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REVIEW

Central nervous system involvement in ANCA-associated vasculitis

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ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) are rare but heterogeneous disorders. Although central nervous system (CNS) involvement is relatively uncommon, it is associated with substantial morbidity. Neurological involvement in AAV spans a broad spectrum. Diagnosis relies on clinical findings together with imaging—magnetic resonance imaging (MRI) being the mainstay—with dural thickening and characteristic signal changes serving as distinguishing features. When indicated, cerebrospinal fluid (CSF) analysis and tissue biopsy increase diagnostic certainty. On clinicoradiologic grounds, two principal phenotypes can be recognized: a granulomatous phenotype (pachymeningitis, intracranial granuloma, hypophysitis) and a vasculitic phenotype (ischemic/hemorrhagic stroke). These phenotypes may differ in immunologic underpinnings, clinical manifestations, therapeutic response, and prognosis. Induction therapy typically consists of high-dose corticosteroids combined with cyclophosphamide or rituximab, followed by long-term maintenance immunosuppression. Recognizing relationships between clinicoradiologic CNS subtypes and accompanying clusters of extra-CNS organ involvement may provide important clues for diagnostic evaluation and management.

Keywords: Anti-neutrophil cytoplasmic antibody–associated vasculitides, central nervous system, neurological involvement.

INTRODUCTION

Central nervous system (CNS) vasculitis poses a significant diagnostic challenge for clinicians due to its rarity and the heterogeneity of its clinical presentation. CNS vasculitides may arise as disorders confined to the CNS—termed primary CNS vasculitis [1]—or occur as part of a systemic vasculitic process. Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) constitute a heterogeneous group of vasculitides with an annual incidence of approximately 20 per million population [2]. This category encompasses three diseases: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA).

Neurological involvement in AAV spans a broad spectrum, including mononeuritis multiplex, sensory neuropathy, cranial nerve abnormalities, intracranial mass lesions, external ophthalmoplegia, and sensorineural hearing loss [3,4]. Peripheral nervous system involvement is common, reported in 20–65% of patients [5]. By contrast, central nervous system (CNS) involvement is observed in <15% of AAV cases [6]. It frequently appears early in the disease course; in some series, CNS manifestations were among the initial presentations in 33–86% of affected patients [5]. In certain studies, the rates are inflated because cranial nerve palsies were counted as CNS involvement; when these are excluded, the actual frequency of CNS disease in GPA is approximately 7–11% [7]. Although relatively uncommon, CNS involvement is associated with substantial morbidity [6].

Neurological manifestations vary according to the underlying histopathological pattern and the

specific anatomical structures involved. Clinically, CNS involvement in AAV is most often categorized into three patterns: cerebrovascular involvement, pituitary involvement, and leptomeningeal/dural involvement [4,8,9]. From a histopathologic standpoint, three principal patterns are recognized: (i) vasculitis of small vessels within the brain and spinal cord; (ii) contiguous invasion by granulomas arising from extracranial sites; and (iii) isolated intracranial granulomatous lesions (parenchymal or meningeal) [7]. On clinicoradiologic grounds, a distinction is commonly made between a granulomatous phenotype (pachymeningitis, intracranial granuloma, hypophysitis) and a vasculitic phenotype (ischemic/hemorrhagic stroke) [7]. Putative immunologic differences have been reported between these phenotypes, with Th1 predominance associated with the granulomatous pattern and Th2 skewing linked to the vasculitic pattern [10]. This dichotomy may influence therapeutic response and guide the selection of immunosuppressive agents [11].

In AAV, extra-CNS organ manifestations often predominate, and the heterogeneity of CNS findings can delay both diagnosis and treatment. Accordingly, recognizing the relationships between clinicoradiologic CNS subtypes and accompanying clusters of extra-organ involvement may yield important clues for diagnostic evaluation and clinical management. This review summarizes the patterns of CNS involvement in AAV, outlines plausible pathogenetic mechanisms, and highlights contemporary therapeutic approaches.

Spectrum of Clinical and Imaging Findings in CNS Involvement of AAV

1) Leptomeningeal/Dural Axis and Hypertrophic Pachymeningitis (HP)

Among the clinical patterns of AAV-related CNS disease, leptomeningeal involvement is the most frequently reported [7]. Hypertrophic pachymeningitis (HP) is a rarer, chronic inflammatory condition characterized by localized or diffuse thickening of the dura mater with inflammation extending to adjacent CNS structures. The etiologic spectrum includes autoimmune disorders as well as neoplasms, trauma, and infections. On leptomeningeal histopathology, findings may comprise granulomatous inflammation, collagen fiber proliferation, vasculitic lesions, and areas of necrosis [12].

