

# Pathology of CNS Vasculitides

This article aims to give an overview of the central nervous system (CNS) vasculitides. Vasculitides are characterised histologically by inflammation within the vessel wall itself, with or without vessel necrosis. Several classification systems have been proposed: by size of vessel affected, by mechanism of damage or, perhaps more usefully, as primary or secondary. Primary CNS vasculitis is an idiopathic disorder restricted to the CNS. Secondary CNS vasculitis occurs as part of a systemic disorder (Table 1). Exact figures for incidence rates are unavailable but primary CNS vasculitis is uncommon relative to secondary causes.

**Table 1: Causes of Secondary CNS Vasculitis**

<b>Infection</b>
<i>Bacterial: pyogenic meningitis, TB, spirochaetes</i>
<i>Fungal: Aspergillus, Histoplasmosis</i>
<i>Parasitic: Malaria, Toxoplasma</i>
<i>Viral: Herpes zoster, Herpes simplex, Varicella zoster, HIV</i>
<b>Malignancy</b>
<i>Lymphoma, lymphomatoid granulomatosis</i>
<b>Primary Systemic Vasculitides</b>
<i>(See table 2)</i>
<b>Connective Tissue Disease</b>
<i>Systemic lupus erythematosus, Rheumatoid arthritis, Sjogrens disease</i>
<b>Drugs</b>
<i>Amphetamine, cocaine, vasoconstrictors</i>
<b>Miscellaneous</b>
<i>Behçets disease, sarcoidosis</i>

## Pathophysiology

In cases due to infection the infectious agent itself may directly invade the vessel wall. Most other cases have an underlying immune-mediated mechanism. Various immunopathogenic mechanisms can be involved, including immune complex deposition, cell mediated immune attack or autoantibody mediated attack. In the case of the latter there are two particular autoantibodies which are strongly associated with vascular inflammation. The first, antineutrophil cytoplasmic antibody (ANCA) is associated with various systemic vasculitides (Table 2). The other, anti-endothelial cell antibody, is directed against vascular endothelial cells in Kawasaki's disease.

The basic mechanism involves an interaction between white blood cells and the vessel wall. An initial triggering event causes circulating white blood cells and the vascular endothelium to express various cell surface markers and release a variety of pro-inflammatory soluble mediators (cytokines). This results in attachment of inflammatory cells to the vascular endothelium with subsequent migration into the vessel wall. The end result is disruption of normal vessel function with mechanical impedance to blood flow, increased vasomotor contractility and increased risk of thrombosis.<sup>1</sup>

## Clinical presentation

The clinical presentation depends on the underlying disorder and distribution of the cerebral vessels affected. Cerebral involvement may be focal (stroke, ataxia, movement disorder, focal seizure) or non-focal (headache, encephalopathy/meningitis, psychiatric symptoms, generalised seizures). Spinal cord involvement may present as transverse myelitis/myelopathy. Other presentations

include visual disturbance, mass lesion and a multiple sclerosis type picture.

Several other disorders can mimic CNS vasculitis clinically (Table 3) and should be considered in the differential diagnosis.<sup>2,3</sup> Evaluation of patients with suspected CNS vasculitis therefore needs to take account of both the large number of causes of secondary CNS vasculitis and the conditions that mimic it.

Useful laboratory tests include inflammatory markers (ESR/CRP), rheumatoid factor and anti-nuclear antibody for connective tissue disease; HIV, syphilis serology and blood cultures to rule out infection. CSF analysis is usually abnormal in CNS vasculitis, typically showing elevated protein levels and a lymphocytic pleocytosis. A chest X-ray is useful if sarcoid, lymphomatoid granulomatosis or malignancy is part of the differential diagnosis. No individual test has sufficient sensitivity or specificity to absolutely rule in or rule out the diagnosis.<sup>4</sup> The diagnostic work up should therefore aim to exclude secondary causes and mimics. If these are excluded then primary CNS vasculitis should be considered.

Since the diagnosis of a primary CNS vasculitis is one of exclusion, we shall discuss some of the secondary causes first.

## Secondary causes of CNS vasculitis

Infectious agents can cause focal or diffuse vasculitis and may present with neurological manifestations in the absence of systemic disease. There is a known association between a variety of lymphomas and the occurrence of granulomatous cerebral vasculitis.

