PART I: INFECTIOUS AND INFLAMMATORY CONDITIONS

1 ISOLATED ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

Mathieu Zuber

Isolated angiitis of the central nervous system (CNS) is a rare condition with an incidence estimated at less than 1:2 000 000 (Moore, 1999). It was defined, in 1959, as an idiopathic vasculitis restricted to small leptomeningeal and parenchymal arteries and veins, without apparent systemic involvement (Cravioto and Feigin, 1959). Almost 50 years later, the affliction remains poorly recognized, and its pathogenesis mysterious, despite the growing pool of knowledge on processes responsible for CNS inflammation. The term "primary angiitis" is sometimes preferred to "isolated angiitis" because complete autopsies are rarely performed and minor abnormalities are occasionally observed in systemic organs of patients who died from so-called isolated CNS angiitis (Johnson *et al.*, 1994). In numerous patients with no histological proof of vascular inflammation, the descriptive term "angiopathy" is more appropriate than "angiitis," but the latter term has often been overused in the recent literature.

Although stroke most often reveals the disease, it appears as the initial manifestation in only a minority of patients. Because of the protean clinical symptoms and blurred diagnostic criteria, identification is a difficult challenge for all clinicians.

Pathology and pathogenesis

Pathological picture

Isolated CNS angiitis has been referred to by several names descriptive of the pathological findings: granulomatous angiitis of the CNS, giant cell granulomatous angiitis of the CNS, and cerebral granulomatous angiitis have all been used interchangeably (Hankey, 1991; Rhodes *et al.*, 1995). This variable terminology partly reflects the difficulty in separating isolated CNS angiitis as a pathological entity from systemic disorders, such as giant cell temporal angiitis or sarcoidosis, themselves occasionally responsible for CNS angiitis.

The nonspecific pathological pattern of isolated CNS angiitis is characterized by infiltrations of the vascular walls with mononuclear cells including lymphocytes, macrophages, and histiocytes. Fibrinoid necrosis is occasionally seen, especially in the acute phase (Craviato and Feigin, 1959; Hankey, 1991; Lie, 1992; Rhodes *et al.*, 1995). In about 85% of patients, granulomas with epithelioid cells and giant Langerhans cells are described. The degree of this granuloma formation is variable. In early disease, granulomas are often not found. The misleading terminology "granulomatous angiitis," should no longer be used to describe isolated CNS angiitis. The inflammatory lesions may sometimes spread to all the vascular wall layers but preservation of the media is the rule. Pure lymphocytic infiltration is rare, but it may be more frequent in childhood (Lanthier *et al.*, 2001).

Vascular abnormalities primarily involve small- and middle-sized arteries and, less frequently, veins and venules. Arteries less than 500 μm in diameter may be solely affected. In most cases, leptomeningeal involvement is a dominating feature, with less consistent parenchymatous vascular involvement in white matter and gray matter. The segmental involvement of vessels may be responsible for false-negative histological results.

Pathogenesis

The pathogenesis of isolated CNS angiitis is unknown and progress is slow because of the rarity of tissue samples acquired from carefully documented cases. CNS inflammation activates the brainstem noradrenergic and trigeminovascular responses, contributing to reduction of regional vascular blood flow (Moore, 1998). This activation could enhance the appearance of arterial stenosis.

Isolated CNS angiitis is now regarded as an immunological, nonspecific T-cell-mediated inflammatory reaction rather than a specific entity (Calabrese *et al.*, 1997; Ferro, 1998; Moore, 1998). This view is in accordance with:

1. the wide spectrum of diseases described in association with isolated CNS angiitis,
2. the limited known responses of the CNS blood vessels to a variety of noxious stimuli, and
3. the clinical and pathological heterogeneity of the disorder (although this may reflect individual differences in the host response).

The reason why the inflammatory response to various factors may be maladaptive and leads to disease remains mostly speculative. Chronicity of the stimuli, concurrent diseases, and genetic susceptibility are probably critical factors (Moore, 1998). According to the view that isolated CNS angiitis is probably a heterogeneous syndrome rather than a single entity, new conditions might emerge in the future that are placed in this category.

Indeed, instances of isolated CNS angiitis have been reported after various infections, such as mycoplasma, varicella zoster, or arbovirus infections (Chu *et al.*, 1998). Both mycoplasma- and virus-like particles were identified in glial cells and cerebral blood

Uncommon Causes of Stroke, 2nd edition, ed. Louis R. Caplan. Published by Cambridge University Press.

vessels of patients with isolated CNS angiitis (Arthur and Margolis, 1977; Linnemann and Alvira, 1980). Moreover, histological patterns very similar to isolated CNS angiitis have been reported in herpes zoster arteritis (Chu *et al.*, 1998) and a well-documented case previously published as CNS angiitis was recently shown to be in fact related to varicella zoster infection (Gilden *et al.*, 1996).

When angiitis is described in association with lymphoma, it usually remains unclear whether it is due to a malignant lymphoproliferative infiltration, the reactivation of some remote viral infection, or to nonspecific inflammatory mechanisms, such as those suspected to be responsible for isolated CNS angiitis (Greer *et al.*, 1988). Angiitis was also found to coexist with cerebral amyloid angiopathy (Fountain and Eberhard, 1996; Gray *et al.*, 1990). Angiitis is more probably an inflammatory response to β-A4-amyloid deposits than itself responsible for the amyloid deposition (Fountain and Eberhard, 1996; Yamada *et al.*, 1996). Patients with such association of both pathological lesions present with unusual clinical features (see the following Section). This so-called amyloid-related angiitis is a good example of a well-defined entity newly extracted from the wide spectrum of isolated CNS angiitis (Scolding *et al.*, 2005). More recently, a case associating isolated CNS angiitis and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was reported (Schmidley *et al.*, 2005).

Clinical features

The clinical presentation of CNS angiitis is highly variable because virtually any anatomic area of the CNS may be affected by the angiitis. Angiitis (whatever its cause) may thus mimic a wide range of CNS diseases. Isolated CNS angiitis has no specific symptoms that help to distinguish it from other causes of CNS vasculopathies, either infectious or noninfectious (Zuber *et al.*, 1999). A wide range of evolution has also been reported, stretching from a quasi-indolent disease to death in a few months (Calabrese and Mallek, 1988; Hankey, 1991; Johnson *et al.*, 1994). A subacute deterioration is most often observed. Relapsing symptoms are described.

Isolated CNS angiitis is twice as frequent in males as in females and onset most often occurs after 40 years of age. However, the disease can affect all age categories and cohorts of children with the condition were recently reported (Aviv *et al.*, 2006; Benseler *et al.*, 2005; Lanthier *et al.*, 2001). Conversely, mean age at presentation is unusually high (more than 65 years of age) in patients with β-amyloid-related angiitis (Scolding *et al.*, 2005).