Epidemiology and Classification of ANCA-Related Hypertrophic Pachymeningitis (HP)

Much of the available evidence on ANCA-related HP derives from single-center, retrospective series reported from East Asia [12,13]. A methodological challenge is that a subset of cases do not fulfill formal AAV classification criteria: in the literature, 14–16% of HP cases linked to AAV could not be classified as "vasculitis" [12–14]. This observation suggests that, in some patients, HP may represent the first and/or sole manifestation of AAV. Indeed, in GPA-associated HP, HP was reported as the initial presentation in ~60% of cases [9]. Several reports propose that ANCA-positive isolated HP can be classified as CNS-limited AAV [6,13].

Autoantibody profiles are heterogeneous. While De Luna et al. [7] found proteinase- 3 ANCA (PR3-ANCA) to predominate among patients with craniospinal pachymeningitis, other series have reported myeloperoxidase ANCA (MPO-ANCA) predominance [13,15–19]. Imafuku et al. [19] estimated that the incidence of AAV-related HP is higher in GPA than in MPA (60.2 vs 3.3 per 1000 patient-years). In the multicenter cross-sectional J-CANVAS cohort, among patients with HP, the proportions of GPA and MPA were similar in both new-onset and relapsing AAV [20]. However, in the overall AAV cohort, GPA classification was more frequent among those with HP than among those without HP; furthermore, among newly diagnosed AAV patients, PR3-ANCA positivity was significantly higher in those with HP [20]. In J-CANVAS, HP was identified in 4.52% (30/663) of AAV patients overall—3.58% (20/558) at the time of new diagnosis and 9.52% (10/105) at relapse [20].

Yokoseki et al. [13] reported that MPO-ANCA-positive HP is more common in older patients and women; this subgroup tends to have lower modified Rankin Scale (mRS) scores, milder neurological injury, lower disease activity, and less frequent progression to generalized disease. Shimojima et al. [20] demonstrated that among newly diagnosed AAV patients, those with HP had a higher prevalence of PR3-ANCA positivity. In summary, MPO-ANCA–

positive HP cases tend to align with CNS-limited AAV, whereas PR3-ANCA–positive cases—though they may initially appear CNS-limited—are more prone to evolve into systemic disease [12,20].

Clinical manifestations in ANCA-associated HP

The presentation varies with the location and extent of inflammation; headache, seizures, cranial neuropathies, and motor dysfunction are common. In granulomatous forms, headache is often severe and refractory to analgesics, typically without meningismus [21]. Dural thickening around cranial nerves can cause compressive/ischemic injury, leading to vision loss, diplopia, or facial palsy. In ANCA-associated HP, cranial neuropathies of virtually all types may occur—except those involving the olfactory nerve (CN I). Additional manifestations include pituitary dysfunction, cerebellar ataxia, myelopathy, papilledema, optic neuropathy, visual field defects, and even blindness [13]. Spread of pachymeningeal inflammation to adjacent parenchyma may precipitate altered consciousness and seizures [6,13].

Imaging findings in ANCA-associated HP

Cranial pachymeningitis may involve the tentorium cerebelli, cranial fossae, cavernous sinus, falx cerebri, and the cerebral convexities without a consistent site predilection. MRI/CT are essential for detecting hypertrophic dural thickening, monitoring disease activity, and assessing damage to adjacent structures [6]. On MRI, diffuse dural thickening with contrast enhancement and central hypointensity may be seen; on coronal, contrast-enhanced T1-weighted images this appearance has been described as the "Eiffel-by-night" sign [22]. The involved dura typically exhibits marked hypointensity on T2-weighted sequences, supporting the presence of a fibrous component [23]. MRI also facilitates evaluation of sinonasal and orbital structures, which are commonly affected in AAV.

Histopathologic findings in ANCA-associated HP

Autopsy/biopsy of pachymeningitic dura mater demonstrates increased T cells, neutrophils, eosinophils, plasma cells, and monocytes/macrophages, suggesting Th1-predominant granulomatous lesions, akin to those described in GPA lung or kidney involvement [13]. In meningeal tissue obtained from GPA patients with leptomeningeal disease, Di Comite et al. [24] most commonly observed necrotizing granulomatous inflammation (61.5%), followed by concomitant granulomatosis with vasculitis (15.4%) and small-vessel vasculitis (7.7%); nonspecific lymphocytic inflammation was present in 11.5%.

