

# Pituitary dysfunction in patients with ANCA associated vasculitis: prevalence, presentation, and outcomes

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*Ther Adv Chronic Dis*

2020, Vol. 11: 1–10

DOI: 10.1177/  
2040622320930636

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## Abstract:

**Background:** The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are rare multisystem autoimmune diseases characterized by inflammatory cell infiltration causing necrosis of small blood vessels. Pituitary involvement in AAV is poorly described. This study aimed to describe the prevalence, clinical characteristics, and outcomes of pituitary involvement in patients with AAV.

**Methods:** A total of 150 patients diagnosed with AAV and hospitalized in the China–Japan Friendship Hospital between 2009 and 2019 were enrolled in this retrospective study. Patients diagnosed with pituitary involvement in AAV were selected for inclusion.

**Results:** Three patients (2%) were identified with pituitary involvement. Two patients had positive ANCA titers, one with proteinase 3 positive and one with myeloperoxidase positive antibodies. Pituitary dysfunction presented as an initial symptom in one patient and developed over the course of the diseases in the other two patients. All three patients had abnormal hormones. Among them, two patients had an enlarged pituitary, shown by magnetic resonance images (MRIs), and one patient had a normal sized pituitary, shown by MRI, but presented with increased linear radioactivity uptake in the pituitary fossa by positron emission tomography-computed tomography. All patients were treated with corticosteroid and immunosuppressive therapy. Both pituitary dysfunction and vasculitis were in remission.

**Conclusion:** Pituitary involvement is uncommon in AAV and it can occur at any point during AAV. The main clinical manifestations are central diabetes insipidus and panhypopituitarism. Immunosuppressive therapy could significantly alleviate clinical symptoms as well as pituitary imaging.

**Keywords:** ANCA associated vasculitis, anti-neutrophil cytoplasmic antibody, neurogenic diabetes insipidus, pituitary involvement

Received: 20 November 2019; revised manuscript accepted: 22 April 2020.

## Introduction

The anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) are a collection of relatively rare autoimmune diseases.<sup>1</sup> It is part of the systemic necrotizing small-vessel vasculitis category, characterized by autoantibodies specific for neutrophil granule components, predominantly myeloperoxidase (MPO) and proteinase 3 (PR3).<sup>2</sup> AAV comprises microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).<sup>3</sup> The clinical characters of AAV include a

skin rash as well as fulminant multisystem disease. Typical features of MPA include severe renal and pulmonary disease. Patients with GPA have a predilection for ear, nose, and throat, upper respiratory tract, lower respiratory tract, and kidney disease. Patients with EGPA typically have a background of peripheral blood eosinophilia, asthma, and nasal polyposis.<sup>1,2</sup> Central nervous system involvement was reported in 7–11% of patients with GPA<sup>4</sup> and 9.8% in MPA.<sup>5</sup> The pituitary gland, the meninges, and the cerebral vasculature are the major structures involved in AAV.<sup>6,7</sup>

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However, pituitary dysfunction is a rare clinical symptom in AAV. Ahlstrom described it for the first time in 1953.<sup>8</sup> Two retrospective cohort studies and dozens of case reports or series about pituitary involvement with GPA were reported.<sup>9–13</sup> In this study, we described the prevalence, presentation, and outcomes of pituitary involvement in AAV.

## Methods

### *Study cohort and patients*

A cohort of 150 Chinese patients, diagnosed with ANCA associated vasculitis, according to 1990 American College of Rheumatology (ACR) criteria for GPA,<sup>14</sup> 2012 Chapel Hill Consensus Conference definitions,<sup>15</sup> and Watts' algorithm,<sup>16</sup> were identified at the Rheumatology Department of the China–Japan Friendship Hospital from January 2009 to June 2019. Clinical manifestations, laboratory data, and radiographic data were extracted from medical records. The study was approved by the Medical Ethics Committee of China-Japan Friendship Hospital (IRB number is 2016-117). Due to the retrospective nature of this study, written informed consent was not given, but oral informed consent was obtained from all enrolled patients.

### *Inclusion criteria*

Patients diagnosed with AAV with pituitary gland involvement, based on characteristic imaging findings and the manifestation of pituitary dysfunction, were selected. Magnetic resonance images (MRIs), positron emission tomography–computed tomography (PET-CT), and blood tests were used to identify patients with pituitary disease in this cohort. Pituitary dysfunction was defined according to the criteria.<sup>17</sup>

### *Detection of ANCA*

The detection of ANCA (MPO-ANCA, PR3-ANCA) in all patients was performed by following both indirect immunofluorescence and ELISA protocols according to the manufacturer's instructions. In brief, to exclude antinuclear antibodies, ethanol-fixed human polymorphonuclear leukocytes were used to detect ANCA and monkey liver sections were used. Perinuclear and cytoplasmic ANCA were identified according to staining patterns by two experienced technicians. The

kit is from Euroimmun Company (FA 1201-1010). The antigen-specific MPO and PR3 were determined by the Enzyme linked immunosorbent assay (ELISA) kit from Euroimmun Company (EA 1211-9601).

