Central Nervous System Involvement in ANCA-Associated Vasculitis

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13.1 Introduction

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) involve small- and medium-sized vessels and can affect the central nervous system (CNS). In opposition to primary CNS vasculitis, extraneurological involvement is common and is helpful in the diagnosis approach. AAV-related CNS involvement is rare, but serious, and is associated with a poor prognosis. The final diagnosis is often clinically based and relies on recognition of extraneurological symptoms and serologies consistent with a diagnosis of AAV [1]. However, CNS involvement can be a diagnosis challenge when neurological manifestations are inaugural or isolated. A large workup is thus required. Occurrence of CNS manifestations in a patient followed for a AAV questions whether the process is linked to a specific vasculitis-related involvement or to another process, such as infection, drug toxicity, or malignancy. Many features are common to the three AAV-related CNS involvement, but some specific characteristics have to be highlighted.

13.2 General Characteristics of AAV Affecting the Central Nervous System

In granulomatosis with polyangiitis (GPA), CNS is involved in 7–11% of patients and probably less frequently in other AAV [2, 3]. In the study from Pinching et al., a rate of 44% was observed but peripheral nervous system was included in neurological involvement [4].

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R. A. Sinico, L. Guillevin (eds.), *Anti-Neutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis*, Rare Diseases of the Immune System,
https://doi.org/10.1007/978-3-030-02239-6_13

Different mechanisms have been described to explain GPA-related CNS involvement. Local extension from ophthalmological or sinus granulomatous lesions to the meninges, pituitary gland, or brain parenchyma is frequently reported. Otherwise, CNS vessels can be independently affected and/or isolated granulomatous lesions can develop within the brain or the spinal cord [1]. Isolated medullar involvement is exceptional [5]. Diagnosis of GPA-related CNS involvement is made in half of the patients at GPA onset and after diagnosis in other patients. In the study by de Luna et al., the median age at GPA diagnosis and onset of CNS involvement was 48 (range 2 78) and 51 (range 2 79) years, respectively, and 26 (74%) patients were male [6].

CNS involvement in eosinophilic granulomatosis with polyangiitis (EGPA) is rarer than in GPA, and may affect 4.6% of patients [7]. More than 85% of patients with EGPA-related CNS involvement showed neurological symptoms at diagnosis. Most cases regard patients in the fourth and fifth decade, and the sex ratio is 1 [7]. CNS involvement in EGPA is particularly associated with an increased mortality [7, 8]. In most patients, a vasculitic process affecting CNS vessels is responsible for neurological symptoms. CNS involvement could also be the consequence of eosinophil-mediated injury [7]. More rarely, myocardial fibrosis can lead to brain embolism, explaining the involvement of small perforant and subcortical arteries [9].

While peripheral neuropathy is common in microscopic polyangiitis (MPA), CNS involvement is rarely reported and no specific case series has been published. Affection of perforant arteries or intracranial hemorrhage has been described separately. Only few observations reported a biopsy-proven diagnosis, often in the setting of an important intracranial hemorrhage requiring a surgical treatment [10, 11].

13.3 Neurological Manifestations

Neurological symptoms in patients with AAV-related CNS involvement are widely polymorph and depend on the affected territory. Neurological onset can be acute in case of stroke or seizures. It can also be more chronic and insidious in patients with headaches, cognitive or vigilance disorders, or psychiatric manifestations.

Headaches are common and may affect 20–60% of the patients [6, 7]. Motor deficits are common (30–45% of patients) and are often explained by small to large brain infarction(s). Other neurological deficits can be observed, such as speech disorders (9% of patients), sensory deficits (16–43% of patients), or cerebellar ataxia (6% of patients) [6, 7]. Cranial nerve involvement may affect 20% of patients [7]. Encephalopathic presentations include confusion (11% of patients), psychiatric manifestations (mainly depression in 9–27% of patients), and vigilance troubles (rising from psychomotor slowdown to coma) [6, 7]. Seizures occur in 2% of patients with EGPA [7]. In the study by de Luna et al., two subgroups of GPA patients have been distinguished with different clinical presentations. Patients with granulomatous disease more likely suffered from headaches linked to pachymeningitis. Conversely, patients with predominant vascular pattern more likely developed neurovascular events with focal deficits linked to stroke on imaging [6]. Medullar

involvement has been rarely described and affect less than 10% of patients with CNS involvement [12]. In patients with GPA, involvement of the pituitary gland can compress the optic chiasm, resulting in partial visual loss. In GPA and EGPA, visual loss can also be the consequence of an optic neuritis [6, 7].