Headache is the most common presenting symptom of isolated CNS (occurring in two-thirds of patients), and it is variable both in quality and severity (Hankey, 1991). Nonfocal symptoms, such as a fluctuating level of consciousness or a decrease in memory, associated with headaches, are typical of CNS angiitis and sometimes combine in an encephalopathic clinical pattern (Calabrese *et al.*, 1997). Abnormalities in cognition and behavior are present in most patients with β-amyloid-related angiitis (Scolding *et al.*, 2005). In some patients, headaches may suggest a chronic meningitis (Reik *et al.*, 1983).

All types of strokes have been observed in CNS angiitis including definite cerebral infarcts, transient ischemic attacks (TIAs), and intraparenchymal and subarachnoid hemorrhages (Biller *et al.*, 1987; Johnson *et al.*, 1994; Koo and Massey, 1988; Kumar *et al.*, 1997; Moore, 1989). Intracranial bleedings could be more prevalent than ischemic strokes but this has not been systematically studied. These various intracranial bleedings are posited to result from

Table 1.1 Causes of cerebral angiitis *(adapted from Zuber et al., 1999)*

Infectious angiitis	Varicella zoster/Herpes zoster
	Cytomegalovirus infection
	Human immunodeficiency virus infection
	Mycotic and parasitic infections
	Syphilis
	Borrelia burgdorferi
	Tuberculosis
	Purulent bacterial meningitis
	Bacterial endocarditis
Primary systemic angiitis	Polyarteritis nodosa
Necrotizing	Churg and Strauss angiitis
Giant cell	Cogan's syndrome
– Granulomatous	Temporal angiitis
– Others	Takayasu's arteritis
	Wegener's granulomatosis
	Lymphomatoid granulomatosis
	Hypersensitivity angiitis, Kawasaki's arteritis
	Bürger's disease
	Susac's syndrome
	Kohlmeier–Degos disease
	Acute posterior multifocal placoid pigment epitheliopathy
Angiitis secondary to systemic disease	Systemic lupus erythematosus
	Sjögren's syndrome
	Behçet's disease
	Sarcoidosis
	Rheumatoid polyarthritis
	Scleroderma
	Mixed connectivitis
	Dermatomyositis
	Ulcerative colitis
	Celiac disease
Angiitis associated with neoplasia	Hodgkin's disease and non-Hodgkin's-type lymphoma
	Malignant histiocytosis
	Hairy cell leukemia
	Neoplastic meningitis
Angiitis associated with drug abuse or treatments	Illicit drugs (cocaine, crack)
	Sympathomimetic agents
	Amphetamine and relatives
	Transplantations
	Radiotherapy
Isolated angiitis of the CNS	

vessel wall weakening resulting from transmural inflammation (Kristoferitsch *et al.*, 1984; Negishi and Sze, 1993). A multi-infarct state has been reported in some patients with CNS vasculitis (Koo and Massey, 1988).

In a critical review of isolated CNS angiitis patients, stroke was not found to be the presenting symptom in any of the histologically proven cases (Vollmer *et al.*, 1993). However, a stroke-like presentation in a patient with pre-existent diffuse cerebral symptoms should prompt a search for radiological signs in favor of angiitis. Subarachnoid hemorrhage was the presenting manifestation in several isolated CNS angiitis patients (Kumar *et al.*, 1997; Nishikawa *et al.*, 1998; Ozawa *et al.*, 1995).

Beside strokes, seizures and cranial neuropathies are other focal symptoms that occur in patients with isolated CNS angiitis (Hankey, 1991). A mass lesion presentation accounts for about 15% of patients. A necrotic unihemispheric presentation has rarely been reported (Derry *et al.*, 2002). Spinal cord involvement may be inaugural with a progressive paraparesis as the most common clinical manifestation (Bhibhatbhan *et al.*, 2006; Calabrese *et al.*, 1997). Exceptionally, the presence of spinal root pain may reveal an angiitis limited to the cauda equina (Harrison, 1976). Isolated CNS angiitis was also diagnosed in three patients with a posterior leukoencephalopathy characterized by major visual disturbances (Wijdicks *et al.*, 2003). On the whole, focal symptoms are observed in about 50% of patients (Calabrese and Mallek, 1988). However, focal symptoms nearly always occur in the setting of diffuse higher cortical impairment.

Fever is observed in 15% of patients and this confounding feature may be responsible for extensive systemic diagnostic testing (Hankey, 1991). If a patient has systemic complaints in addition to the cerebral symptoms, appropriate investigations will usually reveal some diffuse disorder responsible for multiorgan vasculitis. It is well-known that CNS angiitis, although rare, is one of the most serious complications of connective diseases and was described in most of them (Table 1.1).

Depending on the various clinical presentations, the differential diagnostic considerations are numerous. Meningoencephalitis, multiple sclerosis, abscess, and stroke of other mechanisms are the most frequently discussed in patients with acute or subacute onsets. A progressive onset may suggest neoplastic disease or dementia. Specific causes may also be discussed depending on the context, such as giant cell temporal angiitis in the elderly with headaches or Behçet's disease in a young Mediterranean patient with subacute rhombencephalitis.

Isolated CNS angiitis should also be distinguished from reversible cerebral vasoconstriction syndrome (the so-called Call–Fleming syndrome), a disease characterized by arterial vasoconstriction and much more frequent, in fact, than cerebral angiitis (Call *et al.*, 1988) (see Chapter 67). Segmental stenoses are located on medium-sized cerebral arteries and spontaneously resolve within weeks to months, although ischemic or hemorrhagic stroke may occasionally develop (Ducros *et al.*, 2007). The clinical presentation in patients with reversible angiopathy is most often different from cerebral angiitis, with an identified triggering condition for vasoconstriction, severe thunderclap headaches, and rapid improvement under nimodipine or other calcium channel blocker treatment (Zuber *et al.*, 2006). MR angiography shows arterial stenoses supporting the diagnosis in most cases and normalization of the vessel's caliber is observed on serial procedures, in association with clinical relief (Figure 1.1).