## Results

### *Clinical features*

A total of 150 patients with AAV were enrolled in this study. Three patients (2%) were found to have pituitary involvement related to AAV, based on characteristic imaging findings and the presence of pituitary dysfunction. All patients had histological confirmation, two with granulomatous inflammation and one with microscopic polyangiitis. Among them, one patient was MPO-ANCA positive, one patient was PR3-ANCA positive, and the third patient was ANCA negative but was confirmed by the histological biopsy to present with granulomatous inflammation. The mean age of the patients with confirmed pituitary involvement was 49 years (range, 37–61 years). Pituitary problems occurred as the initial symptom in one male patient, which led to a delay in the diagnose with GPA after 8 months. A 51-year-old female patient had polydipsia and diuresis 8 months after she was diagnosed with AAV. In addition, a 37-year-old female patient presented with abnormal lactation 8 months after disease onset. The patient's demographics and their organ involvement with vasculitis are shown in Table 1.

### *Treatment and follow up*

All three patients with pituitary involvement received induction therapy including glucocorticoids in combination with one or two immunosuppressants (Table 2).

A 51-year-old female diagnosed with GPA had headaches, nasal obstruction, running nose, and impaired vision as initial symptoms. The laboratory tests showed white blood cell (WBC)  $11.24 \times 10^9/L$ , erythrocyte sedimentation rate (ESR) 100 mm/h (normal: 0–15 mm/h), C-reactive protein (CRP) 9.25 mg/dl (normal: <0.8 mg/dl), anti-nuclear antibody (ANA) 1:80, PR3-ANCA 92 U/ml. An eye computerized tomography (CT) revealed destruction of the orbit and nasal bone, and high-resolution chest CT showed nodules and an intrapulmonary cavity. Methylprednisolone (MP)

**Table 1.** Clinical features in patients with pituitary dysfunction due to AAV.

Patients	Age, years	Sex	ANCA patterns and titers	Time of pituitary problems	Pituitary dysfunction	Skin	Pulmonary	Renal	ENT	Others
Patient 1	51	F	PR3-ANCA 92 U/ml (normal < 20 U/ml)	8 months after AAV diagnosis	Enlargement of pituitary with abnormal enhancement, irregular margin, thickening of pituitary stalk.	No	Yes	No	Yes	None
Patient 2	37	F	Negative	8 months after onset of AAV	Enlargement of pituitary with abnormal enhancement, protruding to the sellar.	No	No	No	Yes	Muscle
Patient 3	61	M	MPO-ANCA 146 U/ml (normal < 20 U/ml)	At onset of AAV	No abnormality in MRI. Increased linear radioactivity uptake in pituitary fossa in PET-CT.	No	Yes	Yes	No	Muscle, peripheral nerve

AAV, antineutrophil cytoplasmic antibody associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; ENT, ear, nose, and throat; MPO, myeloperoxidase; MRI, magnetic resonance image; PET-CT, positron emission tomography-computed tomography; PR3, proteinase 3.

