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Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis involving the central nervous system: case report and review of the literature

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ABSTRACT

Objectives. *To report a case of biopsy-proven, ANCA-associated vasculitis (AAV) involving the central nervous system (CNS) and to review the relevant literature.*

Methods. *Descriptive case report of one patient with AAV-related CNS vasculitis and review of the relevant literature (PubMed search from 1966 to February 2010).*

Results. *A 61-year-old female patient with AAV developed cognitive impairment. Cerebrospinal fluid analysis was unremarkable, while magnetic resonance (MR) imaging showed multiple left hemisphere infarctions and MR angiography revealed multiple stenoses of the distal branches of the left median cerebral artery. Treatment with glucocorticoids, cyclophosphamide, and intravenous immunoglobulins led to improvement.*

CNS vasculitis often arises when vasculitis is active elsewhere. There is no clear preponderance of gender or of age of onset. Both ANCA-positive and -negative cases of CNS vasculitis are documented. The diagnosis is usually based on clinical CNS manifestations and multiple ischaemic (sometimes haemorrhagic) MR lesions mainly affecting the white matter. Angiography is often negative. Treatment with glucocorticoids and cyclophosphamide, sometimes with adjunctive intravenous immunoglobulins, usually improves clinical features and MR lesions.

Conclusion. *AAV rarely involves the CNS. CNS vasculitis should be suspected if patients have neurological manifestations consistent with CNS involvement, particularly if they have evidence of disease activity elsewhere, and if MR shows multiple ischaemic (sometimes haemorrhagic) lesions mainly affecting the white matter. Sepsis, coagulation disorders, and severe hypertension must be ruled out. Awareness of this rare but severe complication can allow early recognition and prompt treatment.*

Introduction

AAV are rare disorders, characterised by a necrotising small-vessel vasculitis and by circulating ANCA, which comprise Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and renal pauci-immune glomerulonephritis (1, 2). CNS involvement is an uncommon but serious complication (3). We describe a case of AAV with vasculitic brain involvement and review the literature on AAV-related CNS vasculitis.

Methods

PubMed search (1966 – February 2009) using the keywords "vasculitis" [MeSh], "Wegener granulomatosis" [MeSh], "Churg-Strauss syndrome" [MeSh], "microscopic polyangiitis", "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis" [MeSh], and "central nervous system" [MeSh]. Additional references were found by hand search.

Case report

A 61-year-old lady developed in July 2008 fever and arthralgia followed by lower-limb pain and weakness. Past medical history revealed hypertension controlled by amlodipine and congenital epilepsy treated with phenobarbital and carbamazepine. The patient was also known to suffer from depression and anxiety. She was admitted to a Teaching Hospital.

Physical examination showed lower limb weakness and generalised livedo racemosa, which evolved into necrosis of the II and IV right digits and of the V digits bilaterally. Worsening of her mood with swings characterised by depression alternating with anxiety were noted in the absence of overt cognitive dysfunction. Blood tests showed haemoglobin 8 g/dl, ESR 49 mm/1st hour, and C-reactive protein (CRP) 22.4 g/dl (normal <5). c-ANCA were positive. Doppler ultrasonography excluded deep venous thrombosis. Computerised tomography (CT) demonstrated ground glass attenuation (GGA) in the mid-thoracic lung parenchyma bilaterally and mild right pleural effusion, while CT of the abdomen was unremarkable. Angiography disclosed reduced lumen of the left tibial artery, and absence of visualisation of the dorsalis pedis and dorsal arch arteries. Transoesophageal echocardiography showed no vegetations. Fine-needle bone-marrow aspirate revealed no malignant cells, while

renal biopsy showed fibrinoid necrosis consistent with active vasculitis in the absence of crescents. Gadoteric acid (0.2 ml/kg)-enhanced MR demonstrated a non-enhancing lesion in the right temporal area hypointense on T1- and hyperintense on T2-weighted sequences compatible with cortical dysplasia. There were diffuse white-matter high-signal alterations on T2-weighted images consistent with gliosis and *ex vacuum* ventricular enlargement, which were attributed to chronic encephalopathy (not shown).

AAV was diagnosed. The patient was treated with methylprednisolone 60 mg/day subsequently switched to prednisone 25mg x2/day, two pulses of intravenous cyclophosphamide (700 mg), plasma exchange, and two blood transfusions. Her necrotic digits were amputated. She was subsequently referred to our Vasculitis Centre

On admission, the patient looked ill but vigilant. Physical examination of the lower limbs showed decreased deep tendon reflexes, grade 3–4 muscle weakness, and digit amputations. Blood pressure was normal (120/70 mmHg). Complete blood count showed leukocytes 15,840/mm^3, haemoglobin 8 g/dl, and platelets 573,000/mm^3. ESR was 62 mm/1st hour and CRP 180 g/dl. Biochemistry was basically normal including serum creatinine at 0.4 mg/dl. 24-hour urinary protein was 700 mg (normal <150), while urinary sediment analysis revealed numerous, mostly eumorphic erythrocytes. c-ANCA (enzyme immunoassay, anti-proteinase-3 antibodies) tested positive (29.4 U/ml, normal <5), whereas p-ANCA were negative. Anticardiolipin antibodies and lupus anticoagulant were not detected. Colour-Doppler ultrasonography of the aorta, of the supra-aortic branches, and of renal arteries was unremarkable, and in particular there was no evidence of atherosclerosis except for minimal thickening at the left carotid bifurcation.