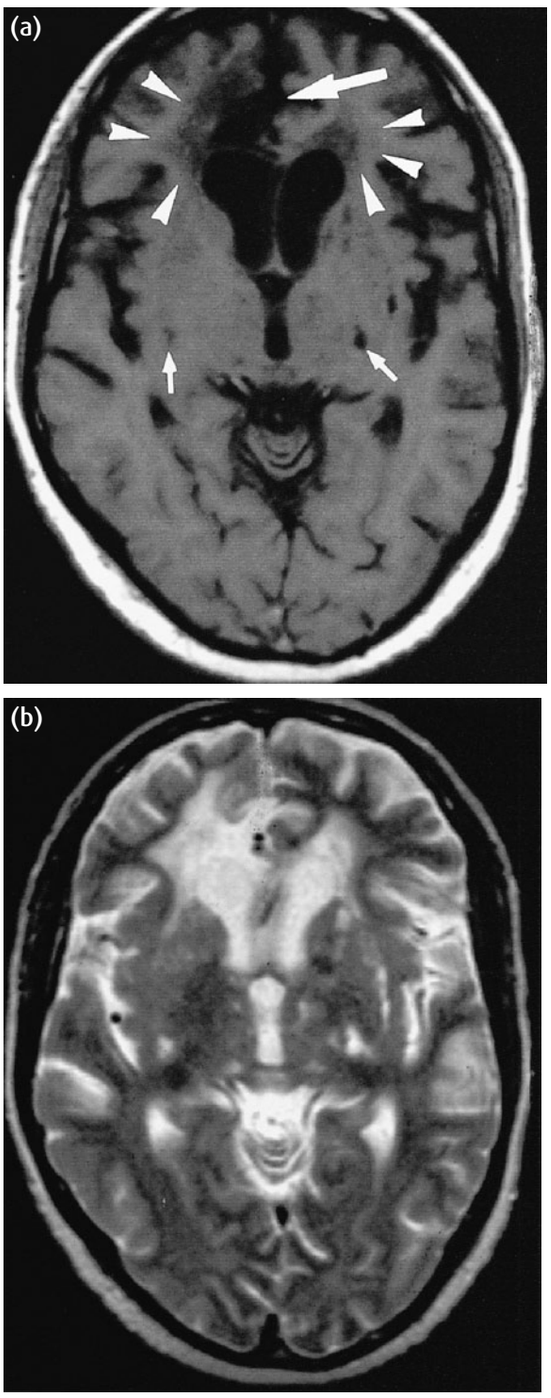

Figure 1.1 MRI abnormalities in patients with IACNS. (a) and (b) (same patient, T1- and T2-weighted sequences). Large infarction in the ACA territory (arrow) associated with deep profound infarctions (small arrows) and anterior leukoencephalopathy (arrowheads). (c) Lobar hemorrhage revealing IACNS.

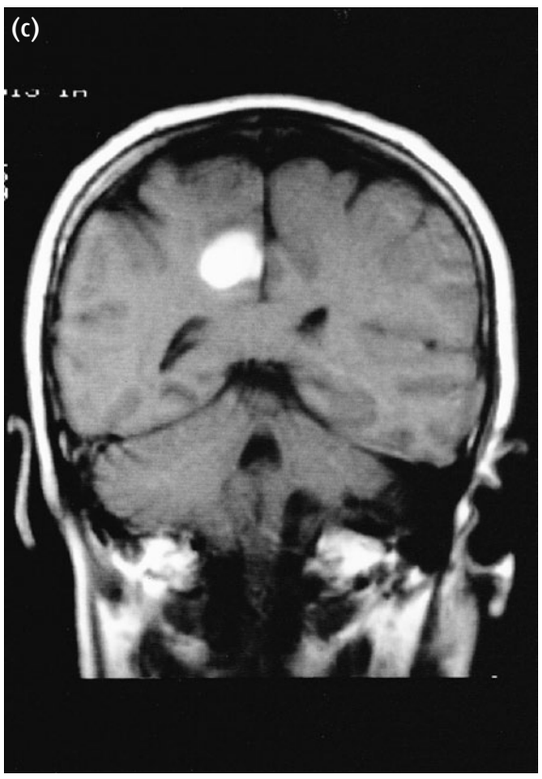

Figure 1.1 (*cont.*)

Diagnostic procedures

The cerebral arteries are separated from brain tissue by the blood–brain barrier so that biological markers supporting the diagnosis of isolated CNS angiitis are not found in most patients. The sedimentation rate is moderately increased in about 30% of biopsy-confirmed isolated CNS angiitis patients (Hankey, 1991). No immunological marker has been identified to date and antinuclear, antiphospholipid, and antineutrophil cytoplasmic antibodies are invariably normal. Cerebrospinal fluid (CSF) inflammation (moderate lymphocytic pleiocytosis, elevated protein, and normal glucose) is observed in about 90% of patients with histologically confirmed isolated CNS angiitis (Calabrese *et al.*, 1997) and is important (although highly nonspecific) for presumption of CNS vasculitis in a patient with stroke of remote origin. Oligoclonal bands are seldom reported. The CSF should always be cultured owing to possible CNS vasculitis due to viral, fungal, or indolent bacterial infections (Table 1.1).

Perivascular inflammatory lesions may be found in the retina, and fundoscopy has been reported as a valuable diagnostic tool in isolated CNS angiitis (Ohtake *et al.*, 1989). Optic fluorescein angiography could also be useful, especially in patients with normal cerebral angiography (Scolding *et al.*, 1997).

Brain imaging

Both cranial CT scans and MRIs show nonspecific abnormalities in CNS angiitis. The sensitivity of CT scan is low, at about 30%. MRI is of course more sensitive (about 80%), especially in detecting small brain lesions (Chu *et al.*, 1998) (Figure 1.2). The most common CT scan finding is focal or multifocal low density areas of varying sizes. Association with multiple parenchymal contrast enhancement and focal cerebral atrophy, or combination of both ischemic and hemorrhagic strokes, in the same patient is suggestive. Apart from signs of recent ischemic or hemorrhagic