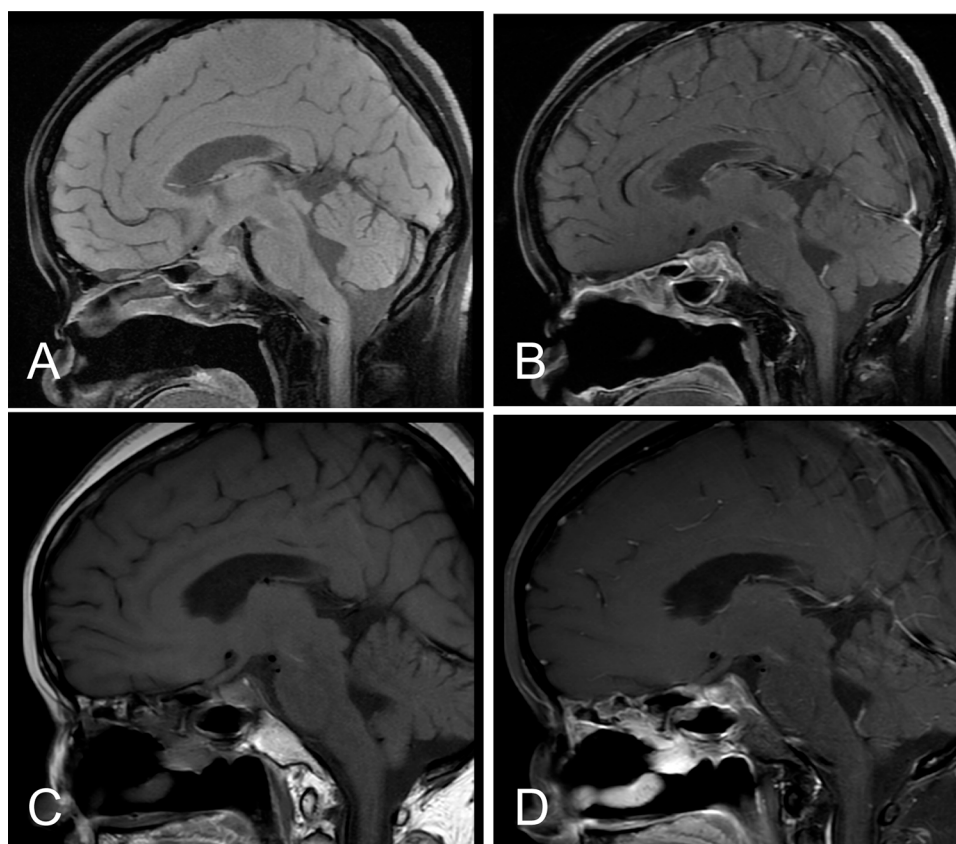
was used at 500 mg/d for 3 days and then MP was reduced back to 40 mg/d with administration of cyclophosphamide (CTX). The symptoms including headaches, nasal obstruction, running nose, and impaired vision were all relieved. Blood tests showed normal ESR and CRP, and negative PR3-ANCA. When MP was tapered to 20 mg/d, the patient had polydipsia, polyuria, blurred vision, and restricted eye abduction. Blood tests showed a high level of CRP and ESR, negative ANCA, and a low level of serum estradiol accompanied with inappropriately low follicle-stimulating hormone (FSH), prolactin and luteinizing hormone (LH) levels. No thyroid-stimulating hormone (TSH) deficiency in this patient [the level of serum free T<sub>4</sub> (fT<sub>4</sub>) was normal]. Pituitary MRIs showed a large pituitary and thickening of the pituitary stalk (Figure 1A, B). Pituitary biopsy was conducted. Pathological findings showed xanthogranuloma: inflammatory lesions with necrosis, swelling and denaturation of pituitary cells, and accumulation of foamy cells in the sphenoid region (Figure 2). This revealed necrotizing vasculitis invading pituitary tissue. Following this, MP was given as 40 mg/d, and cyclosporin was added as second-line drug. The clinical symptoms were gradually resolved, and blood tests showed normal, negative PR3-ANCA. Pituitary MRIs showed no enlargement or abnormal enhancement in the pituitary (Figure 1C, D).

The second patient was a 37-year-old female who had nasal obstruction, headache, and fever as the initial symptoms. She underwent functional endoscopic endonasal sinus surgery and the pathological findings were consistent with necrotizing granulomatous inflammation. Approximately 8 months later, she had galactorrhea. Approximately 3 months later she underwent amenorrhea and had irregular menstruation after progesterone treatment. Pain and swelling occurred in her left leg. Blood tests showed ESR 94 mm/h, CRP 8.55 mg/dl, ANCA negative, a high level of prolactin (845.71 mIU/ml, normal: 70.808–566.464 mIU/L), a slight low level of fT<sub>4</sub> (0.924 ng/dL, normal: 0.93–1.7 ng/dl), and normal TSH. The level of estradiol, LH, FSH, and growth hormone was normal. A pituitary MRI demonstrated pituitary enlargement (Figure 3A, B). A muscle biopsy of the left leg confirmed small vessel vasculitis. The therapy was MP at a dose of 40 mg/d, as well as CTX. When immunoglobulin dropped, considering the high risk of infection, CTX was replaced by azathioprine (50 mg per day). CTX was used for almost 4 months.

**Table 2.** Treatment and outcomes of AAV patients with pituitary dysfunction.

Case	Immunosuppressive therapy	Hormone replacement	Outcome
1	PD-GC followed by HD-GC+CTX+CsA	Desmopressin	Remission
2	HD-GC+CTX replaced by AZA	Progesterone	Remission
3	PD-GC followed by HD-GC+CTX	Desmopressin	Partial remission

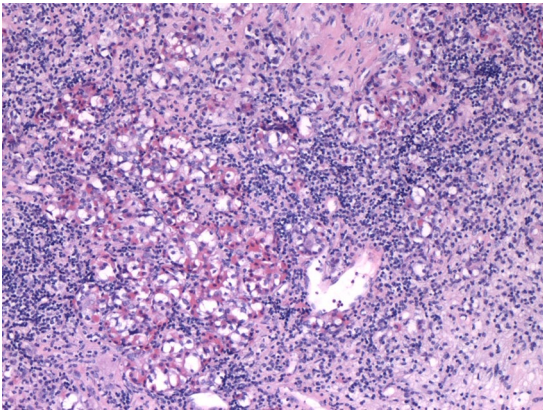
AAV, antineutrophil cytoplasmic antibody associated vasculitis; AZA, azathioprine; CsA, cyclosporin A; CTX, cyclophosphamide; HD-GC, high-dose glucocorticoid; PD-GC, pulse-dose glucocorticoid.