We confirmed the diagnosis of AAV. The patient did not fulfil the American College of Rheumatology classification criteria for WG or CSS, and in particular she had no upper tract respiratory involvement or granulomata as seen in WG, nor asthma or eosinophilia, which

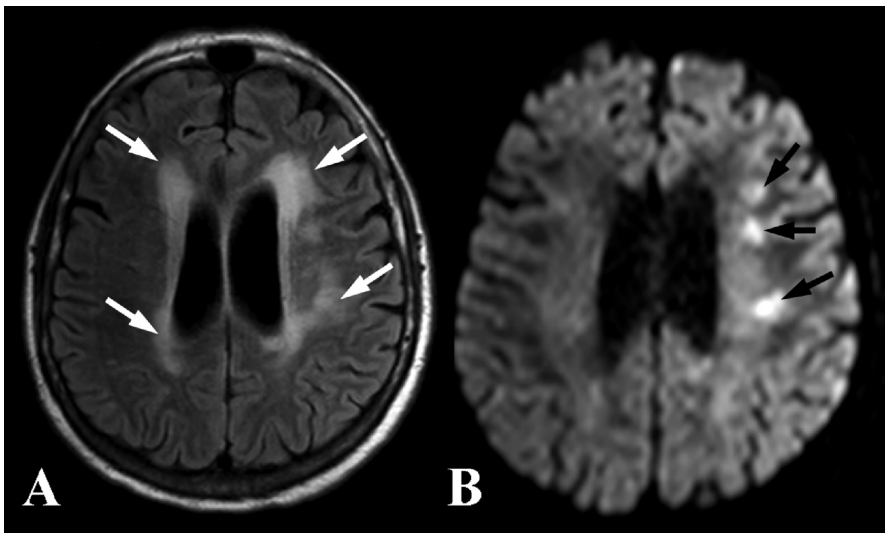

Fig. 1A. Axial Fluid Attenuated Inversion Recovery shows diffuse white matter signal intensity alteration particularly in the periventricular regions (white arrows) associated with ventricular enlargement consistent with volume loss.
B. Axial DWI demonstrates foci of water motion restriction compatible with subacute ischaemic injury (black arrows).

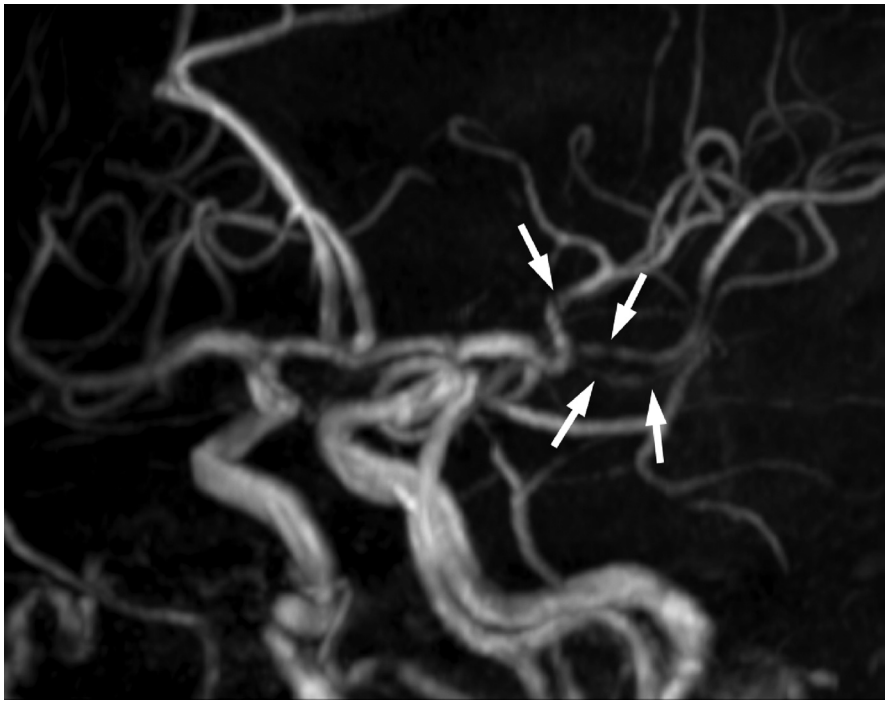

Fig. 2. Three Dimensional Time of Flight MR angiography of the intracranial arteries discloses multiple stenoses involving the left middle cerebral artery trifurcation (white arrows).

are hallmark features of CSS. She did have a pulmonary-renal syndrome with polyneuropathy, which according to the Chapel-Hill nomenclature are suggestive of MPA, although c-ANCA are infrequently seen in MPA (4). Therefore, MPA might also have been an acceptable diagnosis, although owing to the lack of clinical classification criteria the diagnosis of MPA remains difficult to buttress in clinical practice.

Treatment with glucocorticoids was continued. However, on day 2 post-admission, the patient developed a spiking fever (up to 38.8°C), while two days later she also became confused and unable to obey simple commands or to give meaningful answers most of the time.

Two pints of blood were transfused because of her anaemia and we arranged a brain MR. Gadoteric acid (0.2 ml/kg)-enhanced brain MR demonstrated diffuse white-matter gliosis and volume loss (Fig. 1A). Furthermore, multiple foci of diffusion weighted image (DWI) restriction of the left hemisphere consistent with subacute ischaemic lesions (Fig. 1B) were noted. Three-dimensional (3D) time-of-flight (TOF) MR angiography (MRA) revealed multiple stenoses of the distal branches of the left middle cerebral artery (Fig. 2). The right temporal artery and the periventricular lesions previously described were unchanged.