Besides neurological examination, other extraneurological involvements frequently associated with neurological symptoms should be searched. In GPA, ENT involvement was present in 80% of patients, pulmonary disease in 57%, and peripheral nervous system involvement in 49% [6]. At the time of EGPA-related CNS involvement, asthma, peripheral neuropathy, and cardiac involvement were also observed in 98%, 55%, and 41% of patients, respectively [7].

13.4 Imaging

CT scan is often the first imaging performed, but has a poor sensitivity and specificity. Magnetic resonance imaging (MRI) is required in all patients, even in patients with abnormal CT scan. When available, vascular sequences should also be performed.

MRI analysis should include the following sequences: T1, T2, T2∗, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI)/apparent diffusion coefficient mapping, and gadolinium-enhanced T1. Acute and subacute ischemic lesions appeared as hyperintense signal on DWI-weighted sequences, with corresponding restricted diffusion on apparent diffusion coefficient maps [13].

Different patterns of lesions can be observed. Ischemic lesions are common and observed in the three AAV. A vasculitic process should be searched in this setting. Leptomeningeal involvement is also described in the three AAV, but pachymeningitis is more likely secondary to GPA. In GPA, besides ischemic lesions and pachymeningitis, granulomatous or tumor-like lesions can be observed within brain or medullar parenchyma or in the pituitary gland. MRI sequences can also demonstrate orbital or sinus involvement, frequent in GPA.

13.4.1 MRI Findings Suggestive of CNS Vasculitis

Ischemic lesions can be isolated or disseminated. Subacute and chronic ischemic lesions are also observed, often associated with acute lesions. The presence of multiple ischemic lesions of different ages is suggestive of a vasculitic process but can be seen in atherosclerosis, infections, or other vasculopathies. Multiple patterns of acute ischemic lesions are observed, affecting grey and white matter (subcortical, peripheral, superficial, or deep lesions). In GPA and EGPA, unilateral or bilateral cerebral infarcts were observed in 60% and 52% of patients, respectively [6, 7].

Subcortical and white matter FLAIR hyperintense lesions are frequent and affect >90% of patients, but are nonspecific and are seen in other inflammatory and noninflammatory conditions. FLAIR lesions on the cortex or posterior areas are rare and more suspect. Gadolinium injection is required in the diagnosis workup of a CNS

vasculitis and can demonstrate gadolinium-enhanced lesions, suggestive of inflammatory process. However, small infarctions can also be enhanced due to the rupture of the hematoencephalic barrier. Besides parenchyma, meningeal tissues can also be gadoliniium-enhanced [13].

Gradient echo sequences give information of hemosiderin deposits that can be linked to the rupture of small vessels (i.e., microbleeds). Microbleeds are small, round foci of hypointense signals in T2∗ gradient-recalled echo-weighted images, ≤10 mm in brain parenchyma, and allocated to either deep or lobar locations. Hemorrhagic lesions can be within acute ischemic lesions indicating hemorrhagic transformation. However, spontaneous parenchymal or subarachnoid hemorrhages can be observed [13]. In GPA and EGPA, cerebral hemorrhagic lesions were observed in 6% and 24% of patients, respectively [6, 7].

The combination of different abnormalities on MRI is frequent and suggestive of vasculitis when showing multiple ischemic lesions along with small hemorrhages, FLAIR lesions, and gadolinium enhancements. Conversely, CNS vasculitis is not probable in a patient with normal MRI.

13.4.2 Other MRI Findings

Especially in GPA, MRI can demonstrate granulomatous lesions within the CNS, whose aspect can be tumor like. A gadolinium-enhanced ring around the lesions is often observed on T1 sequences with contrast [14]. Tumor-like lesions are more frequently described within the pituitary gland [15]. Spinal cord pachymeningitis is observed in 11% of GPA patients with CNS involvement [6].

13.4.3 Cerebral Angiography

In patients with demonstration of ischemic lesions on CNS imaging or with suspected AAV-related CNS vasculitis, angiography is required. Magnetic resonance angiography (MRA), brain CT angiography (CTA), and digital subtraction angiography (DSA) are the three main procedures used. DSA is the technique with the best spatial resolution, allowing to analyze vessels ≥500 μm. However, it remains an invasive procedure. MRA is limited to explore vessels <700 μm, but the development of 3Tesla units has increased the spatial resolution of the procedure.

