, 17–19]. Next, the relationships between these two manifestations and HP development were evaluated in total AAV. In multivariable logistic regression analyses after adjustment for potential confounding variables including age, sex, and lung and renal manifestations, HP was significantly associated with an incidence of mucous membrane/eye (odds ratio [OR] 5.99, 95% CI 2.59 to 13.86,
Table 2 Incidence and scores of manifestations related to AAV between AAV patients with and without HP

| Manifestation | Total AAV |  | Newly diagnosed AAV |  | Relapsed AAV |  |
|---------------|----------|---|-------------------|---|--------------|---|
|               | HP (n = 30) | Non-HP (n = 633) |  | HP (n = 20) | Non-HP (n = 538) |  | HP (n = 10) | Non-HP (n = 95) |  |
| BVAS, total   |          |          |  |          |          |  |          |          |  |
| Total score   | 13.4 ± 5.56 | 14.9 ± 7.11 | 0.364 | 14.0 ± 5.40 | 15.7 ± 7.01 | 0.362 | 12.3 ± 5.98 | 10.6 ± 6.02 | 0.390 |

In addition, sudden visual loss and conductive hearing loss in those without HP in total AAV (p < 0.0001, p = 0.0008, respectively) and newly diagnosed AAV (p < 0.0001, p = 0.002, respectively), whereas they were not significantly different in relapsed AAV (p = 0.090, p = 0.114, respectively) (Table 2). Patients with HP had significantly higher frequencies of headache and cranial nerve palsy than those without HP in total AAV (p < 0.0001, p < 0.0001, respectively), newly diagnosed AAV (p < 0.0001, p = 0.0003, respectively), and relapsed AAV (p = 0.005, p = 0.003, respectively) (Table 4). The frequency of meningitis and spinal cord lesions was also significantly higher in patients with HP than in those without HP, although meningitis was not significantly different in newly diagnosed AAV. Conversely, mononeuritis multiplex was less

Neurological findings
The incidence and scores of nervous system manifestations were significantly higher in patients with HP than in those without HP in total AAV (p < 0.0001, p = 0.0008, respectively) and newly diagnosed AAV (p < 0.0001, p = 0.002, respectively), whereas they were not significantly different in relapsed AAV (p = 0.090, p = 0.114, respectively) (Table 2). Patients with HP had significantly higher frequencies of headache and cranial nerve palsy than those without HP in total AAV (p < 0.0001, p < 0.0001, respectively), newly diagnosed AAV (p < 0.0001, p = 0.0003, respectively), and relapsed AAV (p = 0.005, p = 0.003, respectively) (Table 4). The frequency of meningitis and spinal cord lesions was also significantly higher in patients with HP than in those without HP, although meningitis was not significantly different in newly diagnosed AAV. Conversely, mononeuritis multiplex was less
frequently observed in patients with HP than in those without HP in total AAV ($p = 0.009$) and newly diagnosed AAV ($p = 0.034$).

**Discussion**

This study used the clinical information from a nationwide survey of AAV in Japan. We ultimately indicated the key findings that patients with HP had a higher prevalence of GPA and higher PR3-ANCA serum positivity than those without HP, and moreover, ENT and mucous membrane/eye manifestations were associated with HP development in AAV. Several single-center studies on ANCA-associated HP have been presented to date; however, it might be difficult to accurately determine the clinical characteristics contributing to HP development in AAV because of the limited number of patients analyzed at each institution. Considering the ethnic viewpoint of ANCA-associated HP, the majority of published studies have been reported from East Asian counties including Japan [8, 10, 15–20].