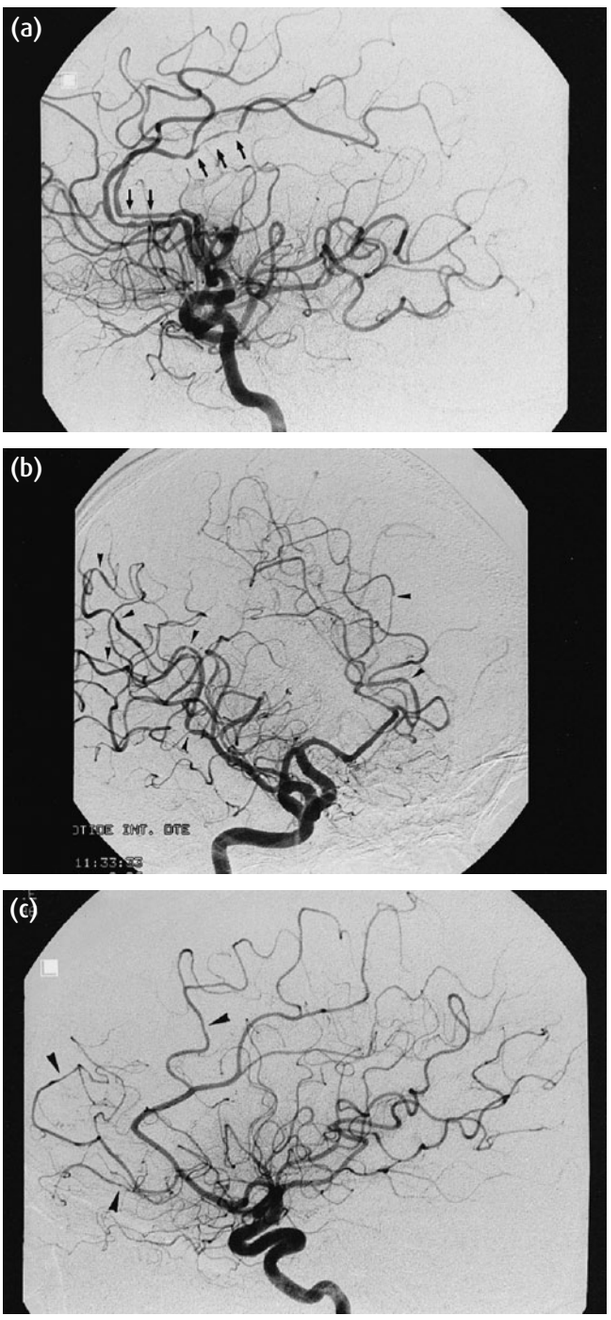

Figure 1.2 (a), (b), and (c). Cerebral angiography in patients with IACNS. Note the multiple stenoses on small- and middle-size arteries (arrows and arrowheads) delineating "sausage-like" appearances.

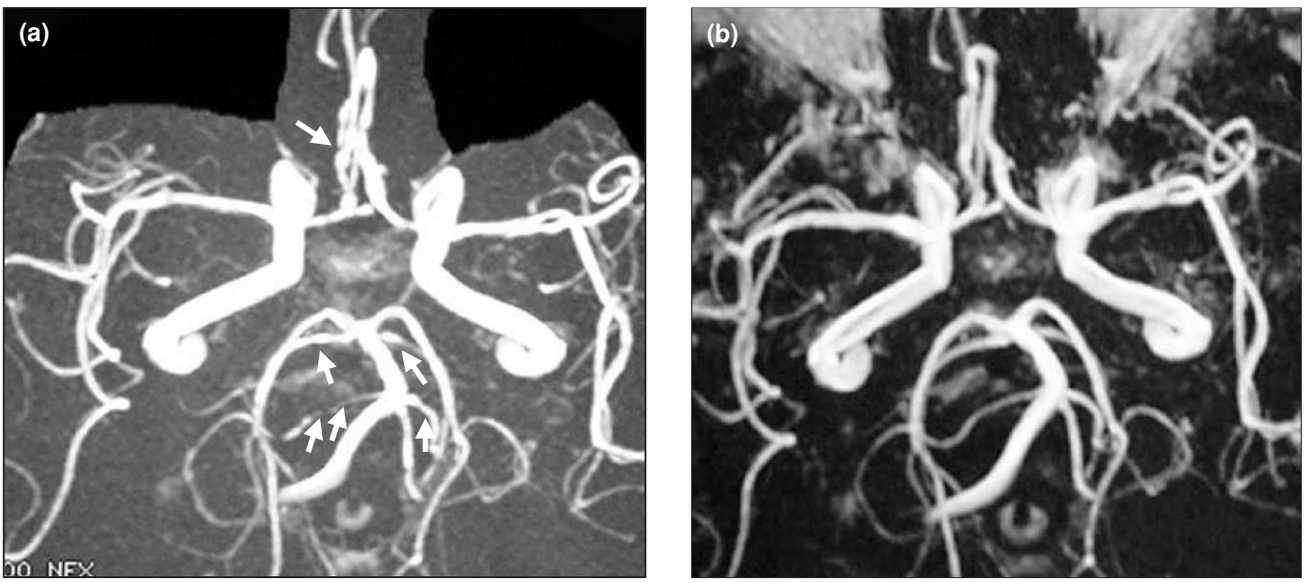

Figure 1.3 Serial MR angiography showing (a) multiple stenoses and filling defects on middle-size cerebral arteries and (b) complete resolution at one month in a reversible cerebral angiopathy. Adapted from Zuber *et al.* (2006) with kind permission of Springer Science and Business Media.

strokes, MRI frequently reveals nonspecific high intensity signals on T2-weighted sequences, sometimes responsible for leukoencephalopathy. Disseminated T2 hypersignals in white matter with no periventricular localization could indicate CNS angiitis, by contrast with the hypersignals described in multiple sclerosis (Miller *et al.*, 1987). Children with isolated CNS angiitis often have multifocal and supratentorial but unilateral lesions (Aviv *et al.*, 2006). Intracerebral hemorrhage, either in the cortex or the white matter, may occur as a result of infarction or focal necrosis of vessel walls (Hunn *et al.*, 1998). Hemorrhage is more frequent in isolated CNS angiitis than in infectious angiitis (Pierot *et al.*, 1991).

The fluid-attenuated inversion recovery (FLAIR) sequence may provide strong suspicion for distal intracranial arterial stenoses by showing several hyperintense vessel signs due to abnormal arterial blood flow kinetics (Iancu-Gontard *et al.*, 2003). Linear and punctate patterns of leptomeningeal enhancement accompanied by both hemispheric and penetrating vessels are observed in up to 60% of patients with isolated CNS angiitis, sometimes without significant parenchymal abnormalities (Chu *et al.*, 1998; Negishi and Sze, 1993). However, in my experience, visualization of leptomeningeal contrast enhancement is much less frequent. Recently, apparent diffusion coefficient mapping of the normal-appearing brain showed that abnormalities in patients with CNS angiitis are more diffuse than previously suspected (White, *et al.*, 2007).

Unusual CT scan and MRI presentations have been occasionally observed, including pseudotumoral lesions, repeated parenchymal or ventricular bleeding, multiple punctuate parenchymal contrast enhancement (milliary appearance), or diffuse white matter involvement suggesting a primary demyelinating disease (Finelli *et al.*, 1997; Hankey, 1991; Kristoferitsch *et al.*, 1984).

Angiography

The angiographic features characteristic of isolated CNS angiitis are multifocal stenoses rendering a sausage-like appearance with ectasia and occasional arterial occlusions (Figure 1.3). If the disease is restricted to arteries less than 500 μm in diameter, angiography will be reported as normal. A normal angiographical pattern is reported in up to 50% of patients, and abnormalities may only appear on repeated procedures (Kadkhodayan *et al.*, 2004; Linnemann and Alvira, 1980; Zuber *et al.*, 1999). Angiography-negative isolated CNS angiitis may be observed whatever the age, including in childhood (Benseler *et al.*, 2006). Intracerebral aneurysms and even multiple vanishing aneurysms have been seldom reported (Nishikawa *et al.*, 1998), but the pattern never mimics large ectasias of the arteries of the circle of Willis, similar to what has been typically reported in children and young adults with infections such as HIV (Kossorotoff *et al.*, 2006). Multiple microaneurysms, a very characteristic radiological pattern in peripheral tissues with vasculitis such as periarteritis nodosa, are invariably absent in isolated CNS angiitis (Chu *et al.*, 1998).