Intracranial vessels can be classified into large-, medium-, and small-sized vessels [16]. Intracranial internal carotid artery and proximal anterior, middle, and posterior cerebral arteries are considered as large-sized vessels; second divisions and downstream vessels are considered as medium- and small-sized vessels, respectively. Small-sized vessels are beyond the detection capacity of DSA but can be demonstrated on biopsy. Large- and medium-sized vessels are seen on angiograms. In AAV-related CNS involvement, small-sized vessels are more likely affected resulting in frequent normal angiography (involvement of branches after A2, M2, and P2 divisions) in half of the patients [1]. However, in some patients, angiography

can be pathologic and suggestive of CNS vasculitis. In GPA patients, more than half of the patients who underwent an angiography had negative results [6]. Typical vasculitis findings include multiple arterial segmental and focal stenoses (>80% of lumen narrowing), occlusions, or fusiform dilations [17, 18].

It is important to note that multiple arterial segmental and focal stenoses can be observed in other conditions such as atherosclerosis or reversible cerebral vasoconstriction syndrome. However, in the two latter conditions, lesions often diffuse and affect more vessels than vasculitis.

13.5 Distinctive Presentations of AAV-Related CNS Involvement

13.5.1 Meningeal Involvement

Among the three AAV, GPA is mainly associated with meningeal involvement. Pachymeningeal involvement is more frequent than the leptominingeal involvement. In GPA and EGPA, pachymeningitis was observed in 46% and 2% of patients, respectively [6, 7]. Pachymeningitis has been associated with the granulomatous form of GPA, but rarely observed in the vasculitic form [6], and more frequently occurs at the onset than during follow-up [19]. Thickening of the dura is linked to the granulomatous inflammation and can cause headaches, seizures, cranial neuropathies, myelopathy, or neuro-ophthalmologic complications [1, 19].

No difference regarding clinical and radiological presentations was observed according to the ANCA anti-MPO or anti-PR3 specificity. Although treatments reported in anti-MPO or anti-PR3 pachymeningitis did not differ, patients with anti-PR3 disease relapsed more frequently [1, 19].

13.5.2 Pituitary Involvement

Pituitary involvement is rare and observed only in GPA. According to different series, it affects 1.1–1.3% of all GPA patients [20, 21]. Three mechanisms are described to explain pituitary involvement, similar to what is observed in other GPA-related CNS involvement. Development of a granulomatous inflammation within the gland and vasculitis of the gland's vessels are two rare mechanisms, whereas the invasion of granulomatous inflammation from neighboring sinus cavities remains the most frequent mechanism. Pituitary involvement can lead to partial or global pituitary dysfunction. Posterior involvement is responsible for diabetes insipidus, whereas anterior involvement leads more likely to secondary hypogonadism. Other hormonal dysfunctions have also been reported [1]. Visual loss can be observed in cases where pituitary enlargement compresses the optic chiasm [22].

MRI is mandated and abnormal in more than 90% of patients, showing an enlargement of the pituitary gland or a stellar mass with peripheral enhancement.

Other differential diagnoses should be evoked, especially when pituitary involvement is inaugural, such as tuberculosis, sarcoidosis, or histiocytosis [23–25].

Biopsy is rarely required in patients with other clinical manifestations of GPA. However, when isolated, biopsy should be discussed.

Treatment is common and relies on classical induction regimen for systemic vasculitis. Cyclophosphamide is probably preferred to rituximab [20]. Pituitary dysfunction often persists after treatment.

13.6 Cerebrospinal Fluid Analysis

Cerebrospinal fluid (CSF) analysis is rarely described in case reports or case series on AAV-related CNS involvement. In primary CNS vasculitis, more than half of the patients show abnormal CSF analysis [26]. In a cohort of GPA patients with CNS involvement, CSF analysis showed a protein level >0.40 g/l in 9/19 (47%) patients and a white blood cells count >10/mm^3 in 7/19 (37%) [6]. In a cohort of EGPA patients with CNS involvement, CSF analysis was abnormal in 44% of patients [7].

Normal CSF analysis does not exclude diagnosis. Pleocytosis is the most common finding, mainly lymphocytic. Increased protein level can be observed and can be >1 g/l. CSF analysis allows ruling out differential diagnoses such as infections (HSV, VZV, tuberculosis), malignancies (histological analysis, research of onconeuronal antibodies), or other inflammatory conditions (angiotensin-converting enzyme).