| Manifestation                                      | Total AAV | p-values | Newly diagnosed AAV | p-values | Relapsed AAV | p-values |
|---------------------------------------------------|-----------|----------|---------------------|----------|-------------|----------|
|                                                   | HP (n = 30) | Non-HP (n = 633) |                       | HP (n = 20) | Non-HP (n = 538) |                      | HP (n = 10) | Non-HP (n = 95) |                      |
| Mucous membranes/eyes, number (%)                 |           |          |                     |          |              |          |
| Mouth ulcers                                      | 0         | 9 (1.4)  | 0.999              | 0        | 9 (1.7)      | –        | 0              | –        |
| Genital ulcers                                     | 0         | 0        | –                   | 0        | 0            | –        | 0              | –        |
| Adnexal inflammation                              | 0         | 0        | –                   | 0        | 0            | –        | 0              | –        |
| Significant proptosis                              | 0         | 5 (0.8)  | 1                   | 0        | 2 (0.4)      | 1        | 0              | 3 (3.2)  | 0.999        |
| Scleritis/episceritis                              | 5 (17)    | 29 (4.6) | 0.015              | 3 (15)   | 26 (4.8)     | 0.079    | 2 (20)         | 3 (3.2)  | 0.070        |
| Conjunctivitis/blepharitis/keratitis               | 0         | 7 (1.1)  | 0.999              | 0        | 7 (1.3)      | 0.999    | 0              | 0        | –            |
| Blurred vision                                     | 2 (6.7)   | 10 (1.6) | 0.099              | 1 (5)    | 8 (1.5)      | 0.282    | 1 (10)         | 2 (2.1)  | 0.262        |
| Sudden visual loss                                 | 6 (20)    | 6 (0.9)  | < 0.0001           | 2 (10)   | 3 (0.5)      | 0.012    | 4 (40)         | 3 (3.2)  | 0.001        |
| Uveitis                                           | 0         | 4 (0.6)  | 0.999              | 0        | 5 (0.9)      | 0.999    | 0              | 0        | –            |
| Retinal changes (vasculitis, thrombois/ exudate/hemorrhage) | 0         | 5 (0.8)  | 0.999              | 0        | 3 (0.5)      | 0.999    | 0              | 1 (1.1)  | 1            |
| ENT, number (%)                                    |           |          |                     |          |              |          |
| Bloody nasal discharge/ crusts/ulcers/ granulomata | 2 (6.7)   | 46 (7.2) | 0.999              | 1 (5)    | 38 (7.1)     | 0.999    | 1 (10)         | 8 (8)    | 0.999        |
| Paranasal sinus involvement                        | 7 (23)    | 108 (17) | 0.334              | 5 (17)   | 76 (17)      | 0.371    | 2 (20)         | 15 (16)  | 0.663        |
| Subglottic stenosis                                | 0         | 1 (0.2)  | 1                   | 0        | 0            | –        | 0              | 1 (1.1)  | 1            |
| Conductive hearing loss                            | 11 (37)   | 42 (6.6) | < 0.0001           | 9 (45)   | 40 (7.4)     | < 0.0001 | 2 (20)         | 2 (2.1)  | 0.044        |
| Sensorineural hearing loss                         | 7 (23)    | 25 (3.9) | 0.0003             | 5 (25)   | 20 (3.7)     | 0.001    | 2 (20)         | 5 (5.3)  | 0.133        |

Statistical significance was set at $p$-value < 0.05

ANCA antineutrophil cytoplasmic antibody, AAV ANCA-associated vasculitis, ENT ear, nose, and throat, HP hypertrophic pachymeningitis
Consequently, this was the first study to assess the clinical characteristics of HP using the enrolled information from many Japanese patients with AAV, demonstrating the epidemiological findings, especially the frequency of HP and classification in AAV, as more reliable results than those in single-institutional studies. In addition, we also performed the analyses separately for newly diagnosed and relapsed AAV, elucidating consistent or different characteristics depending on the clinical stage of AAV in patients with HP. Our results showed

![Multivariable logistic analyses of significant manifestations related to antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis in patients with hypertrophic pachymeningitis after adjustment for potential confounding variables. Incidence (a) and scores (b) of the mucous membrane/eye and ear, nose, and throat (ENT) manifestations and incidence of sudden visual loss and conductive hearing loss (c) were analyzed. OR, odds ratio; CI, confidence interval.](image-url)
an equal prevalence of GPA and MPA in patients with HP. Moreover, a higher classification of GPA was significant in patients with HP than in those without HP in the analyses of total and newly diagnosed AAV. It has also been suggested that patients with HP could be predominantly classified as having GPA in AAV [8, 10, 17–19], although the predominant prevalence of MPA has been found as an epidemiologic feature of AAV in Japan despite the dominance of GPA in European countries and the USA [22, 23]. The GPA classification could be dominantly found overall in patients with AAV who develop HP, even in Japan. Moreover, PR3-ANCA serum positivity in newly diagnosed AAV was significantly higher in patients with HP than in those without HP. Taken together, our results suggest that GPA with PR3-ANCA positivity may be predominantly observed in patients with HP in newly diagnosed AAV. PR3-ANCA serum positivity was found to be a risk factor for AAV relapse [24], but it might not be applicable to HP development in relapse. In contrast, HP related to MPO-ANCA could broadly develop in patients with both MPA and GPA throughout the course of AAV. In fact, the prevalence of HP was significantly lower in newly diagnosed AAV than in relapsed AAV, supporting the theory that CNS involvement could develop in the chronic phase of AAV [6, 7]. However, some cases of HP in AAV, whose initial diagnosis of MPA was changed to GPA, have been reported [8, 19, 25], suggesting that HP could be the initial episode of GPA.