Because of the recent widespread development of the techniques, MR angiography and CT angiography are increasingly used as the first line radiological procedures for exploration of the intracerebral arteries in case of suspected CNS vasculitis. The sensitivity of both techniques for small cerebral vessel visualization has unquestionably improved over the past years. However, this sensitivity remains lower than with conventional angiography. Angiography has not been found to provide excessive risk in a large number of patients with suspected CNS vasculitis (0.8% of persistent morbidity) (Hellman *et al.*, 1992). For these different reasons, we believe that conventional angiography should still be regarded as the gold standard when CNS vasculitis is suspected.

Brain biopsy

The diagnosis of definite isolated CNS angiitis relies upon brain-leptomeningeal biopsy in all cases. The ideal diagnostic brain biopsy is a 1 cm wedge of cortex including leptomeninges and preferably containing a cortical vessel (Moore, 1989). Including leptomeninges in the biopsy is crucial because leptomeningeal involvement is a dominating pathological feature in isolated CNS angiitis (Hunn *et al.*, 1998; Zuber *et al.*, 1999). Among ten histologically confirmed isolated CNS angiitis patients, diagnostic changes were observed solely in leptomeningeal vessels in three patients (Chu *et al.*, 1998). False-negative biopsy results may be observed, particularly because of the segmental involvement of vessels, and cases with pathological features typical of isolated CNS angiitis recognized only on a recurrent biopsy have been reported. For patients without focal lesions, the preferred biopsy site is the prefrontal area or the temporal tip of the nondominant hemisphere. Nonspecific abnormalities found on brain imaging should provide useful information for selecting the biopsy site. However, mismatches between the radiological abnormalities and histological predominant lesions may explain false-negative biopsy results (Oliveira *et al.*, 1994). The use of stereotactic needle biopsies may account for a significant number of sampling errors because it lowers the sensitivity of biopsy to approximately 50% (Duna and Calabrese, 1995). This procedure should therefore be confined to cases with an isolated profound pseudotumoral lesion. Cultures of brain tissue and leptomeninges using special stains for various microorganisms should be systematically performed. The morbidity rate of brain biopsy (0.03%–2%) (Chu *et al.*, 1998; Hankey, 1991) cannot be overlooked but must be balanced against the risks of unnecessary immunosuppression.

Table 1.2 Causes of segmental intracranial arterial narrowing *(adapted from Zuber* et al.*, 1999)*

Cerebral angiitis, either:
– primary or secondary
– inflammatory or infectious
Intracranial dissection:
– traumatic
– spontaneous
– underlying vasculopathy (fibromuscular dysplasia)
Intracranial atherosclerosis
Recanalizing embolism
Vasospasm:
– acute hypertension
– reversible cerebral angiopathy
– migraine
Moya-moya
Cerebral radiotherapy
Tumor encasement:
– meningioma
– chordoma
– pituitary adenoma
– gliomatosis cerebri
Sickle cell anemia
Neurofibromatosis
Dysgenesis

Diagnostic strategy

Recognizing CNS angiitis is one of the most challenging neurological diagnostic problems. The reasons for this include:

1. relative rarity of the disorders,
2. lack of specificity for clinical signs and symptoms,
3. lack of efficient noninvasive diagnostic tests, and
4. inaccessibility of the end organ tissues for pathologic examination (Touzé and Méary).

The following diagnostic criteria were proposed by Moore (1989):

1. association of headaches and multiple neurological deficits that persist for at least 6 months,
2. segmental arterial stenoses on cerebral angiograms,
3. exclusion of any infectious or inflammatory cause, and
4. inflammatory lesions of the vascular wall on cerebral and/or leptomeningeal biopsy or exclusion of all other causes of cerebral angiitis.

Because of lack of specificity, there is currently no consensus regarding the appropriate use of brain imaging, angiography and brain biopsy for the diagnosis of isolated CNS angiitis (Duna and Calabrese, 1995; Harris *et al.*, 1994; Kadkhodayan *et al.*, 2004). There has been a recent trend towards diagnosing isolated CNS angiitis with angiography without tissue confirmation, at least in a subset of patients with a self-limited clinical course (Abu-Shakra *et al.*, 1994). The problem is that we do not have early prognostic markers of isolated CNS angiitis and the disease may rapidly kill in the absence of appropriate treatment.

Few but important studies focused on the specificity of radiological signs suggestive for isolated CNS angiitis and asked whether these signs were predictive of a positive biopsy. Among MRI signs useful for the diagnosis of isolated CNS angiitis, leptomeningeal enhancement was found to be more sensitive than parenchymal abnormalities (Chu *et al.*, 1998; Duna and Calabrese, 1995). It should be stressed that the combination of normal MRI and CSF test results had a strong negative predictive value and allowed exclusion of CNS vasculitis in most clinical situations (Calabrese *et al.*, 1997). Whether high-resolution 3 Tesla MRI could provide more information than standard MRI for the diagnosis of isolated CNS angiitis remains to be determined.

In addition to a rather low sensitivity in showing arterial abnormalities when isolated CNS angiitis is suspected, conventional angiography has a low positive predictive value and specificity. As shown in Table 1.2, arterial stenoses in the brain may result from to various conditions, among which intracranial atherosclerosis and hypertensive vasospasms are the most frequently observed. The classical sausage-like segmental stenoses seem to be even more frequent in atherosclerosis or reversible cerebral angiopathy than in isolated CNS angiitis (Chu *et al.*, 1998). Topographical

considerations may help for the differentiation: involvement of the supraclinoid carotid arteries and of the proximal MCA is usual in intracranial atherosclerosis, while more distal arteries are predominantly affected in isolated CNS angiitis. Arterial calcifications on a CT scan in the vicinity of stenoses may also be considered as indicative for intracranial atherosclerosis (Zuber *et al.*, 1999). Variations in stenoses on serial angiography are seen in CNS angiitis, but the pattern is also observed in reversible cerebral angiopathy.

Given first the lack of specific clinical and radiological features of isolated CNS angiitis, second the statistical likelihood of dealing with an alternative disorder, and third the morbidity associated with immunosuppressive regimens, we believe that early biopsy verification should be discussed in all patients with clearly suspected CNS angiitis (Calabrese *et al.*, 1997; Chu *et al.*, 1998). This assertion is reinforced by the recent publication of 25 patients with suspected primary CNS angiitis and negative brain biopsy: those who received an immunosuppressive therapy were not found to have a better outcome (Alreshaid and Powers, 2003).

The accuracy of diagnosis should be revisited periodically when the surgical procedure is delayed because of lack of evidence for CNS angiitis. Among stroke patients, the biopsy should be especially considered when headaches are prominent and associated with CSF and MRI abnormalities.