The patient's status remained unchanged over the next five days with recurrent spiking fever and cognitive dysfunction. Repeated blood cultures and procalcitonin were negative, while transoesophageal echocardiography showed no cardiac vegetations. One week after her admission, in view of the persistent fever and altered mental status we performed a cerebro-spinal fluid (CSF) aspiration. CSF analysis revealed normal protein and cellularity without oligoclonal bands, while search for common microorganisms including a broad panel of viruses was negative. CT of the abdomen and chest was also organised. Chest CT showed minimal GGA in the left inferior right lobe and mild left pleural effusion, while abdomen CT revealed multiple splenic infarctions with decreased spleen volume, thrombotic occlusion of the proximal splenic artery, and multiple, bilateral renal infarctions.

AAV-related brain vasculitis was diagnosed, and treatment with pulse cyclophosphamide (1 g/intravenously/month) and intravenous immunoglobulins (IvIg 5 g over 4 days) organised. IvIg were administered in two separate cycles, the first three days post-admission and the second one one month later. Cyclophosphamide was initially withheld because the patient had already received two pulses (700 mg each) prior to being referred to us, and because of concerns of a possible sepsis pending the results of the investigations, and administered only on day 11 post-admission. The patient's status and her limb lesions remained overall stable without evidence of worsening over the next two weeks, albeit she appeared soporous on a couple of occasions (in both cases the temperature had risen to 38.6° compared to an average body temperature of 37–37.5° as from day 14 post-admission), while at week three post-admission she had a single episode of generalised seizures witnessed by another patient, although not by a physician. However, progressive improvement of the mental status was subsequently observed, the fever gradually disappeared, no more seizures nor new ischaemic limb lesions occurred, and creatinine remained within limits.

MR performed on day 23 post-admission showed multiple microhaemorrhagic lesions on T2-weighted fast-field gradient-echo sequences in the pericortical regions, but resolution of the supratentorial multifocal DWI restriction (not shown). Contrast enhanced-MRA performed after injecting 0.1 ml/kg of Gadobedonate dimeglumine disclosed resolution of the multiple stenoses of the left middle cerebral artery (not shown). The spinal cord showed no alterations. An EMG demonstrated severe axonal and myelinic damage of the right peroneal and tibialis nerves on the right (the exam was stopped prematurely because the patient did not tolerate it).

The patient was discharged with prednisone 75 mg daily and received further (altogether six) monthly cyclophosphamide pulses (subsequently switched to every other month) and six courses of monthly intravenous immoglobulins, while her prednisone dose could be tapered to 5 mg/day. To date, there has been no recurrence of brain vasculitis.

Discussion

Herein, we have reported a case of AAV with CNS vasculitis. The diagnosis of cerebral vasculitis was made on the basis of the clinical manifestations mainly characterised by cognitive dysfunction, by the abnormal brain MR and MRA findings consistent with vasculitis, and by the absence of other causes of cerebral lesions such as thromboembolism and infection. More specifically, the patient had no cardiovascular risk factors apart from longstanding hypertension which, however, was controlled by amlodipine. Infection including generalised sepsis and bacterial endocarditis were also considered in the differential diagnosis. In particular, bacterial endocarditis was carefully considered in our patient since it may cause cerebral lesions akin to those observed in AAV (5). However, blood cultures and transoesophageal echocardiography, which are the key investigation that allow to diagnose bacterial endocarditis (5), were both negative in our patient. Finally, last but not least, response to immunosuppressive treatment with marked improvement of the clinical features and of MR/MRA findings at follow-up confirmed the diagnosis.

CNS involvement in ANCA vasculitis is quite uncommon. Broadly speaking, CNS disease related to ANCA vasculitis can be classified into three patterns: meningitis, pituitary gland involvement, and vasculitis (3, 6). Vasculitis typically affects the brain and only rarely the spinal cord (7). Meningeal and pituitary gland involvement are infrequent but recognised features of WG (8, 9), whereas their occurrence in CSS (10) and MPA (11, 12) is very rare.

Overall, CNS disease has been described in about 0%–10% of WG patients (7, 13, 14) and in 1%–8% of patients with Churg-Strauss syndrome (CSS) (15, 16). Occasionally, CNS disease has also been reported in patients with microscopic polyangiitis (MPA) (11, 17, 18). CNS manifestations in ANCA vasculitis may be due to vasculitis affecting the brain, but also to granulomata, uncontrolled hypertension, sepsis, and coagulation disorders (6, 7, 19). Teasing out CNS vasculitis from other causes of cerebral lesions is challenging due to the scarcity of published data and difficulty in confirming this diagnosis. Our search revealed only few cases in which the diagnosis of CNS vasculitis was sufficiently secured by the appropriate investigations (Table I). For example, in the original paper by Churg and Strauss, CNS disease was diagnosed in eight of thirteen patients with CSS, and was a cause of death in three patients (19). However, seven of the thirteen patients reported and two of the three patients who died because of cerebral complications also

Table I. Published cases of patients with ANCA-associated vasculitis involving the central nervous system.