In the absence of signs of intracranial hypertension, CSF analysis should be performed.

13.7 Biopsy

The biopsy of meningeal and parenchymal tissue remains the gold standard to demonstrate vasculitis. However, given the invasive nature of this procedure, biopsy is rarely performed. Moreover, CNS involvement of AAV is mostly suspected when other extraneurologic symptoms specific of AAV exist. Biopsy is more frequently discussed in patients with isolated or inaugural involvement of CNS and when other diagnosis should be evoked besides AAV (e.g., tumor-like lesions). Image-guided biopsy increases the yield of the procedure. However, biopsy of the frontal lobe of the minor hemisphere can be done in the absence of easily accessible lesions. Biopsy can be stereotactic or open wedged [27].

Three different histological patterns are described [28] and can overlap: granulomatous lesions are more likely observed in GPA [3, 29]; otherwise lymphocytic or necrotizing lesions can be observed.

Histological samples allow ruling out other differential diagnoses such as infections or malignancies, especially lymphoma. Complementary analyses can be carried out such as culture or clonality testing.

13.8 Biological Analyses

In opposition to the systemic manifestations of AAV, inflammatory parameters (C-reactive protein level) are moderately increased in isolated CNS vasculitis.

Some studies suggested that CNS involvement more frequently occurred in patients with negative or atypical ANCA [30]. However, in a large cohort of GPA patients with CNS involvement, ANCA were positive in 90% of patients [6]. In EGPA patients, ANCA are positive in half of the patients [7].

Dosage of ANCA in CSF has been reported in a patient with pachymeningitis, but is still not validated in clinical practice [31].

Laboratory tests are also required to search other conditions that can affect CNS vessels, especially in patients with isolated or inaugural CNS involvement. A complete immunological screening is required (ANCA, antinuclear antibodies, complement dosage, research of cryoglobulin, antiphospholipid antibodies, angiotensin-converting enzyme). Exhaustive infective serologies have to be searched for HCV, HBV, HIV, CMV, EBV, syphilis, borrelia, tuberculosis (interferon-gamma release assays). Other laboratory tests can be carried out according to the context, such as toxicological screening.

13.9 Diagnosis Approach

In a patient with uncontrolled AAV, occurrence of a neurological event can indicate a specific CNS involvement. However, other frequent neurovascular diseases (atherosclerosis, infection, malignancy) should be eliminated before retaining the AAV as responsible.

In a patient with controlled disease, occurrence of CNS involvement may indicate a treatment-related complication or a relapse of the disease.

Isolated or inaugural CNS involvement in the absence of systemic AAV remains the most challenging presentation and many conditions have to be researched.

Whatever the situation, a complete workup is required, including a dosage of ANCA. MRI is helpful and should be completed by angiography.

Although required, angiography is often negative and biopsy is in practice rarely performed [32]. AAV-related specific CNS involvement is thus often retained on the systemic context, the ANCA positivity, and the exclusion of other differential diagnosis [1].

13.10 Differential Diagnosis

Many conditions, some of them more frequent than AAV, should be searched in the setting of a CNS involvement.

We described in Table 13.1, not exhaustively, some conditions mimicking CNS vasculitis, pachymeningitis, and CNS granulomatous lesions.

Table 13.1 Differential Diagnoses of AAV-Related CNS Involvement (Not Exhaustive)

Differential diagnoses of CNS vasculitis		
Vasculopathies	*Thrombotic conditions*	*Embolic conditions*
Reversible vasoconstriction syndrome	Antiphospholipid syndrome	Aortic arch atherosclerosis
Intracranial atherosclerosis	Disseminated intravascular coagulation	Intracardiac shunt
Intracranial arterial dissection	Thrombotic microangiopathy	Intracardiac myxoma
Fibromuscular dysplasia	Sneddon syndrome	Endocarditis
Moyamoya		
Other conditions		
Endovascular lymphoma	Fabry disease	Homocystinuria
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)	ADEM (acute disseminated encephalomyelitis)
Paraneoplastic syndrome		
Differential diagnoses of pachymeningitis		
Idiopathic pachymeningitis	Acute infective meningitis	Tuberculosis
Syphilis	Sarcoidosis	Intracranial hypotension
Primary diffuse leptomeningeal gliomatosis	Meningeal amylosis	Thrombophlebitis
Post neurosurgery	Other systemic vasculitis	Sjogren syndrome
Differential diagnoses of CNS granulomatous-like lesions		
Infections	*Tumoral lesions*	*Other*
Tuberculosis	Primitive tumor	Sarcoidosis
Intracranial abscesses	Secondary tumor	Behcet disease
Endocarditis	Lymphoma	Crohn disease
Mycosis (aspergillosis)	Lymphomatoid granulomatosis	
Parasites (toxoplasmosis)		