Treatment and prognosis

Reports before 1980 uniformly concluded that isolated CNS angiitis is a more or less rapidly fatal disease. This failed to account for the fact that isolated CNS angiitis was invariably diagnosed late in the evolution of the disease. In addition, no treatment regimen had been proposed in most patients.

Owing to the rarity of the disease, no controlled therapeutic trial has been conducted in isolated CNS angiitis to date, either diagnosed by leptomeningeal biopsy or by angiography. In a review of 46 patients, 19 of the 20 nontreated patients rapidly progressed either to death or to the persistence of severe sequelae, while 4 of the 13 patients treated by corticosteroids alone and 10 of the 13 treated by a combination of corticosteroids and cyclophosphamide showed favorable progression (Calabrese and Mallek, 1988). More recent analysis of isolated CNS angiitis patients suggests that the prognosis of the disease is not uniformly unfavorable. The results of a retrospective series of 105 patients showed that isolated CNS angiitis is more prone to relapse during prolonged periods when arterial abnormalities are located on small-sized arteries rather than on middle-sized arteries (MacLaren *et al.*, 2005). Combined aggressive therapy should be reserved for those patients with histologically proven isolated CNS angiitis and a deteriorating clinical status. In these patients, the combination therapy should be pursued for at least 6–12 months after the patient is in remission. According to the treatment of systemic vasculitis, cyclophosphamide is usually prescribed intravenously. Alternative treatment with azathioprine or methotrexate can be proposed when cyclophosphamide is not well-tolerated, but no valuable experience with other immunosuppressive drugs than cyclophosphamide has yet to be published. To our knowledge, intravenous gammaglobulins, a treatment regimen occasionally proposed in cerebral angiitis with systemic diseases (Canhao *et al.*, 2000), has not been used in isolated CNS angiitis patients.

The activity of the disease under treatment is appreciated using clinical, biological, and radiological monitoring. Regression of CSF abnormalities may parallel clinical improvement (Oliveira *et al.*, 1994). The successful use of serial angiography has been reported (Alhalabi and Moore, 1994), but MR angiography or angio CT scans are also increasingly used for follow-up. Transcranial doppler occasionally reveals improvement of the cerebral circulation under treatment (Ritter *et al.*, 2002). Clinical stabilization for years with discontinuation of treatment has been described in occasional cases, as well as improvement of the MRI appearance, and the disappearance of vessel wall inflammation years after immunosuppression (Ehsan *et al.*, 1995; Johnson *et al.*, 1994; Riemer *et al.*, 1999), but a prolonged neurological supervision is necessary because relapsing episodes are possible.

In patients with a unique focal presentation such as stroke, and with isolated CNS angiitis suspected on the basis of angiography alone, a course of several-weeks of high-dose corticosteroids associated with a calcium channel blocker and no immunosuppressor has been proposed (Calabrese *et al.*, 1997). The diagnosis of reversible cerebral angiopathy should be carefully considered in these patients. Any additive vasoconstrictive stimuli including uncontrolled hypertension should be avoided.

REFERENCES

Abu-Shakra, M., Khraishi, M., Grosman, H., *et al.* 1994. Primary angiitis of the CNS diagnosed by angiography. *Q J Med*, **87**, 351–8.

Alhalabi, M., and Moore, P. M. 1994. Serial angiography in isolated angiitis of the central nervous system. *Neurology*, **44**, 1221–6.

Alreshaid, A. A., and Powers, W. J. 2003. Prognosis of patients with suspected primary CNS angiitis and negative brain biopsy. *Neurology*, **61**, 831–3.

Arthur, G., and Margolis, G. 1977. Mycoplasma-like structures in granulomatous angiitis of the central nervous system: case reports with light and electron microscope studies. *Arch Pathol Lab Med*, **101**, 382–7.

Aviv, R. I., Benseler, S. M., Silvermann, E. D., *et al.* 2006. MR imaging and angiography of primary CNS vasculitis of childhood. *Am. J Neuroradiol*, **27**, 192–9.

Benseler, S. M., de Veber, G., Hawkins, C., *et al.* 2005. Angiography-negative primary central nervous system vasculitis in children. *Arthritis Rheum*, **52**, 2159–67.

Bhibhatbhan, A., Katz, N. R., Hudon, M., *et al.* 2006. Primary angiitis of the spinal cord presenting as a conus mass: long term remission. *Surg Neurol*, **66**, 622–5.

Biller, J., Loftus, C. M., Moore, S. A., *et al.* 1987. Isolated central nervous system angiitis first presenting as spontaneous intracranial hemorrhage. *Neurosurgery*, **20**, 310–15.

Calabrese, L. H., and Mallek, J. A. 1988. Primary angiitis of the central nervous system. Report of 8 cases, review of the literature and proposal for diagnostic criteria. *Medicine*, **108**, 815–23.

Calabrese, L. H., Duna, G. F., and Lie, J. T. 1997. Vasculitis in the central nervous system. *Arthritis Rheum*, **40**, 1189–201.

Call, G. K., Fleming, M. C., Sealfon, S., *et al.* 1988. Reversible cerebral segmental vasoconstriction. *Stroke*, **19**, 1159–70.

Canhao, H., Fonseca, J. E., and Rosa, A. 2000. Intravenous gammaglobulin in the treatment of central nervous system vasculitis associated with Sjogren's syndrome. *J Rheumatol*, **27**, 1102–3.

Chu, C. T., Gray, L., Goldstein, L. B., and Hulette, C. M. 1998. Diagnosis of intracranial vasculitis: a multi-disciplinary approach. *J Neuropathol Exp Neurol*, **57**, 30–8.

Cravioto H., and Feigin I. 1959. Noninfectious granulomatous angiitis with a predilection for the nervous system. *Neurology*, **9**, 599–609.

Derry, C., Dale, R. C., Thom, M., Miller, D. H., and Giovanni, G. 2002. Unihemispheric cerebral vasculitis mimicking Rasmussen's encephalitis. *Neurology*, **58**, 327–8.

Ducros, A. Boukobza, M., Porcher, A., *et al.*, 2007. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain*, **130**, 3091–101.

Duna, G., and Calabrese, L. H. 1995. Limitations of invasive modalities in the diagnosis of primary angiitis of the central nervous system. *J Rheumatol*, **22**, 662–7.

Ehsan, T., Hasan, S., Powers, J. M., and Heiserman, J. E. 1995. Serial magnetic resonance imaging in isolated angiitis of the central nervous system. *Neurology*, **45**, 1462–5.

Ferro, J. M. 1998. Vasculitis of the central nervous system. *J Neurol*, **245**, 766–76.