Ref.	Study population	n	Clinical features, principal investigations, and therapy
(3)	6 WG patients with CNS manifestations	1	CNS vasculitis at disease onset characterised by cranial nerve involvement, headache, and cerebellar symptoms. ANCA were negative, CSF showed pleiocytosis and increased protein. T2 MR images showed hyperintense white-matter lesions. Cerebellar biopsy revealed giant-cell granulomatous vasculitis.
(41)	14 WG patients (4 with CNS manifestations)	2	Two patients (a 49-year-old male and a 59-year-old female) had CNS vasculitis. The first patient had haemianesthesia, haemiparesis, cranial nerve involvement and cerebellar symptoms, the second patient had vertigo. c-ANCA were positive. MR showed diffuse white-matter hyperintense lesions. Cyclophosphamide and glucocorticoids induced remission.
(21)	Case report of WG	1	A 35-year-old woman developed seizures followed by cortical blindness. CT revealed small infarctions near both occipital poles and in the parietal region. Recovery was poor despite treatment.
(40)	Case report of WG	1	A 42-year-old male presented with right sensimotor haemisyndrome and motor aphasia. MR revealed a haemorrhagic stroke in the left basal ganglia. c-ANCA (anti-proteinase-3) antibodies were positive. CSF analysis was negative. The patient subsequently developed other manifestations of WG. Intravenous glucocorticoids and cyclophosphamide led to recovery.
(8)	3 WG patients with severe CNS manifestations	1	A 22-year-old male with established WG developed CNS vasculitis three years after WG onset. ANCA were negative. Clinical manifestations included headache, tetraspasm, and loss of sphincter control. CSF showed pleiocytosis and increased protein. MR showed diffuse perivascular white-matter lesions. Cerebral angiography was negative. The patient died despite aggressive treatment.
(14)	158 patients with WG	(?)	8% of patients had CNS manifestations including stroke. No details are provided to determine how many had CNS vasculitis.
(48)	128 patients with WG	(?)	Nine patients had CNS manifestations. No details are provided to determine how many had CNS vasculitis.
(22)	3 patients with WG with CNS manifestations	1	A 60-year-old male developed three months after WG onset confusion, paresthesias, and right haemiparesis. MR revealed T2-hyperintense lesions in the pulvinar and thalamus on the left side and in the white matter and pons. CSF showed pleiocytosis and increased protein. Cerebral angiography was negative. Glucocorticoids led to improvement.
(7)	324 patients with WG	(?)	13 patients had cerebrovascular attacks. 12 patients had infarction, and one atraumatic subdural haematoma. Cerebral angiography was negative in the 2 patients in whom it was performed. 12 patients had CT or MR done, 5 had multiple infarctions.
(33)	Case report of WG	1	Cerebral vasculitis with positive angiography and lesions on brain CT.
(13)	85 WG patients	0	No patient had CNS involvement other than cranial neuropathy.
(49)	Original report of two WG cases and review of 247 published cases	(?12)	12 patients with CNS vasculitis. However, the criteria for diagnosing CNS vasculitis were not clearly stated. This review includes the cases published in (50).
(50)	104 WG patients	(?)	9 patients suffered cerebrovascular attacks. It is unclear how many of these had CNS vasculitis.
(34)	Case report of WG	1	A 26-year-old male with biopsy-proven WG suffered a brainstem stroke. Angiography revealed mid-basilar artery occlusion.
(51)	7 WG patients referred to Radiology for suspected CNS disease	(?0)	No patients had clinical manifestations of CNS vasculitis.
(6)	19 WG patients referred to Radiology for suspected CNS disease	3	Three patients had clinical and MR features suggestive of CNS vasculitis.
(44)	Case report of WG	1	CNS vasculitis successfully treated with intravenous immunoglobulins.
(27)	Case report of WG	1	CNS vasculitis successfully treated with rituximab.
(52)	Case report of WG	1	CNS vasculitis (autopsy positive).
(53)	Case report of WG	1	CNS vasculitis (autopsy positive).
(54)	18 WG patients with severe renal disease	(?3)	This series included WG patients with severe renal disease but no severe hypertension. Three had pyramidal signs possibly consistent with CNS vasculitis.
(55)	25 WG patients referred for head MR	(?)	Six patients had small (single or multiple) white-matter high-signal areas on T2 sequences, and one had an infarction.