CNS central nervous system

13.11 Therapeutic Strategy (See Specific Chapter in This Book)

According to the new five-factor score, CNS involvement is no longer included in the five items given the rarity of this involvement [8]. However, CNS involvement is serious and is considered as an affection requiring an aggressive treatment.

Once the other differential diagnoses affecting CNS have been ruled out, treatment does not differ from an AAV with a FFS ≥1. Treatment relies on the combination of glucocorticoids (GC) and an immunosuppressant.

GC is the first step of the treatment and can rapidly improve clinical condition. In patients with severe neurological deterioration, intravenous pulses of methylprednisolone can be used (15 mg/kg for 1–5 days). Oral prednisone should be started at 1 mg/kg for at least 2–4 weeks and then progressively tapered.

Cyclophosphamide (CYC) remains the most used agent allowing to achieve remission in 80% of cases [33]. It can be administered by intravenous pulses or orally. In France and in most European countries, intravenous pulses are preferred. Both administration ways showed comparable remission rates, but higher cumulative doses were reached in patients with oral administration, increasing then the risk of toxicity.

Rituximab (RTX) is another option to achieve remission in combination with GC. RTX is approved in severe GPA. In AAV patients with CNS involvement, little information exists on the efficiency of RTX in this setting. In primary CNS vasculitis, RTX showed to be effective only in few case reports [34, 35]. Consequently, in CNS involvement of AAV, RTX should probably be used in patients with a contraindication for CYC or in relapsing patients who already received important cumulative doses of CYC (>20 g). Except CYC and RTX, other immunosuppressive agents, such as TNFα blockers, anti-IL1, or anti-IL6 biotherapy, should probably not be used as first intention for induction or should be discussed individually according to the situation.

Once remission has been achieved, a maintenance treatment is required, as in other form of AAV with a FFS ≥1. Experiences in primary CNS vasculitis showed better outcomes (better relapse-free survival with low damages) in patients who received maintenance therapy [26]. Azathioprine (AZA, 2–3 mg/kg/day) was the most used agent in the French PCNSV cohort, but other publications indicated good outcomes with mycophenolate mofetil (MMF, 2 g/day), especially in children [26]. In AAV, MMF showed poorer outcomes when compared to AZA [36]. Methotrexate is another option and can be used at 0.3 mg/kg/week [26, 37]. Few information exists on maintenance therapy with RTX in CNS involvement. The best duration of maintenance is not known, but probably should reach at least 2 years.

Finally, treatment relies in most patients with CNS involvement on a combination of GC and an immunosuppressant (mainly CYC) followed by a maintenance therapy.

13.12 Outcomes

In the study by de Luna et al., 30/35 patients with GPA-related CNS involvement achieved a response to treatment combining GC and immunosuppressant, mainly CYC in 34 patients. Among responders, 8/30 (27%) patients relapsed after a median time of 14 months (range 9–96). Thirteen relapsing patients required another induction regimen, RTX in 8 and CYC in 5 others. CYC showed improvement of neurological symptoms in 80% and stabilization in 20%, whereas RTX showed improvement in 50% and stabilization in 50%. Neurological sequelae assessed with the modified Rankin Scale indicated a score ≥2, in 18/35 (51%) patients. In this study, only one patient died from another cause than AAV [6].

In the study by André et al., all patients (n = 84) received GC combined with CYC in 63% of them. Follow-up information was available in 81 patients, and a complete response was observed in 43%, partial response in 43%, and no response

in 14%. Relapse occurred in 14% (11/81) of patients, including CNS relapse in six cases. In this study, 11 (13%) patients died, mainly from cerebral hemorrhage. Of patients, 57% had persistence of neurological sequelae, including persistent visual impairment in 18/27 (67%) patients, motor and/or sensory deficiency in 21/45 (47%) patients with ischemic lesions and 8/16 (50%) patients with intracerebral hemorrhages, and persistent cranial nerve palsy in 4/16 (25%) patients [7].

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