Primary systemic vasculitides are commonly classified

**Table 2: Classification of Systemic Vasculitides**

	<b>ANCA positive</b>	<b>ANCA negative</b>
<i>Small Vessel</i>	<i>Wegener's granulomatosis Churg-Strauss syndrome Microscopic polyangiitis</i>	<i>Henoch-Schonlein purpura Essential cryoglobulinaemia</i>
<i>Medium Vessel</i>		<i>Polyarteritis nodosa Kawasaki disease</i>
<i>Large Vessel</i>		<i>Giant cell arteritis Takayasu's disease</i>

**Table 3: Conditions mimicking CNS vasculitis**

<b>Cerebral Vasospasm</b>
<i>Migraine</i>
<i>Malignant systemic hypertension</i>
<i>Eclampsia</i>
<i>Phaeochromocytoma</i>
<b>Coagulopathies</b>
<i>Disseminated intravascular coagulation</i>
<i>Thrombotic thrombocytopenic purpura</i>
<i>Hyperviscosity syndromes (paraproteinaemia, polycythemia)</i>
<b>Arterial Disease</b>
<i>Atherosclerosis</i>
<i>Cerebral amyloid angiopathy</i>
<i>CADASIL</i>
<i>Moya-Moya disease</i>
<i>Fibromuscular dysplasia</i>
<b>Cardiac emboli</b>
<i>Causes of embolus including atrial fibrillation, infective endocarditis</i>
<b>Multiple Sclerosis and other demyelinating disease</b>



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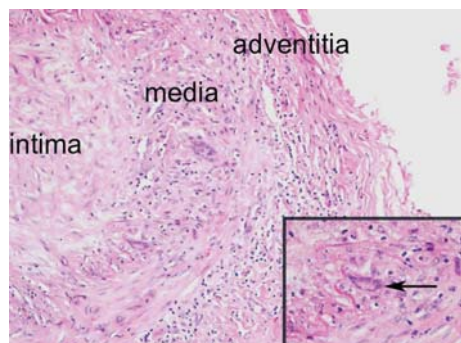


Figure 1: Giant cell arteritis: Chronic inflammatory cell infiltrate within temporal artery wall. The artery is composed of an inner endothelial layer (intima), a middle muscular layer (media), and an outer connective tissue layer (adventitia). The inflammation is centered predominantly on the internal elastic lamina (at the junction of the intima and media) and adventitia. Note the prominent intimal oedema on the left hand side of the picture (haematoxylin and eosin, x10 objective). Inset: giant cell (arrow) adjacent to pink staining fragments of disrupted internal elastic lamina (haematoxylin and eosin stain, x40 objective).

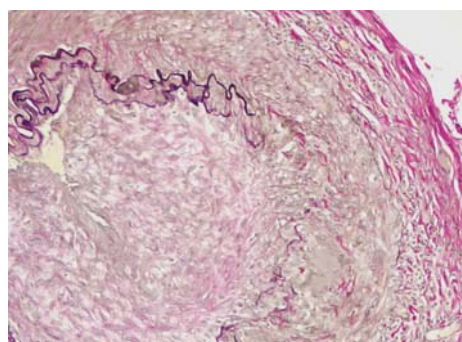


Figure 2: Giant cell arteritis: temporal artery biopsy demonstrating focal destruction of internal elastic lamina. Note the abrupt discontinuity of the black staining internal elastic lamina (elastic van Gieson stain, x10 objective).

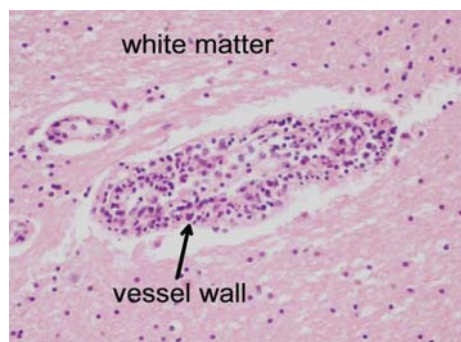
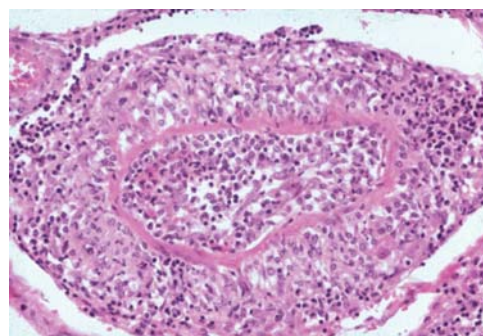
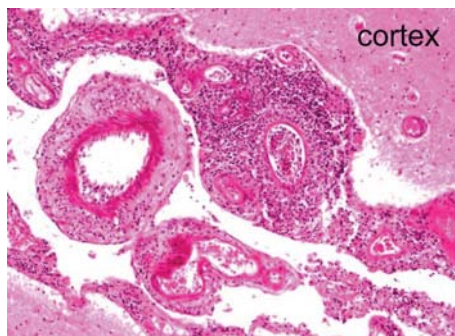


Figure 3: Cerebral systemic lupus erythematosus with a lymphocytic vasculitis - the vessel wall is expanded by a dense lymphocytic infiltrate. The surrounding tissue is cerebral white matter. (haematoxylin and eosin stain, x20 objective).

by size of vessel affected and the presence of ANCA (Table 2). Giant cell arteritis (GCA) and Takayasu's arteritis are both granulomatous primary systemic vasculitides. GCA is the more common. Both affect the aorta and its branches, GCA tending to affect the extracranial branches of the carotid, Takayasu's tending to affect the proximal branches of the aorta. The commonest cerebral manifestations of GCA are visual symptoms due to retinal ischaemia and ischaemic optic neuropathy. Temporal artery biopsy in GCA typically shows granulomatous inflammation centred on the internal elastic lamina (Figures 1 and 2). CNS involvement in Takayasu's is usually a result of carotid artery stenosis or cerebral hypoperfusion.