Ref.	Study population	n	Clinical features, principal investigations, and therapy
(56)	Series of 21 patients with non-primary cerebral vasculitis	2	1 patient with WG had vasculitis-associated intracranial haemorrhage and died due to systemic disease progression. 1 patient with CSS had cerebral vasculitis presenting with transient ischaemic attacks.
(42)	Case report of ANCA vasculitis (probable WG)	1	A 53-year-old MPO-ANCA-positive woman developed hearing loss, dizziness, and postural instability. MRI revealed enhancing meningitis and lesions at Luschka's foramen as well as multiple lesions in the cerebellum and bulb. Treatment with glucocorticoids and cyclophosphamide led to remission.
(57)	Case report of p-ANCA positive vasculitis	1	A 62-year-old woman with systemic sclerosis and p-ANCA-(MPO)-associated rapidly progressive glomerulonephritis developed cerebral infarction and haemorrhage not due to hypertension. Cerebral angiography was normal. She died despite immunosuppressive therapy.
(17)	Case report of MPA	1	Case report of a 66-year-old woman with MPO-ANCA-positive MPA complicated by multiple bilateral cerebral infarctions. MR angiography was normal. Improvement was attained with glucocorticoids.
(18)	Case report of MPA	1	Case report of a 55-year-old man with p-ANCA-positive MPA complicated by bilateral cerebral infarctions. CSF analysis and MR angiography were normal. Treatment with glucocorticoids and cyclophosphamide led to improvement but sequelae persisted.
(23)	Case report of CSS	1	Report of a MPO-ANCA-positive 47-year-old male who developed sensory symptoms, cognitive impairment, and aphasia. MR of the brain showed multiple T2-hyperintense hemispheric lesions. Treatment with cyclophosphamide and intravenous immunoglobulins was effective.
(25)	Case report of CSS	1	Report of a 62-year-old woman with multifocal enhancing MR cortical lesions. ANCA were not detected, MR angiography was negative.Therapy with cyclophosphamide and high-dose glucocorticoids tapering led to remission with small MR leftover lesions.
(28)	Case report of CSS	1	Report of a 46-year-old woman with cortical blindness due to extensive haemorrhagic infarctions of the occipital lobes seen on MR. ANCA were negative. Therapy with cyclophosphamide and high-dose glucocorticoids tapering led to partial improvement.
(24)	Case report of CSS	1	Report of a 27-year-old male who presented with blurred vision and impaired motion and speech. Brain MR revealed multiple intracerebral haemorrhages in the parietal lobes. p-ANCA were positive. The patient responded to cyclophosphamide and high-dose glucocorticoids tapering.
(16)	Case series of 96 patients with CSS	8	In this case series, 6 patients suffered an ischaemic stroke, one asymptomatic patient was found to have diffuse ischaemic brain lesions, and one had cognitive impairment attributed to vasculitis.
(15)	Case series of 47 patients with CSS	2	Case series extending a previous study (58). Three patients had cerebral infarction, which was attributed to vasculitis in two of them.
(29)	Case report of CSS	1	Case report of a 47-year-old female who presented with lower limb weakness and upper limb numbness. CT of the head showed subarachnoid and ventricular haemorrhage, while histology revealed fibrinoid necrosis and transmural inflammatory infiltrates of the choroid plexus. The patient died despite glucocorticoid and cyclophosphamide treatment.
(19)	Original case series by Churg and Strauss describing 13 patients	(?8)	Eight patients had CNS involvement; cerebral and subarachnoid haemorrhage were causes of death in 2 and 1 patients, respectively. Whether CNS manifestations were due to vasculitis is unclear (hypertension was found in 7/13 patients and in 2 of the 3 patients who died because of CNS involvement).
(26)	Case series of 2 patients with CSS	2	Two patients presented with haemiplegia. Brain MR showed diffuse ischaemic lesions, cortical in one patient and periventricular-subcortical in the other. CSF analysis and cerebral angiography performed in the patient with cortical lesions were unremarkable. ANCA were negative in both patients. Both patient remitted with glucocorticoids and with combined glucocorticoids and cyclophosphamide, respectively.
(59)	Case series of 16 patients with CSS	(?)	CNS disease was observed in 4/16 cases. The Authors also reviewed the literature on 138 patients and found evidence of CNS disease in 22/82 reviewed patients. It is unclear how many had CNS vasculitis proper.
(43)	Case report of CSS	1	A 39-year-old man with optic neuritis was found to have multiple asymptomatic brain lesions on MR consistent with haemorrhagic infarcts. p-ANCA were detected. Treatment with glucocorticoids and cyclophosphamide induced a near-complete resolution of the brain lesions.
(30)	Case report of CSS	1	Report of a 47-year-old woman with headache and xantochromic and haemorrhagic CSF consistent with subarachnoid haemorrhage. Brain CT was normal, while angiography showed narrowing and stenoses of the basilar artery. ANCA against myeloperoxidase were detected. Treatment with glucocorticoids and cyclophosphamide led to clinical remission and resolution of the angiographic abnormalities.
(20)	Case report of CSS	1	Report of a 48-year-old woman with headache and right upper limb paresthesia. ANCA were negative. Brain MRI showed a left frontoparietal lesion, while pathology revealed granulomatous and vasculitic lesions.

n: patients with central nervous system vasculitis; ANCA: anti-neutrophil cytoplasmic antibodies; (c-ANCA: cytoplasmic ANCA; p-ANCA: perinuclear ANCA); CNS: central nervous system; CSF: cerebro-spinal fluid; CSS: Churg-Strauss syndrome; CT: computerised tomography; MPA: microscopic polyangiitis; MPO: myeloperoxidase; MR: magnetic resonance; (MRI: magnetic resonance imaging; MRA: magnetic resonance angiography); PR-3: proteinase-3; WG: Wegener's granulomatosis.

had hypertension, which is a known risk factor for cerebral lesions. Subsequent studies which have specifically endeavoured to define the prevalence of true CNS vasculitis in patients with ANCA vasculitis have found much lower frequency rates. In this regard, in a series of nineteen WG patients with CNS disease, only three had clinical and imaging features suggestive of vasculitis (6), while CNS vasculitis was diagnosed in only 4% of a population of unselected CSS patients (15).

CNS vasculitis usually affects patients with AAV that have evidence of active disease elsewhere (3), as in our case. It can develop at any time, even though CNS complications considered together are thought to represent late events (3). We could not find a clear predominance of gender or age at onset.

Clinically, CNS vasculitis can present with a panoply of manifestations, including paresis, headache (8, 20), cranial nerve palsy (3), seizures (21), altered consciousness (22), sensory symptoms, cognitive dysfunction (23), speech disturbances (23, 24) and coma (3). ANCA are not invariably positive (3, 20, 25, 26). MR T2-weighted sequences usually show hyperintense white-matter lesions thought to be ischaemic (3, 6, 26), but haemorrhagic lesions (as in our case) may also be observed (6, 24, 27, 28). Haemorrhagic lesions are most likely secondary to weakening of the vessel wall caused by vasculitis (6) and may occur not only in the cerebral hemispheres, but also in the subarachnoid space, in the ventricula, and in the choroid plexus (19, 29, 30). MR is very sensitive in detecting CNS lesions related to vasculitis, but is not specific. CT may also detect CNS lesions, although it is less sensitive than MR (3).