**Figure 1.** Magnetic resonance image scans of patient one. (A) Sagittal pituitary T1-weighted MRI showing an enlargement of the pituitary measuring 12 mm × 28 mm. (B) Sagittal pituitary T1-weighted MRI after intravenous administration of gadolinium showing enhancement of the enlarged pituitary. Sagittal pituitary T1-weighted MRI before (C) or after (D) intravenous administration of gadolinium showing no enlargement or abnormal enhancement in the pituitary after 1 month of treatment.

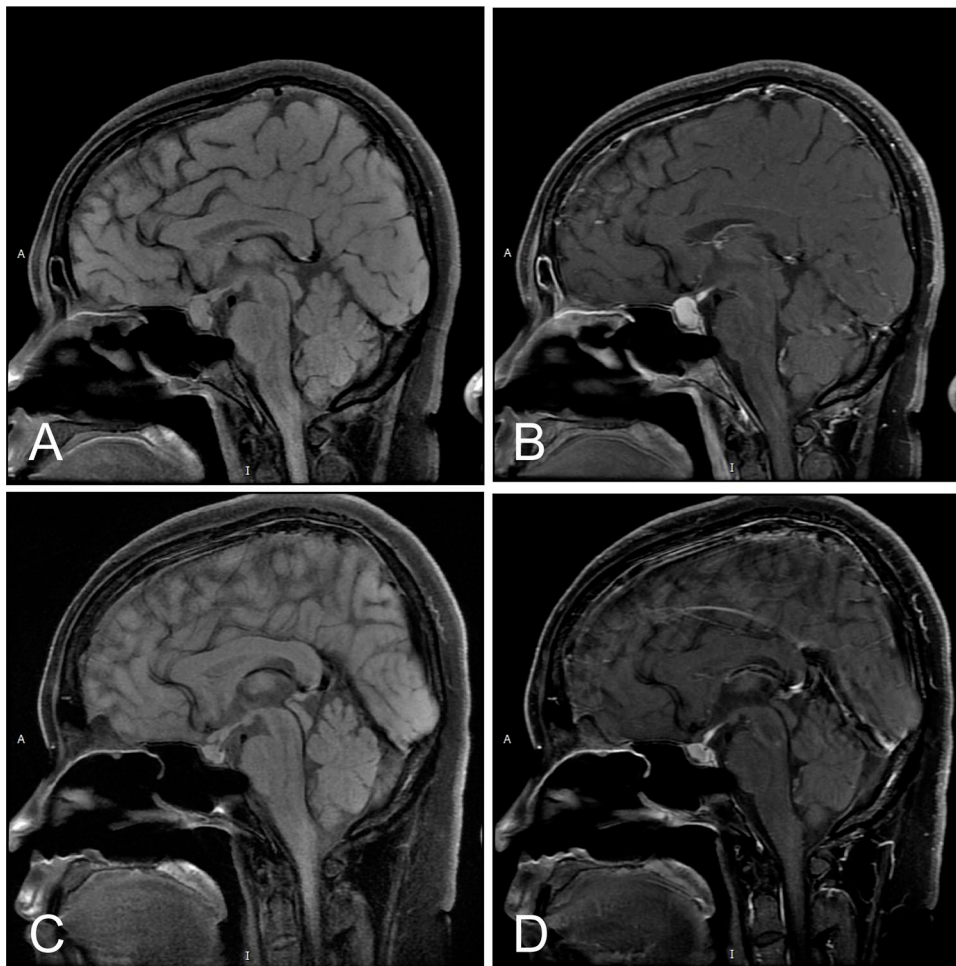
Azathioprine was started when CTX was stopped. The fever and pain resolved. The menstrual cycle partially recovered. ESR, CRP, fT4, and prolactin were back to normal 1 month later. After 2 months, the pituitary MRI revealed a smaller pituitary than before (Figure 3C, D).