Figures 4 (left) and 5 (right): Primary angiitis of the central nervous system. Florid mononuclear inflammation of small meningeal arteries. The vessel walls are expanded by a variably dense infiltrate composed predominantly of lymphocytes. The surrounding tissue in figure 4 represents the underlying cerebral cortical tissue. The vessel wall in figure 5 is expanded by a dense lymphocytic infiltrate (haematoxylin and eosin stain, figure 4: x10 objective, figure 5: x20 objective).

Polyarteritis nodosa is a systemic necrotising vasculitis of medium and small vessels typically causing peripheral neuropathy. CNS involvement occurs in up to 40% of cases but is variable in its presentation. Kawasaki disease is an acute febrile multisystem vasculitis affecting medium sized vessels. It usually affects children under five years and is associated with conjunctival and oral erythema, oedema of palms and soles. CNS involvement is relatively rare. A variety of small vessel vasculitides affect the CNS and can be subclassified according to their association with ANCA. Neurological involvement is highly variable.

Several connective tissue diseases and drugs are also associated with cerebral vasculitis (Table 1 and Figure 3) but will not be discussed in further detail here.

### Primary CNS vasculitis

Primary CNS vasculitis (primary angiitis of the CNS: PACNS) is a rare idiopathic vasculitis predominantly affecting small leptomeningeal vessels without evidence of systemic disease. A recent survey showed that 29 European neurologists from 15 countries collectively made a diagnosis of cerebral vasculitis in 140 patients per annum.<sup>5</sup> It occurs at any age but is commonest between ages 40 and 60.

Patients usually have an abnormal CSF with increased numbers of mixed chronic inflammatory cells and increased protein. MRI is usually abnormal but the features are non-specific (infarcts, leptomeningeal disease, diffuse white matter disease). Angiography is classically said to show alternating stenosis and ectasia affecting multiple vessels in multiple vascular beds. However, a wide variety of less specific findings are also described such that atheroma and vasoconstrictive disorders can mimic PACNS angiographically.

Biopsy is considered the gold standard for diagnosis (although some clinical subsets show no biopsy abnormality - see below). It is important in confirming the diagnosis and excluding other causes. In one series of biopsies for suspected PACNS alternative diagnoses requiring different management were identified in 39% of cases.<sup>6</sup> The serious morbidity rate associated with brain biopsy in suspected vasculitis is 3.3%, which compares favourably with that associated with the immunosuppressive treatment that a mistaken diagnosis of PACNS might entail.<sup>7</sup>

The main histopathological findings are chronic inflammatory cells in and around the walls of leptomeningeal and intracerebral vessels (Figures 4 and 5). The distribution is focal and segmental (explaining the angiographic appearances) and can be granulomatous, lymphocytic or mixed. Biopsy yield can be increased by sampling radiologically abnormal areas and including both leptomeninges and cortex in the sample.<sup>8</sup> The histological differential diagnosis includes lymphoproliferative disease, sarcoid and infection (special stains for organisms should always be performed). If the inflammatory infiltrate is predominantly lymphocytic then angiocentric lymphoma should be considered and if granulomatous then other causes of granulomatous inflammation (including tuberculosis, sarcoid and fungal infection) should be excluded.

### Clinical subsets of PACNS

Increasing evidence suggests that PACNS is in fact composed of at least three differing clinical subsets with varying prognoses and treatment requirements.<sup>9</sup> Granulomatous angiitis of the CNS (GACNS) is the most severe form - characterised by granulomatous inflammation of small to medium vessels. CSF analysis is always abnormal but angiography may show no abnormality. Benign angiopathy of the CNS (BACNS) is a subset of PACNS which tends to follow a more benign course.<sup>10</sup> Angiography typically shows alternating stenosis and ectasia and these findings disappear within three to four months of symptom onset. The presentation is usually acute with focal or multi-focal neurological deficits but CSF analysis is usually normal or near normal and biopsy is negative. The aetiology is uncertain but is probably vasospastic in origin. The majority of cases fall into the grouping of "atypical PACNS". These patients fail to meet criteria for PACNS or BACNS and exhibit a lymphocytic vasculitis at biopsy. CSF analysis is typically abnormal and angiographic findings, if present, are non-reversible.