Finelli, P. F., Onyiuke, H. C., and Uphoff, D. F. 1997. Idiopathic granulomatous angiitis of the CNS manifesting as diffuse white matter disease. *Neurology*, **49**, 1696–9.

Fountain, N. B., and Eberhard, D. A. 1996. Primary angiitis of the central nervous system associated with cerebral amyloid angiopathy: report of two cases and review of the literature. *Neurology*, **46**, 190–7.

Gilden, D. H., Kleinschmidt-DeMasters, B. K., Wellish, M., *et al.* 1996. Varicella zoster virus, a cause of waxing and waning vasculitis: the *New England Journal of Medicine* case 5–1995 revisited. *Neurology*, **47**, 1441–6.

Gray, F., Viners, H. V., Le Noan, H., *et al.* 1990. Cerebral amyloid angiopathy and granulomatous angiitis: immunohistochemical study using antibodies to the Alzheimer A4 peptide. *Hum Pathol*, **21**, 1290–3.

Greer, J. M., Longley, S., Edwards, L., Elfenbein, G. J., and Panush, R. S. 1988. Vasculitis associated with malignancy. Experience with 13 patients and literature review. *Medicine*, **67**, 220–30.

Hankey, G. J. 1991. Isolated angiitis/angiopathy of the central nervous system. *erebrovasc Dis*, **1**, 2–15.

Harris, K. G., Tran, D. D., Sickels, W. J., Cornell, S. H., and Yuh, W. T. C. 1994. Diagnosing intracranial vasculitis: the roles of MR and angiography. *Am J Neuroradiol*, **15**, 317–30.

Harrison, P. E. 1976. Granulomatous angiitis of the central nervous system. Case report and review. *J Neurol Sci*, **29**, 335–41.

Hellmann, D. B., Roubenoff, R., Healy, R. A., and Wang, H. 1992. Central nervous system angiography: safety and predictors of a positive result in 125 consecutive patients evaluated for possible vasculitis. *J Rheumatol*, **19**, 568–72.

Hunn, M., Robinson, S., Wakefield, L., Mossman, S., and Abernethy, D. 1998. Granulomatous angiitis of the CNS causing spontaneous intracerebral haemorrhage: the importance of leptomeningeal biopsy. *J Neurol Neurosurg Psychiatry*, **65**, 956–7.

Iancu-Gontard, D., Oppenheim, C., Touzé, E., *et al.* 2003. Evaluation of hyperintense vessels on FLAIR MRI for the diagnosis of intracerebral arterial stenoses. *Stroke*, **34**, 1886–91.

Johnson, M. D., Maciunas, R., Creasy, J., and Collins, R. D. 1994. Indolent granulomatous angiitis. *J Neurosurg*, **81**, 472–6.

Kadkhodayan, Y., Alreshaid, A., Moran, J. C., Cross, D. T., Powers, W. J., and Derdeyn, C. P. 2004. Primary angiitis of the central nervous system at conventional angiography. *Radiology*, **233**, 878–82.

Koo, E. H., and Massey, E. W. 1988. Granulomatous angiitis of the central nervous system: protean manifestations and response to treatment. *J Neurol Neurosurg Psychiatry*, **51**, 1126–33.

Kossorotoff, M., Touz, E., Godon-Hardy, S., *et al.* 2006. Cerebral vasculopathy with aneurysm formation in HIV-infected young adults. *Neurology*, **66**, 1121–22.

Kristoferitsch W, Jellinger K, and Böck F. 1984. Cerebral granulomatous angiitis with atypical features. *J Neurol*, **231**, 38–42.

Kumar, R., Wijdicks, E. F. M., Brown, R. D. Jr., Parisis, J. E., and Hammond, C. A. 1997. Isolated angiitis of the CNS presenting as subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*, **62**, 649–51.

Lanthier, S., Lortie, A., Michaud, J., Laxer, R., Jay, V., and de Veber, G. 2001. Isolated angiitis of the CNS in children. *Neurology*, **56**, 837–42.

Lie, J. T. 1992. Primary (granulomatous) angiitis of the central nervous system: a clinical pathologic analysis of 15 new cases and a review of the literature. *Hum Pathol*, **23**, 164–71.

Linnemann, C. C., and Alvira, M. M. 1980. Pathogenesis of varicella-zoster angiitis in the CNS. *Arch Neurol*, **37**, 239–40.

MacLaren, K., Gillepsie, J., Shrestha, S., Neary, D., and Ballardie, F. W. 2005. Primary angiitis of the central nervous system: emerging variants. *Q J Med*, **98**, 643–54.

Miller, D. H., Ormerod, I. E. C., Gibson, A., *et al.* 1987. MR brain scanning in patients with vasculitis: differentiation from multiple sclerosis. *Neuroradiology*, **29**, 226–31.

Moore, P. M. 1989. Diagnosis and management of isolated angiitis of the central nervous system. *Neurology*, **39**, 167–73.

Moore, P. M. 1998. Central nervous system vasculitis. *Curr Opin Neurol*, **11**, 241–6.

Moore, P. M. 1999. The vasculitides. *Curr Opin Neurol*, **12**, 383–8.

Negishi, C., and Sze, G. 1993. Vasculitis presenting as primary leptomeningeal enhancement with minimal parenchymal findings. *AJNR Am J Neuroradiol*, **14**, 26–8.

Nishikawa, M., Sakamoto, H., Katsuyama, J., Hakuba, A., and Nishimura, S. 1998. Multiple appearing and vanishing aneurysms: primary angiitis of the central nervous system. *J Neurosurg*, **88**, 133–7.

Ohtake, T., Yoshida, H., Hirose, K., and Tanabe, H. 1989. Diagnostic value of the optic fundus in cerebral angiitis. *J Neurol*, **236**, 490–1.

Oliveira, V. C., Povoa, P., Costa, A., and Ducla-Soares, J. 1994. Cerebrospinal fluid and therapy of isolated angiitis of the central nervous system. *Stroke*, **25**, 1693–5.

Ozawa, T., Sasaki, O., Sorimachi, T., and Tanaka, R. 1995. Primary angiitis of the central nervous system: report of two cases and review of the literature. *Neurosurgery*, **36**, 173–9.

Parisi, J. E., and Moore, P. M. 1994. The role of biopsy in vasculitis of the central nervous system. *Semin Neurol*, **14**, 341–8.

Pierot, L., Chiras, J., Debussche-Depriester, C., Dormont, D., and Bories, J. 1991. Intracerebral stenoting arteriopathies. Contribution of three radiological techniques to the diagnosis. *J Neuroradiol.*, **18**, 32–48.

Reik, L., Grunnet, M. L., Spencer, R. P., and Donaldson, J. O. 1983. Granulomatous angiitis presenting as chronic meningitis and ventriculitis. *Neurology*, **33**, 1609–12.