The third patient was a 61-year-old male. The initial symptoms were polydipsia and polyuria, with erectile dysfunction subsequently, diagnosed as central diabetes insipidus (CDI) by the local hospital based on water deprivation test. Desmopressin could relieve polydipsia and polyuria. However,

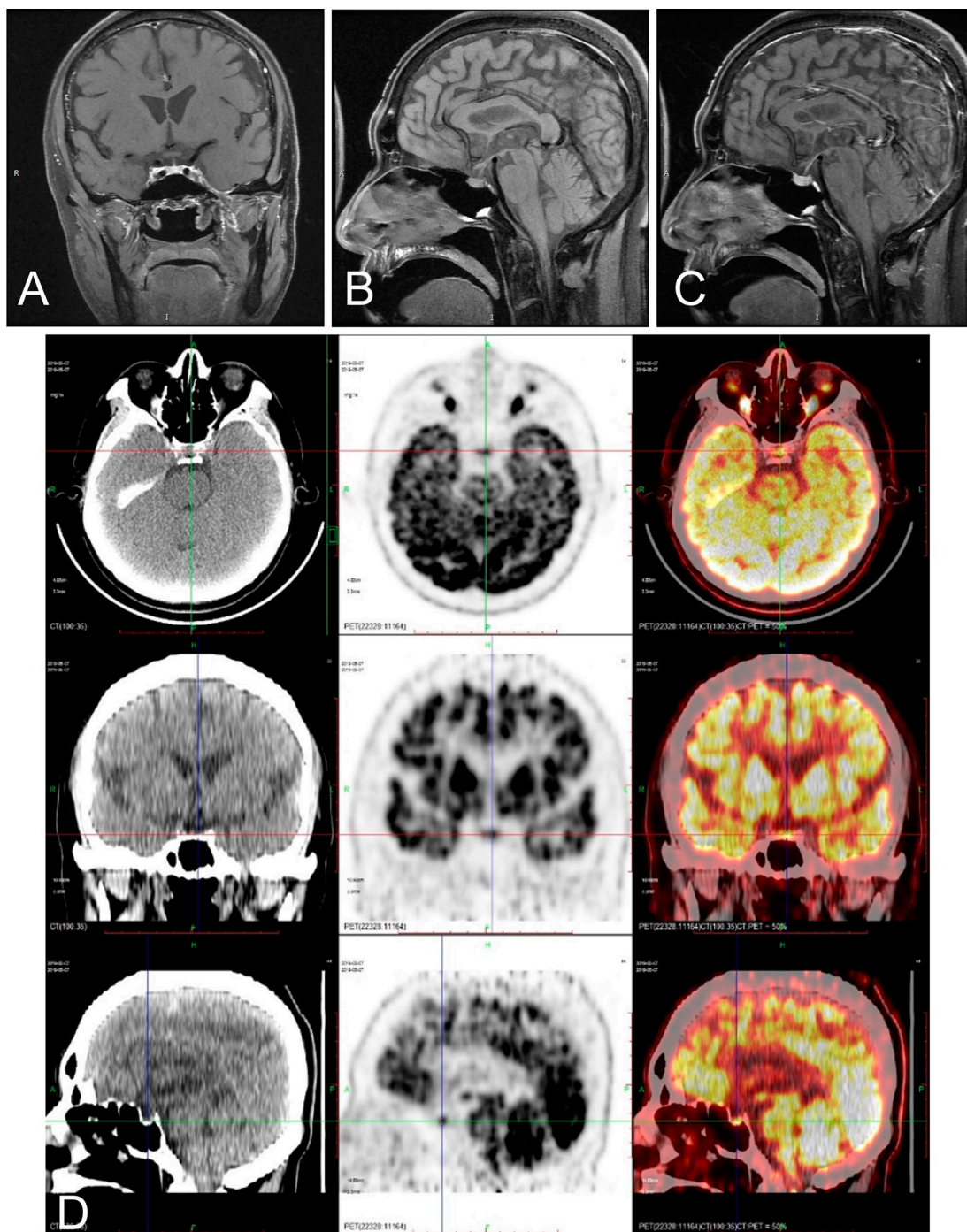


**Figure 2.** The pituitary pathological images of patient one. The pituitary pathology showed inflammatory lesions with necrosis, swelling and denaturation of pituitary cells, and accumulation of foamy cells.