Angiography is one of the standard investigations for vasculitis. Digital subtraction angiography clearly depicts vessel luminal changes and typically shows stenoses and sometimes occlusions and aneurysms in patients with large-vessel vasculitis (31). For example, in primary angiitis of the central nervous system, a vasculitis involving the large vessels of the brain, angiography shows alterations consistent with vasculitis in 90% of affected patients (32). Compared with digital subtraction angiography, CT angiography and MRA have the advantage of visualising both the vessel wall and the lumen, however, they cannot adequately delineate the small vessels either (31). In AAV-related CNS vasculitis angiography is often negative because this type of vasculitis predominantly involves small-sized CNS vessels, whose diameter is below the detection threshold of angiography (3, 7). Nevertheless, angiographic alterations compatible with vasculitis have been described in some patients (33, 34).

In our patient, 3D TOF MRA initially revealed multiple stenoses of the distal branches of the left middle cerebral artery. This appearance of multiple stenoses is strongly suggestive of vasculitis. Contrast enhanced-MRA performed three weeks later, after the onset of cyclophosphamide and intravenous immunoglobulin treatment, disclosed resolution of the multiple stenoses of the left middle cerebral artery.

A known disadvantage of TOF MRA is artifactual narrowing of vessels close to the skull base and around the sphenoid sinus because of bone and/or air related susceptibility artefacts. In our patient the vessels affected were the M3 segments of the middle cerebral artery, thus excluding the possibility of bone- or air-related artefacts. Focal discontinuity of signal within the affected vessels was present in our patient at the first TOF MRA evaluation, thus confirming vessel stenosis. In severely stenotic vessels, discontinuity in a vessel is caused by intravoxel spin dephasing and the acceleration of flow through the stenosis. This represents a limitation of TOF MRA, because the degree of stenosis may be overestimated, but indirectly confirms the stenosis. With regard to 3D TOF MRA, the potential role of MRA in evaluating the degree of stenosis has reported as having a sensitivity ranging from 71% to 91% and a specificity ranging from 89% to 100% (35-37). Sensitivity and specificity of different MRA techniques are lower than that of digital subtraction angiography, which remains the gold standard to evaluate the degree of stenosis. Among the non-invasive imaging techniques, MRA allows more accurate evaluation of intracranial steno-occlusive disease and is widely used as a screening tool in stroke patients (38). On contrast-enhanced MRA, signal depends more on T1 shortening than on flow-related signal, thus obviating the problem of the artefacts related to 3D-TOF MRA. However, sensitivity in revealing vessels' stenosis is similar in TOF and contrast enhanced-MRA (39). Therefore, the discontinuity of signal observed in the distal branches of the MCA in our patient most likely represented severe stenosis. In fact, TOF MRA represents a useful tool in depicting occlusion even of smaller arteries if careful analysis of the images is performed (39). Furthermore, correlation with DWI and clinical presentation supported the MRA patterns of multiple stenosis disclosed by 3D TOF MRA. The resolution of brain lesions and of the stenoses on contrast enhanced-MRA after commencing treatment with cyclophosphamide and intravenous immunoglobulins correlated with the clinical improvement, thus confirming their vasculitic nature.

CSF analysis is useful to rule out infection, and may show pleiocytosis, increased protein content, or both in active CNS disease related to AVV (3, 8), while the presence of erythrocytes and xantochromia in the CSF suggests subarachnoid haemorrhage (30). However, CSF may also be entirely unremarkable (18, 26, 40) as in our case.

Finally, CNS biopsy is considered the "gold standard" to diagnose intracranial vasculitis (32), although is rarely done because of its invasive nature and potential risks.

There is no standardised treatment for ANCA vasculitis affecting the CNS, but combined glucocorticoid and cyclophosphamide therapy (3, 18, 24-26, 28, 30, 40-43), sometimes with the adjunct of intravenous immunoglobulin (23, 44), have been shown to be often, although not universally (29) effective in published and in our case.

Plasma exchange (PE) has also been used to treat refractory AAV based on the rationale of a humoural pathogenic mechanism that could theoretically

be abrogated by such procedure (45). However, to date, the role of PE in AAV remains debated. A randomised controlled trial showed that in AAV patients with advanced renal failure (creatinine >500 μm/l (>5.8 mg/dl)) PE was able to reduce dialysis rates, although not survival (46). Uncontrolled observations also suggest a role for PE in treating diffuse alveolar haemorrhage in AAV patients (47). According to the American Society of aphaeresis, PE can be tried "in fulminant cases (of ANCA-associated vasculitis) or with pulmonary haemorrhage" (45). There is no published data on the efficacy of PE in AAV-related CNS vasculitis, but the absence of evidence of efficacy of PE in the treatment of AAV-related CNS vasculitis does not necessarily equate evidence of absence of efficacy.

In conclusion, CNS vasculitis should be suspected in patients with AAV if there is clinical evidence of CNS involvement, if MR shows multiple ischaemic (sometimes haemorrhagic) lesions mainly affecting the white matter, and if infection, severe hypertension, and systemic coagulation disorders are excluded. Awareness of this serious complication can allow early recognition and prompt treatment.