In ANCA-associated HP, CSF analysis typically shows mild to moderate pleocytosis with elevated protein and an increased IgG index [12]. TGF-β1 levels are elevated in immune-mediated HP—including ANCA-related forms—and have been implicated in the fibrosis of the thickened dura mater [14]. Members of the TNF superfamily, BAFF and APRIL, are also increased in CSF, correlate positively with the IgG index, and support the possibility of intracranial B-cell activation within the CNS [14,25–30]. Their decline in parallel with clinical improvement suggests that CSF BAFF/APRIL may serve as candidate CSF biomarkers of disease activity in AAV-related CNS involvement [31].

Association Between Disease Activity and Extra-Organ Involvement in ANCA-Associated HP

Several single-center AAV series have reported lower Birmingham Vasculitis Activity Score (BVAS) in patients with HP compared with those without HP [32–34]. In contrast, the J-CANVAS study found no significant differences in disease activity scores between patients with and without HP, whether at the time of new onset or relapse [20]. Ear, nose, and throat (ENT) and mucosal/ocular involvement have been confirmed to be associated with the development of HP [20]. Approximately 30% of patients with otitis media–associated AAV (OMAAV) develop HP [35–37]. HP lesions most commonly involve the middle cranial fossa, followed by the internal acoustic canal, tentorium cerebelli, and posterior cranial fossa—regions that are frequently contiguous with primary middle-ear pathology [36]. Accordingly, HP in OMAAV may reflect locally contiguous CNS disease rather than a purely systemic manifestation [38]. Notably, conductive hearing loss related to otitis media and sudden vision loss were associated with HP development in a multicenter AAV cohort [20].

Conversely, the incidence of cutaneous and renal involvement is lower in patients with HP [20]. In AAV, granulomatous inflammation tends to be accentuated in the upper and lower airways and, plausibly, the meninges through contiguous spread, whereas necrotizing vasculitis targets small- to medium-sized vessels and is more closely linked to renal involvement and mononeuritis multiplex; therefore, a weak association between HP and these latter manifestations is anticipated [20,39,40].

Prognosis and Treatment of ANCA-Associated HP

CNS involvement in AAV—particularly in the presence of meningeal inflammation or retro-orbital disease—is regarded as organ-threatening [6]. For induction therapy in ANCA-associated HP, high-dose corticosteroids are recommended: 0.5–1.0 g/day intravenously for three consecutive days, followed by oral corticosteroids at 0.5–1 mg/kg/day with a structured taper [12]. Corticosteroid monotherapy is insufficient for sustaining remission [12]. In granulomatous GPA—for example, orbital masses, subglottic/tracheobronchial stenosis, and/or pachymeningitis—clinical responses to rituximab may be less consistent, less complete, and/or more delayed compared with cyclophosphamide [41–44]. Consistent with this, the French vasculitis guideline recommends cyclophosphamide as first-line therapy for manifestations that include pachymeningitis within the spectrum of orbital mass or tracheal stenosis [11].

For remission maintenance, combinations of a low-dose glucocorticoid with an immunosuppressive agent such as azathioprine, methotrexate, mycophenolate mofetil, or rituximab are used [45]. During maintenance immunosuppression, relapse of ANCA-associated HP has been observed in approximately 8–57% of patients [12]. De Luna et al. [7] found that the presence of spinal cord pachymeningitis was significantly associated with the need for a new induction regimen due to relapse or refractory disease. In contrast, cerebral pachymeningitis tended to require retreatment less frequently. Rituximab may be employed when relapse occurs or in a refractory course [11]. Its efficacy in refractory HP has also been reported [33,46,47], supporting rituximab as a reliable option, particularly in patients resistant to standard therapy [12]. In patients presenting with HP as an isolated manifestation of AAV, the use of methotrexate in combination with corticosteroids is suggested as a beneficial option [48,49]. Given the potential severity of neurological involvement and the risk of relapse/refractoriness, prolonged maintenance therapy (>36 months) should be implemented, as it has been associated with a 66% reduction in relapse risk [7,50].

In patients with ANCA-associated HP, adding an immunosuppressive agent to corticosteroids during remission induction is preferable [12]. This combination both reduces relapse risk and facilitates effective steroid tapering. The choice of immunosuppressant should be individualized based on the patient's clinical context, including coexisting organ involvement and overall disease severity.