6 months after the initial symptoms, he had pain in the bilateral calf muscles and numbness on both feet. Blood tests showed WBC  $9.27 \times 10^9/L$ , ESR 104 mm/h, CRP 15.6 mg/dl ( $<0.8$ ), CR 268.3  $\mu\text{mol/L}$ , microscopic hematuria, 24h urinary protein 1.04g, ANA 1:80, MPO-ANCA 146 U/ml, LH (40.84 mIU/ml normal: 1.24–8.62 mIU/mL), and prolactin (853.8 mIU/ml, normal: 55.968–278.356 mIU/L). The levels of testosterone, estradiol and fT4 were normal. A pituitary MRI showed no specific damage (Figure 4A, B, C). However, PET-CT displayed increased fluorodeoxyglucose (FDG) uptake in the pituitary fossa (Figure 4D). MP at 40 mg/d was given to the patient; however, he had oliguria and creatinine increased to 332.3  $\mu\text{mol/L}$  in 2 days. Renal pathology suggested that the AAV related renal injury



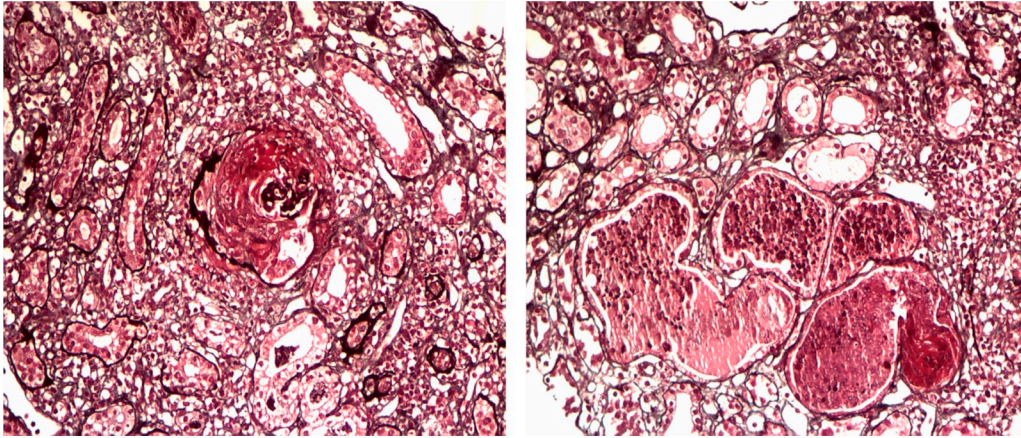
**Figure 3.** Magnetic resonance image (MRI) scans of patient two. (A) Sagittal pituitary T1-weighted MRI showing pituitary enlargement, with a height of 12mm. (B) Sagittal pituitary T1-weighted MRI after intravenous administration of gadolinium showing enhancement of the enlarged pituitary. Sagittal pituitary T1-weighted MRI before (C) or after (D) intravenous administration of gadolinium showing a smaller pituitary after 2 months of treatment.



**Figure 4.** MRI scans and PET-CT of patient three. Corona (A), sagittal (B) and gadolinium enhancement (C) pituitary T1-weighted MRI showing no abnormalities. (D) PET-CT showed increased linear radioactivity uptake in the pituitary fossa, SUVmax=7.5. MRI, magnetic resonance image; PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value.

was consistent with ischemic renal injury and sub-acute tubular interstitial nephropathy, while crescentic glomerulonephritis was also found in the kidney biopsy (Figure 5). The kidney potentially

had severe damage so a steroid impulse therapy with MP at 500mg/d for 3 days was prescribed. Then, MP was reduced to 80mg/d with 0.4 g CTX every 2 weeks. The polydipsia and polyuria



**Figure 5.** The kidney pathological images of patient three. Crescentic glomerulonephritis was found in the kidney biopsy.

disappeared, and pain was relieved in both lower limbs. PET-CT showed decreased FDG uptake in the pituitary fossa after 2 months of immunosuppression therapy (Figure 6).