References

1. PHILLIP R, LUQMANI R: Mortality in systemic vasculitis: a systematic review. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S94-104.
2. GUILLEVIN L, LHOTE F: Classification and management of necrotising vasculitides. *Drugs* 1997; 53: 805-16.
3. SEROR R, MAHR A, RAMANOELINA J, PAGNOUX C, COHEN P, GUILLEVIN L: Central nervous system involvement in Wegener granulomatosis. *Medicine* (Baltimore) 2006; 85: 54-65.
4. JENNETTE JC, FALK RJ, ANDRASSY K *et al*.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
5. BERLIT P: Isolated angiitis of the CNS and bacterial endocarditis: similarities and differences. *J Neurol* 2009; 256: 792-5.
6. MURPHY JM, GOMEZ-ANSON B, GILLARD JH *et al*.: Wegener granulomatosis: MR imaging findings in brain and meninges. *Radiology* 1999; 213: 794-9.
7. NISHINO H, RUBINO FA, DEREMEE RA, SWANSON JW, PARISI JE: Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. *Ann Neurol* 1993; 33: 4-9.
8. REINHOLD-KELLER E, DE GROOT K, HOLL-ULRICH K *et al*.: Severe CNS manifestations as the clinical hallmark in generalized Wegener's granulomatosis consistently negative for antineutrophil cytoplasmic antibodies (ANCA). A report of 3 cases and a review of the literature. *Clin Exp Rheumatol* 2001; 19: 541-9.
9. YONG TY, LI JY, AMATO L *et al*.: Pituitary involvement in Wegener's granulomatosis. *Pituitary* 2008; 11: 77-84.
10. TOKUMARU AM, OBATA T, KOHYAMA S *et al*.: Intracranial meningeal involvement in Churg-Strauss syndrome. *AJNR Am J Neuroradiol* 2002; 23: 221-4.
11. FUNAUCHI M, NOZAKI Y, HASHIMOTO K *et al*.: Microscopic polyangitis as a possible cause of diabetes insipidus. *Clin Rheumatol* 2002; 21: 540.
12. HAYASHI Y, SUGAWARA H, OTSUKA M, YAMADA S, TABEI K, UEKI A: Fatal hemoperitoneum preceded by cranial hypertrophic pachymeningitis in a patient with ANCA-positive microscopic polyangitis. *Intern Med* 2008; 47: 1061-3.
13. FAUCI AS, HAYNES BF, KATZ P, WOLFF SM: Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; 98: 76-85.
14. HOFFMAN GS, KERR GS, LEAVITT RY *et al*.: Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; 116: 488-98.
15. SEHGAL M, SWANSON JW, DEREMEE RA, COLBY TV: Neurologic manifestations of Churg-Strauss syndrome. *Mayo Clin Proc* 1995; 70: 337-41.
16. GUILLEVIN L, COHEN P, GAYRAUD M, LHOTE F, JARROUSSE B, CASASSUS P: Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine* (Baltimore) 1999; 78: 26-37.
17. KU BD, SHIN HY: Multiple bilateral nonhemorrhagic cerebral infarctions associated with microscopic polyangiitis. *Clin Neurol Neurosurg* 2009; 111: 904-6.
18. TANG CW, WANG PN, LIN KP, HUANG DF, WANG SJ, CHEN WT: Microscopic polyangiitis presenting with capsular warning syndrome and subsequent stroke. *J Neurol Sci* 2009; 277: 174-5.
19. CHURG J, STRAUSS L: Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol* 1951; 27: 277-301.
20. BAAJ AA, VALE FL, CARTER JD, ROJIANI AM: Granulomatosis with CNS involvement: a neuroimaging clinicopathologic correlation. *J Neuroimaging* 2009; 19: 194-7.
21. PAYTON CD, JONES JM: Cortical blindness complicating Wegener's granulomatosis. *Br Med J* (Clin Res Ed) 1985; 290: 676.
22. NISHINO H, RUBINO FA, PARISI JE: The spectrum of neurologic involvement in Wegener's granulomatosis. *Neurology* 1993; 43: 1334-7.
23. BERETTA L, CARONNI M, VANOLI M, SCORZA R: Churg-Strauss vasculitis with brain involvement following hepatitis B vaccination. *Clin Exp Rheumatol* 2001; 19: 757.
24. LIOU HH, LIU HM, CHIANG IP, YEH TS, CHEN RC: Churg-Strauss syndrome presented as multiple intracerebral hemorrhage. *Lupus* 1997; 6: 279-82.
25. HAGIWARA K, TOMINAGA K, SHIDA N, YAMASHITA Y: Multifocal enhancing cortical lesions in a patient with Churg-Strauss syndrome. *Neurology* 2008; 71: 1546-8.
26. SONNEVILLE R, LAGRANGE M, GUIDOUX C *et al*.: (The association of cardiac involvement and ischemic stroke in Churg Strauss syndrome). *Rev Neurol* (Paris) 2006; 162: 229-32.
27. MEMET B, RUDINSKAYA A, KREBS T, OELBERG D: Wegener granulomatosis with massive intracerebral hemorrhage: remission of disease in response to rituximab. *J Clin Rheumatol* 2005; 11: 314-8.
28. DINC A, SOY M, PAY S, SIMSEK I, ERDEM H, SOBACI G: A case of Churg-Strauss syndrome presenting with cortical blindness. *Clin Rheumatol* 2000; 19: 318-20.
29. CHANG Y, KARGAS SA, GOATES JJ, HOROUPIAN DS: Intraventricular and subarachnoid hemorrhage resulting from necrotizing vasculitis of the choroid plexus in a patient with Churg-Strauss syndrome. *Clin Neuropathol* 1993; 12: 84-7.
30. CALVO-ROMERO JM, DEL CARMEN BONILLA-GRACIA, BUREO-DACAL P: Churg-Strauss syndrome presenting as spontaneous subarachnoid haemorrhage. *Clin Rheumatol* 2002; 21: 261-3.
31. PIPITONE N, VERSARI A, SALVARANI C: Role of imaging studies in the diagnosis and follow-up of large-vessel vasculitis: an update. *Rheumatology* (Oxford) 2008; 47: 403-8.
32. SALVARANI C, BROWN RD JR, CALAMIA KT *et al*.: Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol* 2007; 62: 442-51.
33. YAMASHITA Y, TAKAHASHI M, BUSSAKA H, MIYAWAKI M, TOSAKA K: Cerebral vasculitis secondary to Wegener's granulomatosis: computed tomography and angiographic findings. *J Comput Tomogr* 1986; 10: 115-20.
34. SAVITZ JM, YOUNG MA, RATAN RR: Basilar artery occlusion in a young patient with Wegener's granulomatosis. *Stroke* 1994; 25: 214-6.
35. ANZALONE N, RIGHI C, SIMIONATO F *et al*.: Three-dimensional time-of-flight MR angiography in the evaluation of intracranial aneurysms treated with Guglielmi detachable coils. *AJNR Am J Neuroradiol* 2000; 21: 746-52.
36. BOULIN A, PIEROT L: Follow-up of intracranial aneurysms treated with detachable coils: comparison of gadolinium-enhanced 3D time-of-flight MR angiography and digital subtraction angiography. *Radiology* 2001; 219: 108-13.
37. KAHARA VJ, SEPPANEN SK, RYYMIN PS, MATTILA P, KUURNE T, LAASONEN EM: MR angiography with three-dimensional time-of-flight and targeted maximum-intensity-projection reconstructions in the follow-up of intracranial aneurysms embolized with Guglielmi detachable coils. *AJNR Am J Neuroradiol* 1999; 20: 1470-5.
38. HEISERMAN JE, DRAYER BP, KELLER PJ, FRAM EK: Intracranial vascular stenosis and occlusion: evaluation with three-dimensional time-of-flight MR angiography. *Radiology* 1992; 185: 667-73.
39. WILMS G, BOSMANS H, DEMAEREL P, MAR-