2) Pituitary Involvement

Pituitary involvement is an uncommon manifestation, reported in 1.1–3.9% of patients with GPA [6,51–53]. Proposed mechanisms include contiguous granulomatous invasion from neighboring structures (e.g., the ENT region, orbit, and meninges), primary vasculitis of the pituitary gland, or in situ granulomatous formation within the gland itself [54]. Thickened dura surrounding the cavernous sinus and optic nerves may be associated with pituitary dysfunction, visual loss, and cranial neuropathy [12]. Constitutional symptoms such as fatigue, malaise, headache, weight loss, and anorexia are frequent. GPA-associated hypophysitis can result in partial or global hypopituitarism. Central diabetes insipidus and hypogonadotropic hypogonadism are prominent endocrine features. Enlargement of the pituitary may compress the pituitary stalk, leading to hyperprolactinemia, while visual impairment typically results from compression of the optic chiasm [6].

The differential diagnosis of pituitary involvement in GPA includes other infectious and inflammatory granulomatous disorders, such as tuberculosis, sarcoidosis, Crohn's disease, and giant cell arteritis, as well as primary hypophysitis, particularly the lymphocyte-predominant variant [4]. MRI abnormalities are present in up to 90% of cases [55], although a normal MRI does not exclude pituitary involvement in some patients [53]. A brain MRI typically demonstrates an enlarged pituitary

gland or a thickened pituitary stalk with peripheral enhancement on post-contrast sequences. Loss of the posterior pituitary bright spot on T1-weighted images is another characteristic finding [6]. HP frequently involves the falx cerebri and tentorium cerebelli; involvement around the cavernous sinus is less common, and when present on imaging, should raise suspicion for pituitary dysfunction [51]. If there is concurrent extra-organ involvement and the clinical–serologic profile strongly supports GPA, histologic confirmation may not be required [4].

Pituitary disease in GPA is treated with the standard induction regimens used for systemic vasculitides. Although clinical remission has been reported in up to 69% of patients receiving one of these immunosuppressive approaches, relapse rates are lower when cyclophosphamide is used as the initial agent compared with alternatives [4,53]. In pituitary disease where granulomatous inflammation predominates—and given that rituximab's efficacy is more pronounced against the vasculitic component—cyclophosphamide is generally preferred over rituximab [53]. Pituitary enlargement may regress following immunosuppressive therapy [51]; however, long-term hypopituitarism frequently persists despite clinical and radiologic remission, and lifelong hormone replacement may be necessary in some cases [4].

3) Brain Parenchymal Involvement

Cerebrovascular events

As in other systemic vasculitides, AAV can cause inflammation of the CNS vasculature [4,9]. Clinico-radiologically, this corresponds to a vasculitic phenotype, which differs markedly from the granulomatous type in terms of presentation and prognosis [7]. Ischemic infarctions and intracranial hemorrhages, although uncommon, may represent the initial clinical manifestation of AAV and are invariably associated with substantial morbidity [6].

Ischemic infarctions typically present as isolated or multiple white matter lesions, reflecting predominant involvement of distal penetrating vessels. They are the most common ischemic complications and may manifest as transient ischemic attack or stroke with motor deficits, ischemic myelopathy, encephalopathy, cognitive impairment and dementia, mood disorders, seizures, and cortical blindness [4]. These events are characteristically refractory to antiplatelet therapy and tend to recur in the absence of appropriate immunosuppression [6]. Compared with patients who have cerebral pachymeningitis or pituitary involvement, those with a vasculitic cerebrovascular phenotype are at higher risk of neurological sequelae and of hemorrhagic transformation following reperfusion therapy for ischemic stroke [7,56].

Patients with AAV—particularly early in the disease course—have an increased risk of stroke and venous thromboembolism [57]. Although stroke incidence is higher than in the general population, it can be challenging to determine whether these events reflect vasculitic involvement or atherosclerosis-related mechanisms [5]. In addition, many patients receive long-term, high-dose glucocorticoids, which may exacerbate the intrinsic vascular fragility of AAV and thereby increase the risk of vascular events [58]. Features supporting a vasculitic etiology include a younger age, the absence of traditional atherosclerotic risk factors, concurrent AAV activity in other organ systems, and cranial imaging that demonstrates subacute and hemorrhagic acute ischemic lesions of varying ages and vascular territories [5]. In the series by De Luna et al. [7], no patients adjudicated as having a vasculitic CNS phenotype were MPO-ANCA–positive, whereas all were PR3-ANCA–positive.