### Discussion

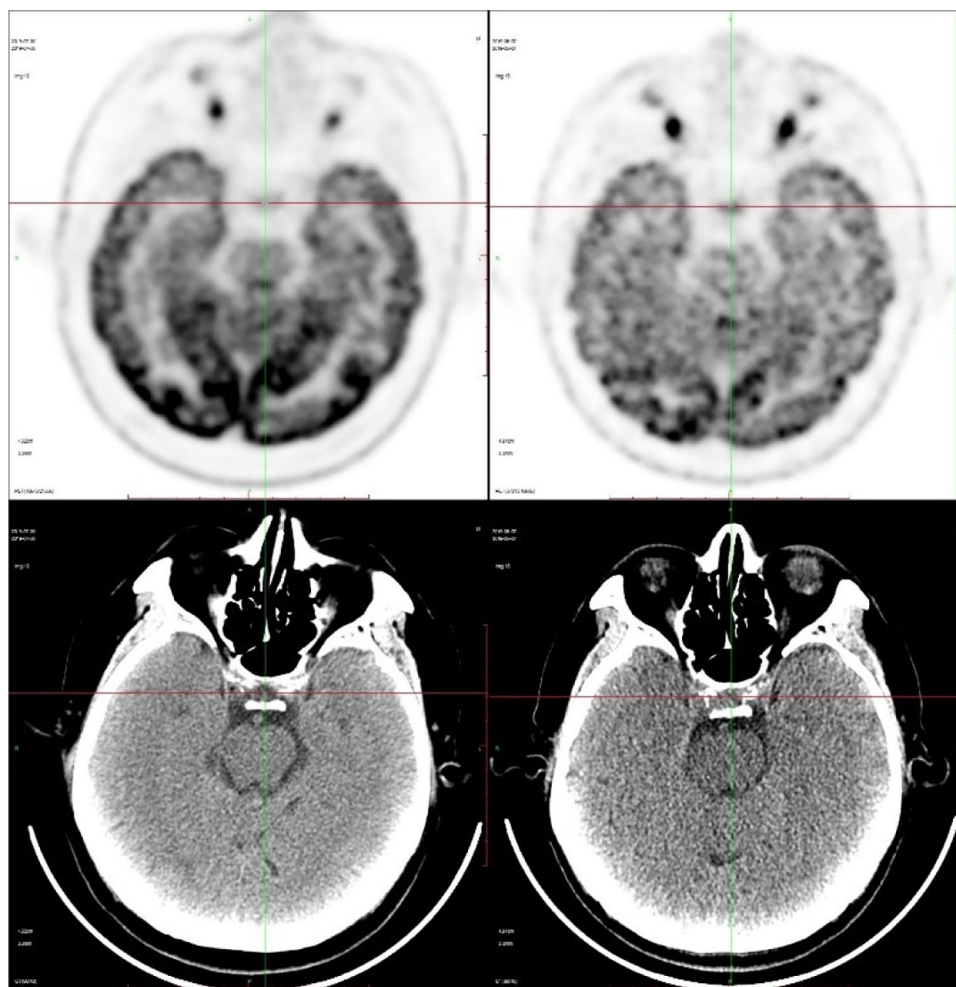
Pituitary dysfunction is an uncommon complication of AAV. In this study, only 2% AAV patients (3/150) could be confirmed as having pituitary involvement. A recently published study showed the incidence rate of pituitary involvement in GPA was 3.9%,<sup>11</sup> which was slightly higher than our data. A retrospective series of 819 GPA patients reported pituitary involvement in 1.1%.<sup>10</sup> One large longitudinal cohort research indicated the ratio was 1.3%.<sup>9</sup> There has been no research about pituitary involvement in MPA or EGPA. In our study, two out of the three patients had an ANCA positive status; one was PR3-ANCA positive and diagnosed with GPA and one was MPO-ANCA positive and diagnosed with MPA. Another patient was GPA, confirmed by manifestations and histopathology.

Pituitary dysfunction can occur before or after other organs are involved. Our study showed that one patient had pituitary involvement as the initial symptom. The other two patients had pituitary problems 5 and 8 months after onset, respectively. One case series reported pituitary dysfunction was concomitant in one case, and the other eight patients were diagnosed after the diagnoses of GPA.<sup>10</sup> Another longitudinal cohort study revealed one in eight pituitary involvement

GPA patients presented with pituitary dysfunction as the first manifestation.<sup>9</sup> Pituitary lesions occur mainly in the course of AAV and rare as the first symptom.

The main symptoms of pituitary involvement were polydipsia, polyuria hypogonadism, galactorrhoea, and amenorrhoea. Blood tests showed aberrant gonadotropin and prolactin. CDI and hypogonadotropic hypogonadism were the prominent manifestations reported in GPA patients with pituitary involvement, reported as patients suffering with polyuria, polydipsia, decreased libido, and erectile dysfunction.<sup>9,10,18,19</sup> Hyperprolactinemia and galactorrhoea can occur when the pituitary stalk is compressed by granulomatous inflammation.<sup>20</sup>

Besides hormone detection, imaging plays an important role in confirmation of pituitary dysfunction.<sup>21–24</sup> In our study, two patients had an enlarged pituitary, abnormal strengthening of the pituitary, and thickening of the pituitary stalk shown in pituitary MRIs. Enlarged pituitary gland, enhancement of the periphery of the pituitary gland, sellar mass, and pituitary mass were the most common lesions in MRIs.<sup>24–26</sup> Patient three had a normal pituitary MRI image. However, PET-CT showed increased linear radioactivity uptake in the pituitary fossa. Other scientists have used PET-CT, getting positive findings in the pituitary fossa of AAV patients.<sup>27,28</sup> Therefore, PET-CT offers an additional diagnostic tool in certifying pituitary involvement in AAV patients.