CHAL G: Magnetic resonance angiography of the intracranial vessels. *Eur J Radiol* 2001; 38: 10-8.
40. GRANZIERA C, MICHEL P, ROSSETTI AO, LURATI F, REYMOND S, BOGOUSSLAVSKY J: Wegener granulomatosis presenting with haemorragic stroke in a young adult. *J Neurol* 2005; 252: 615-6.
41. KONATE A, LE FALHER G, CROZAT-GROSLERON S, RIVIERE S, LE QUELLEC A: (Incidence and presentation of the central neurological manifestations of Wegener's granulomatosis: a monocentric study of 14 cases). *Rev Med Interne* 2004; 25:183-8.
42. CARAMASCHI P, BIASI D, CARLETTO A, BAMBARA LM: A case of ANCA-associated vasculitis with predominant involvement of central nervous system. *Joint Bone Spine* 2003; 70: 380-3.
43. LIOU HH, YIP PK, CHANG YC, LIU HM: Allergic granulomatosis and angiitis (Churg-Strauss syndrome) presenting as prominent neurologic lesions and optic neuritis. *J Rheumatol* 1994; 21: 2380-4.
44. TAYLOR CT, BURING SM, TAYLOR KH: Treatment of Wegener's granulomatosis with immune globulin: CNS involvement in an adolescent female. *Ann Pharmacother* 1999; 33: 1055-9.
45. SZCZEPIORKOWSKI ZM, BANDARENKO N, KIM HC *et al*.: Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. *J Clin Apher* 2007; 22: 106-75.
46. JAYNE DR, GASKIN G, RASMUSSEN N *et al*.: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007; 18: 2180-8.
47. NGUYEN T, MARTIN MK, INDRIKOVS AJ: Plasmapheresis for diffuse alveolar hemorrhage in a patient with Wegener's granulomatosis: case report and review of the literature. *J Clin Apher* 2005; 20: 230-4.
48. DE GROOT K, SCHMIDT DK, ARLT AC, GROSS WL, REINHOLD-KELLER E: Standardized neurologic evaluations of 128 patients with Wegener granulomatosis. *Arch Neurol* 2001; 58: 1215-21.
49. ANDERSON JM, JAMIESON DG, JEFFERSON JM: Non-healing granuloma and the nervous system. *Q J Med* 1975; 44: 309-23.
50. DRACHMAN DD: Neurological complications of Wegener's granulomatosis. Archives of *Neurology* 1963; 8:145-55.
51. PROVENZALE JM, ALLEN NB: Wegener granulomatosis: CT and MR findings. *AJNR Am J Neuroradiol* 1996; 17: 785-92.
52. FRED HL, LYNCH EC, GREENBERG SD, GONZALEZ-ANGULO A: A patient with Wegener's granulomatosis exhibiting unusual clinical and morphologic features. *Am J Med* 1964; 37: 311-9.
53. LUCAS FV, BENJAMIN SP, STEINBERG MC: Cerebral vasculitis in Wegener's granulomatosis. *Cleve Clin Q* 1976; 43: 275-81.
54. PINCHING AJ, LOCKWOOD CM, PUSSELL BA *et al*.: Wegener's granulomatosis: observations on 18 patients with severe renal disease. *Q J Med* 1983; 52: 435-60.
55. ASMUS R, KOLTZE H, MUHLE C *et al*.: MRI of the head in Wegener's granulomatosis. *Adv Exp Med Biol* 1993; 336:319-21.
56. KRAEMER M, BERLIT P: Systemic, secondary and infectious causes for cerebral vasculitis: clinical experience with 16 new European cases. *Rheumatol Int* 2009.
57. AKKARA VEETIL BM, SCHIMMER BM: A case of limited systemic sclerosis with p-ANCA, complicated by multiple cerebral hemorrhages. *Rheumatol Int* 2009; 29: 325-9.
58. CHUMBLEY LC, HARRISON EG JR, DE REMEE RA: Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. *Mayo Clin Proc* 1977; 52: 477-84.
59. LANHAM JG, ELKON KB, PUSEY CD, HUGHES GR: Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine* (Baltimore) 1984; 63: 65-81.