### Treatment and prognosis of PACNS

No randomised trials have been performed for the treatment of PACNS. At present the usual recommendation in cases of GACNS is a regimen combining glucocorticoids plus cytotoxic drugs (usually cyclophosphamide). Response can be assessed with follow-up MRI and or

angiography. There are no specific guidelines with respect to duration of therapy but treatment is usually continued for a minimum of 6 to 12 months following remission. Atypical PACNS should be treated with glucocorticoids plus additional immunosuppressive treatment if necessary to achieve remission. Treatment of BACNS is less aggressive, usually glucocorticoids for six months, often with adjunctive calcium channel blockers.

The outcome in patients with PACNS treated with immunosuppressive treatment is less bleak than previously supposed with less than 10% mortality and approximately 20 to 30% developing significant disability.<sup>11</sup> Patients diagnosed with BACNS usually do well, with 94% showing significant recovery and 71% showing no evidence of long term disability.<sup>12</sup>

### Conclusions

The central nervous vasculitides encompass a large number of primary and secondary disorders with a wide differential diagnosis. The presentation is variable and specific tests are lacking. Accurate diagnosis is important in order to exclude possible mimics which may require different therapeutic approaches and to avoid unnecessary immunosuppressive treatment with its attendant risks. There is increasing evidence that primary CNS vasculitis is composed of differing clinical subsets (on the basis of clinical, laboratory, angiographic and pathological findings) and these subsets vary in both their prognoses and treatment.

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## Neurological Signs

# Carphologia, or Floccillation

Respecting the movement of the hands, I have these observations to make: when in acute fevers, pneumonia, phrenitis, or headache, the hands are waved before the face, hunting through empty space, as if gathering bits of straw, picking the nap from the coverlet, or tearing chaff from the wall – all such symptoms are bad and deadly.

Hippocrates *Book of Prognostics* 4

Apparently aimless plucking movements have been named either carphologia or floccillation, because of their fancied likeness to picking up pieces of straw or wool, respectively. The term carphologia has recently been adopted by a columnist in a rival journal,<sup>1</sup> but it is difficult to find any specific articles on the subject of these movements (see absence of references on Medline). Perhaps the account by Hippocrates (or his school), which I believe to be the original, said all that needs to be said. The movements have apparently been observed in dementing disorders such as Alzheimer's disease or vascular dementia, delirium (phrenitis, literally "brain fever", whence our word frenzy, may perhaps be equivalent to delirium), and some psychiatric disorders, and may possibly reflect frontal lobe dysfunction.<sup>2</sup> Although their description is of great antiquity, these movements may still be misinterpreted.

A 58-year-old man presented with rest and action tremor of the right (dominant) arm, slow quiet speech, hypomimia, and with examination findings of mild rigidity, micrographia, and reduced right arm swing. Concurrently, he had developed progressive memory problems sufficient to prevent him from running his business; Mini-Mental State Examination score was 19/30, with slowed responses. Neuropsychological assessment showed severe impairment on the Mattis Dementia Rating Scale, particularly on subtests of initiation/perseveration and attention, and also on the Delis-Kaplan Executive Function System, indicating a frontal-subcortical profile of dementia. Neurological signs were unresponsive to levodopa preparations. Over the subsequent two year period the patient developed progressive cognitive decline, slow saccadic eye movements, levator inhibition, retrocollis, the applause sign, and recurrent falls, on

one occasion causing a fracture of the proximal phalanx of the ring finger, all felt to be consistent with a clinical diagnosis of progressive supranuclear palsy (PSP).<sup>3</sup>

Shortly after admission to a nursing home because of ongoing falls, care staff reported the patient to be "self-harming". Specifically, he was reported to pinch repeatedly the skin on his left arm and chest with his right arm in a rough, jerky manner, sometimes sufficiently hard to cause bruising or even draw blood. These movements were observed in the clinic as intermittent picking or plucking movements on the clothing or skin with the tremulous right hand. Patient questioning revealed no suicidal ideation or desire to self-harm.

The superimposition of a jerky action tremor on carphologia may increase the amplitude and reduce the accuracy of these otherwise innocuous movements, such that they might pinch and even break the skin, and hence be misinterpreted as self-injurious behaviour. Clearly, the identification of individuals who self-harm is of fundamental importance because of the greatly increased risk of subsequent suicide.<sup>4</sup> Passive self-harm in patients with dementia resident in nursing homes, such as refusal to eat, drink, or take medications, is of similar concern since this may be associated with increased mortality.<sup>5</sup> Self-injurious behaviour is rare in movement disorders, although it may be a feature in some (e.g. neuroacanthocytosis, Lesch-Nyhan disease). Involuntary, tremulous carphologia should not be mistaken for self-harm.

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