Mucous membrane/eye manifestations were significantly more common in patients with HP than in those without HP; notably, sudden visual loss in this category [21] was a pivotal involvement in patients with HP. ENT manifestations were also significantly observed in patients with HP in total AAV and newly diagnosed AAV. In contrast, ENT dominance could not be significantly proved in relapsed AAV, suggesting that there was no significant difference in GPA classification between patients with and without HP because of increased GPA in patients without HP. However, conductive hearing loss in the ENT category, which is ascribable to middle ear impairment [21], was significantly involved in patients with HP even in relapsed AAV. Accordingly, mucous membrane/eye and ENT manifestations have been suggested as relevant clinical factors for HP development in AAV. Furthermore, sudden visual loss and conductive hearing loss were identified as principal involvements. Previous studies have suggested a relationship between otitis media and HP in AAV [8, 10, 17, 19, 26]. Only one study has revealed that visual impairment was more frequently observed in patients with HP than in those without HP in GPA [18]. In our study, both involvements were simultaneously demonstrated as significantly related manifestations in patients developing HP in AAV. Conversely, renal manifestations were relatively less involved in patients with HP, suggesting that the pathogenesis of renal damage may be less implicated in the development of HP. Considering the pathological aspects of AAV, granulomatosis with inflammatory cell infiltration has

| Table 4 | Comparison of neurological symptoms between patients with and without HP |
|---------|---------------------------------------------------------------|
|         | Total AAV | Newly diagnosed AAV | Relapsed AAV |
|         | HP (n = 30) | Non-HP (n = 633) | p-values | HP (n = 20) | Non-HP (n = 538) | p-values | HP (n = 10) | Non-HP (n = 95) | p-values |
| Nervous system, number (%) | | | | | | | | | |
| Headache | 21 (70) | 34 (5.7) | < 0.0001 | 16 (80) | 29 (5.4) | < 0.0001 | 5 (50) | 10 (11) | 0.005 |
| Meningitis | 3 (10) | 2 (0.3) | 0.0007 | 1 (5) | 1 (0.2) | 0.071 | 2 (20) | 1 (1.1) | 0.023 |
| Organic confusion | 1 (3.3) | 6 (0.9) | 0.278 | 1 (5) | 6 (1.1) | 0.227 | 0 | 0 | – |
| Seizures | 0 | 4 (0.6) | 1 | 0 | 2 (0.3) | 1 | 0 | 2 (2.1) | 0.999 |
| Stroke | 0 | 9 (1.4) | 0.999 | 0 | 8 (1.5) | 0.999 | 0 | 1 (1.1) | 0.999 |
| Spinal cord lesion | 3 (10) | 2 (0.3) | 0.008 | 1 (5) | 1 (0.2) | 0.007 | 2 (20) | 1 (1.1) | 0.023 |
| Cranial nerve palsy | 10 (33) | 19 (3) | < 0.0001 | 5 (25) | 15 (2.8) | 0.0003 | 5 (50) | 4 (4.2) | 0.003 |
| Sensory peripheral neuropathy | 3 (10) | 166 (26) | 0.052 | 3 (15) | 145 (27) | 0.307 | 0 | 21 (22) | 0.206 |
| Mononeuritis multiplex | 0 | 105 (17) | 0.009 | 0 | 93 (17) | 0.034 | 0 | 12 (13) | 0.599 |

Statistical significance was set at a p-value < 0.05

ANCA antineutrophil cytoplasmic antibody, AAV ANCA-associated vasculitis, HP hypertrophic pachymeningitis
been more prominently exhibited in the upper and lower respiratory tracts, whereas necrotizing vasculitis, which widely affects small- to medium-sized vessels, typically indicates renal involvement [27, 28]. Although patients with HP rarely had mononeuritis multiplex, which is also ascribable to small- to medium-sized vasculitis [4, 29], the manifestations typically attributable to vasculitis might be little associated with HP development. It has been assumed that direct extension and/or transfer to the CNS from upper respiratory lesions, including granulomatosis inflammation, may be implicated in the mechanism for developing HP related to AAV [15, 16, 30]. Accordingly, our study also suggested that inflammatory lesions adjacent to the CNS, notably including eye and middle ear involvement, may be robustly implicated in HP development in AAV. In fact, it was demonstrated that HP, which was related to otitis media with AAV (OMAAV), was the most commonly localized in a cranial fossa [31].