Hemorrhagic events are less common but most often involve the brain parenchyma, and occasionally the subarachnoid space [6]. In a pooled review of AAV-related intracranial hemorrhage cases by Achkar et al. [59], EGPA—despite being the least prevalent of the three major AAV subtypes—emerged as the most frequently represented subtype among AAV-associated intracranial hemorrhage. CNS involvement in EGPA has been reported in 5–20% of cases and is thought to be partially related to eosinophil-mediated neurotoxicity [60,61]. Among patients with AAV-related CNS hemorrhage, cytoplasmic ANCA (c-ANCA) positivity has been identified significantly more often than perinuclear ANCA (p-ANCA) staining [59]. Management of ANCA-associated CNS ischemic and hemorrhagic events parallels the therapeutic approach used for other severe, organ-threatening manifestations of GPA and MPA.

Posterior Reversible Encephalopathy Syndrome (PRES)

Case reports have documented PRES in patients with AAV [62,63]. Clinically, onset is typically acute, with symptoms most commonly including encephalopathy, seizures, headache, and visual disturbances [6]. PRES has been associated with hypertension, eclampsia, renal insufficiency, immunosuppressive medications, and connective tissue diseases [62]. Brain imaging characteristically demonstrates findings consistent with vasogenic edema, predominantly involving the bilateral parieto-occipital regions. In most cases, marked improvement occurs within days with supportive management alone.

Isolated Parenchymal Mass Lesion

In patients with GPA, intracranial parenchymal space-occupying lesions are rare [64]. Clinico-radiologically, they fall within the granulomatous phenotype (pachymeningitis, intracranial granuloma, hypophysitis) [7]. Parenchymal granulomas are thought to arise predominantly via vasculitis and disruption of the blood–brain barrier [13]. Clinical manifestations vary by lesion location, but seizures are the most common presenting feature [6,65]. On brain MRI, isolated parenchymal granulomas typically appear as a well-circumscribed mass, hyperintense on T2-weighted images with prominent enhancement on gadolinium-enhanced sequences [66].

Cognitive Impairment

Diffuse cerebral involvement has been reported in patients with small-vessel vasculitis and severe dementia and is considered a poor prognostic factor [67]. Cognitive deficits have also been described in AAV, and are thought to reflect underlying CNS involvement [6]. In patients with AAV, cognitive decline—most often subclinical and mild—may occur, with an estimated prevalence of ~30% [67]. On brain MRI, multiple white-matter lesions, typically located in the periventricular or juxtacortical regions, are frequently associated with these cognitive abnormalities [67].

Spinal Cord Involvement

Only a limited number of cases of ANCA-associated spinal pachymeningitis have been described, and available data suggest a female predominance, involvement of the cervical and thoracic segments, a nonspecific back-pain onset, and progression to motor and sensory deficits most consistent with thoracic myelopathy [68]. Three mechanisms may underlie spinal cord involvement: necrotizing inflammation of the spinal vasculature, compression of the cord by inflamed and thickened meninges, and the formation of primary spinal granulomas [69]. Li et al. [70] reviewed 12 AAV cases with spinal HP and reported that dural thickening was observed predominantly in the thoracic spine. Cases of myelopathy secondary to cord compression from thickened spinal dura have also been documented [12]. Contrast-enhanced spinal MRI has high diagnostic value, and biopsy is often required to confirm the diagnosis [6].

CONCLUSION

In summary, although CNS involvement in AAV is uncommon, it carries substantial morbidity, and its clinico-radiologic heterogeneity can delay diagnosis. By highlighting the leptomeningeal/dural axis (particularly hypertrophic pachymeningitis), pituitary disease, cerebrovascular events (ischemia/hemorrhage), isolated parenchymal granulomas, cognitive dysfunction, and the spectrum of spinal cord involvement, this review underscores the value of a phenotype-based approach. Induction with high-dose corticosteroids plus cyclophosphamide or rituximab, followed by prolonged maintenance immunosuppression, reduces the risk of relapse. Clinicians should remain mindful of the increased risk of vascular events and thromboembolism, antiplatelet refractoriness, and the possibility of hemorrhagic transformation after reperfusion. Finally, standardized diagnostic criteria, phenotype-specific treatment algorithms, and multicenter prospective cohorts are crucial for enhancing the quality of care and patient outcomes.

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