**Figure 6.** PET-CT of patient three before and after treatment. The left panel shows more linear radioactivity uptake in the pituitary fossa before immunosuppression therapy (SUVmax=7.5). The right panel shows a lower increase in linear radioactivity uptake in the pituitary fossa after 2 months of treatment (SUVmax=5.4). PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value.

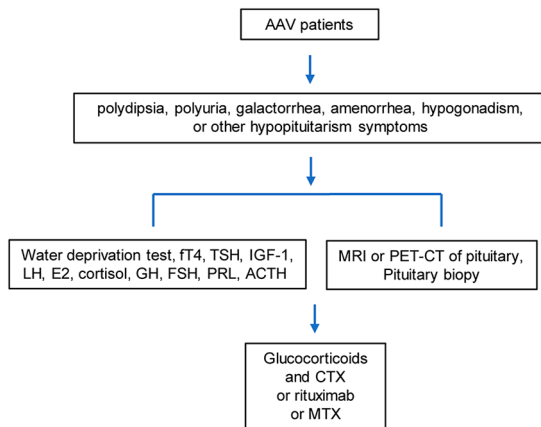
Classical induction therapies for systemic vasculitis are commonly used to treat pituitary dysfunction in GPA patients. According to 2017 recommendations for the induction therapy of AAV, glucocorticoids and CTX should be used in AAV patients with active disease.<sup>29</sup> Rituximab and methotrexate are alternatives to cyclophosphamide in the induction therapy in AAV patients.<sup>29</sup> All three patients were given glucocorticoids and CTX at the onset of treatment. One female patient added cyclosporine when she had pituitary involvement. Another female patient replaced CTX with azathioprine when her immunoglobulin dropped. All of them had clinical alleviation. One female patient had a smaller pituitary, displayed in pituitary MRIs. The male patient had lower increased linear

radioactivity uptake in the pituitary fossa after 2 months of treatment.

Furthermore, we also compared with the commonalities and differences between our study cases and those published (shown in supplementary). According to our cohort characteristics and other previous studies, a diagnostic and treatment algorithm for sellar dysfunction in patients with AAV was created (Figure 7).

As a retrospective study, the present study has several limitations. First, this study is a cohort study in which there were no large number of cases from a single center. The incidence might not be investigated accurately. However, each





**Figure 7.** Diagnostic and treatment algorithm for sellar dysfunction in patients with AAV. When AAV patients have hypopituitarism symptoms, water deprivation test, hormones checking, scanning pituitary with MRI or PET-CT, as well as pituitary biopsy should be performed. Glucocorticoids and CTX are recommended in AAV patients with sellar dysfunction. Rituximab and MTX are alternatives to cyclophosphamide.

AAV, antineutrophil cytoplasmic antibody associated vasculitis; ACTH, adrenocorticotropic hormone; CTX, cyclophosphamide; E2, estradiol; FSH, follicle-stimulating hormone; ft4, serum free T<sub>4</sub>; GH, growth hormone; IGF-1, insulin-like growth factors-1; LH, luteinizing hormone; MRI, magnetic resonance image; MTX, methotrexate; PET-CT, positron emission tomography-computed tomography; PRL, prolactin; TSH, thyroid-stimulating hormone.

case was described in detail in our study. This may be helpful to illustrate the characteristics of the disease. Second, not all patients had pituitary biopsy. Patient two had surgery twice at another hospital, but neither of the original pathological reports were present. Past medical records showed necrotizing granulomatous inflammation in the pituitary. Lastly, as a retrospective study, there was no rigorous before-and-after analysis of each case. Although each case had major blood test and imaging examinations, some hormones, like FSH and LH, were not tested regularly in patient one. It is a pity that we did not use the IGF-1 to ascertain pituitary dysfunction. IGF-1 will be detected in the future clinical study.

In conclusion, pituitary involvement is uncommon in AAV. It can occur at any stage over the course of AAV, even before the typical lung and kidney features. Therefore, AAV should be considered in the differential diagnosis of pituitary dysfunction. Furthermore, pituitary lesions can appear in GPA as well as MPA patients. The

main clinical manifestations are CDI and panhypopituitarism. Patients may suffer with polyuria, polydipsia, galactorrhea, amenorrhea, decreased libido, and erectile dysfunction. As an additional diagnostic tool, PTE-CT could help identify pituitary involvement in AAV patients when there are no findings in MRIs. Immunosuppressive therapy could significantly alleviate clinical symptoms, as well as pituitary imaging.


### Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Youth Program of the National Natural Science Foundation of China [grant numbers 81401363, 81601367], the Major Research Plan of the National Natural Science of China [grant number 91542121], and the Capital Health Research and Development of Special Programs [grant number 2014-4-4062].

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### Supplemental material

Supplemental material for this article is available online.

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