This study also demonstrated that headache and cranial neuropathies were common neurological symptoms associated with HP in both newly diagnosed and relapsed AAV, consistent with previous reports [8, 10, 15–20]. In addition, our results indicated meningitis and spinal cord lesion as significant conditions in patients with HP. Cerebrospinal fluid (CSF) pleocytosis can be observed in ANCA-associated HP [10, 13, 17, 19]. However, the dura mater is outside the subdural space, which is anatomically separate from the CSF space [32, 33], suggesting that HP-mediated inflammation might extensively invade leptomeninges when pleocytosis can be observed. Moreover, meningitis may be involved in immune-mediated HP. Meanwhile, it was impossible to ascertain the types of spinal cord lesions that were analyzed because this study was performed using comprehensive items based on the BVAS. Therefore, localization of the thickened dura mater was uncertain, although HP can also develop in the spinal cord [10, 17, 34, 35].

There are other limitations in this study. First, some studies have suggested that mastoiditis, which was not evaluated in our study, is also frequently observed in patients with ANCA-related HP [10, 16, 19]. Nevertheless, this could develop as a result of the spreading effect of middle ear inflammation [36], suggesting that results are analogous to conductive hearing loss. Meanwhile, the frequency of mixed conductive-sensorineural hearing loss was found to be 9-fold higher than that of conductive hearing loss in patients with OMAAV [26]. However, it is difficult to differentiate conductive hearing loss from mixed conductive-sensorineural hearing loss in our study design based on BVAS. Second, cranial neuropathies were found to be significant manifestations of HP; however, it was impossible to identify specific types of impaired cranial nerves. Third, EGPA was ultimately not included in patients with HP, whereas some cases of HP in EGPA have been recently reported [17, 20, 37–39]. Although our study focused on the overview of HP in GPA or MPA, it is also necessary to elucidate the characteristics of HP in EGPA. Forth, brain MRI was not performed on all patients in the database of this study because the clinical information was retrospectively enrolled from the medical records. Therefore, it is necessary to establish the study design in which all patients perform brain MRI for more precise epidemiological analyses.

**Conclusions**

GPA was classified in 50% of the patients with HP. The prevalence of GPA was significantly higher in patients with HP than in those without HP in total AAV and newly diagnosed AAV. Furthermore, patients with HP showed significantly higher PR3-ANCA serum positivity than those without HP in newly diagnosed AAV. Conversely, MPO-ANCA serum positivity was significantly higher in patients with HP than in those without HP in relapsed AAV. Taken together, GPA can be predominantly classified in patients with HP. Moreover, patients with HP classified as PR3-ANCA-positive GPA could be significantly observed in newly diagnosed AAV. HP with MPO-ANCA serum positivity could develop throughout the clinical course of AAV. ENT and mucous membrane/eye manifestations, notably sudden visual loss and conductive hearing loss, were relevantly identified in patients who develop HP in AAV. We expect that the accumulation of significant results determining clinical characteristics can be useful for predicting HP development in AAV. However, this study was performed using limited clinical information despite the first attempt at a multi-institutional survey. Accordingly, further investigation, by analyzing more detailed information from a larger number of patients, is required to elucidate the pathogenesis of HP in AAV.

**Supplementary Information**

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**Authors’ contributions**

YS, DK, TI, and YSE were involved in the study design and developed the structure and argument for this study. YS, DK, TI, NK, NT, AN, YK, NY, YY, TY, KE, SH, KM, TT, HI, MKA, KY, YR, RN, RQ, TTA, TIT, MM, AT, and YM obtained the clinical data. YS analyzed the obtained data. YS, TK, AT, and NY interpreted the analyzed data. YS prepared the draft of this manuscript.
and contributed to the revision of the manuscript. All authors revised and approved the final manuscript.

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Availability of data and materials
The data for the analyses in this study are available on reasonable request.

Declarations

Competing interests
The authors declare that they have no competing interests.

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