Rhodes, R. H., Madelaire, N. C., Petrelli, M., Cole, M., and Karaman, B. A. 1995. Primary angiitis and angiopathy of the central nervous system and their relationship to systemic giant cell arteritis. *Arch Pathol Lab Med*, **119**, 334–9.

Riemer, G., Lamszus, K., Zschaber, R., *et al.* 1999. Isolated angiitis of the central nervous system: lack of inflammation after long-term treatment. *Neurology*, **52**, 196–9.

Ritter, M. A., Dziewas, R., Papke, K., and Liemann, P. 2002. Follow-up examinations by transcranial doppler ultrasound in primary angiitis of the central nervous system. *Cerebrovasc Dis*, **14**, 139–42.

Schmidley, J. W., Beadle, B. A., and Trigg, L. 2005. Co-occurrence of CADASIL and isolated CNS angiitis. *Cerebrovasc Dis*, **19**, 352–4.

Scolding, N. J., Jayne, D. R., Zajicek, J. P., *et al.* 1997. Cerebral vasculitis – recognition, diagnosis and management. *Q J Med*, **90**, 61–73.

Scolding, N. J., Joseph, F., Kirby, P. A., *et al.* 2005. Aβ-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain*, **128**, 500–15.

Vollmer, T. L., Guarnaccia, J., Harrington, W., Pacia, S. V., and Petroff, O. A. C. 1993. Idiopathic granulomatous angiitis of the central nervous system: diagnosis challenges. *Arch Neurol*, **50**, 925–30.

White, M. L., Hadley, W. L., Zhang, Y., and Dogar, M. A. 2007. Analysis of central nervous system vasculitis with diffusion-weighted imaging and apparent diffusion coefficient mapping of the normal-appearing brain. *Am J Neuroradiol*, **28**, 933–7.

Wijdicks, E. F. M., Manno, E. M., Fulgham, J. R., and Giannini, C. 2003. Cerebral angiitis mimicking posterior leukoencephalopathy. *J Neurol*, **250**, 444–8.

Yamada, M., Itoh, Y., Shintaku, M., *et al.* 1996. Immune reactions associated with cerebral amyloid angiopathy. *Stroke*, **27**, 1155–62.

Zuber, M., Blustajn, J., Arquizan, C., *et al.* 1999. Angiitis of the central nervous system. *J Neuroradiol*, **26**, 101–17.

Zuber M, Touzé E, Domigo V, *et al.* 2006. Reversible cerebral angiopathy: efficacy of nimodipine. *J Neurol*, **253**, 1585–8.

2 TEMPORAL ARTERITIS

A. Wesley Thevathasan and Stephen M. Davis

Introduction

Temporal (giant cell) arteritis is a systemic disease, involving various medium-sized and larger arteries, that occurs mostly in elderly patients. In addition to the classical clinical symptoms of headache, jaw claudication, and polymyalgia rheumatica syndrome, neurological manifestations are common. Blindness due to ischemic optic neuropathy is probably the most common and most feared sinister manifestation of the disease, but stroke is the leading cause of death in patients with temporal arteritis (Caselli *et al.*, 1988). Temporal arteritis was first described by Hutchinson (1890) and later by Horton *et al.* (1934). The original clinical report described an elderly man, who was unable to wear his hat because of scalp pain. He had inflamed and hardened superficial temporal arteries on examination. The disease is variously called either "temporal arteritis" or "giant cell arteritis." The term "temporal arteritis" refers to the characteristic involvement of the superficial temporal arteries, while the term "giant cell arteritis" emphasizes the systemic nature of the disease and the characteristic pathology, with giant cells being typically present in the vessel wall (Figures 2.1 and 2.2).

On a sinister historical note, it was even suggested that Adolf Hitler might have had the disease in the 1940s, with recorded symptoms of headache, impaired vision, sensitivity to pressure in the temporal regions, swollen temporal arteries, constitutional symptoms, and a raised erythrocyte sedimentation rate (Redlich, 1993). Others however, have suggested cluster headache as an alternative diagnosis (Schmidt, 1994).

Pathology

Temporal arteritis is a medium- and large-vessel vasculitis that tends to involve cranial branches of the aorta. Additionally, preference for vessels with a high elastic component means that the ophthalmic, posterior ciliary, and vertebral branches of the external carotid are most commonly affected (Goodman, 1979; Wilkinson and Russell, 1972). Intracranial involvement is very rare (Gibb *et al.*, 1985; Mclean *et al.*, 1993).

However, temporal arteritis is a systemic vasculitis with a well-described extracranial involvement. (Klein *et al.*, 1975). Involvement of mesenteric vessels can cause abdominal pain. Limb claudication and Raynaud's phenomena can result from subclavian and femoral artery disease (Klein *et al.*, 1975). Angiography is sometimes a useful procedure when used to distinguish arteritis from atherosclerotic disease in these settings (Gillanders, 1969; Klein *et al.*, 1975;). Aortic aneurysm and dissection is now increasingly recognized as a late complication of temporal arteritis (Evans *et al.*, 1995). One dramatic case report has even described a death resulting from an aortoduodenal fistula (Lagrand *et al.*, 1996).

At a microscopic level, there is an inflammatory infiltrate of the vessel wall. This is usually focal and segmental, resulting in the "skip lesions" that can cause sampling error when too little of the artery is removed for a biopsy. Three histological patterns have been described (Goodman, 1979; Lie, 1990). The classical finding is granulomatous inflammation with giant cells at the junction of intima and media. (Figures 2.1 and 2.2) However, these changes are found in only about 50% of positive biopsies. Just as common is a nonspecific panarteritis without giant cells. Rarely, only a small vessel vasculitis surrounding a normal temporal artery is seen (Esteban *et al.*, 2001).

Epidemiology and clinical features

A number of epidemiological studies have evaluated the incidence, age, and gender associations of temporal arteritis. In Olmstead County, Minnesota, the annual incidence of the disease was 17.8

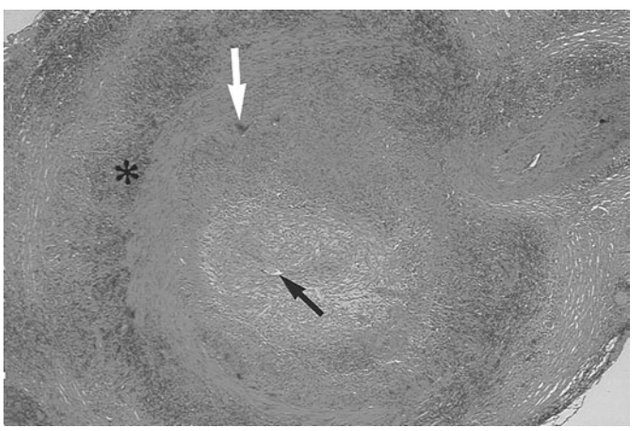

Figure 2.1 Low-powered view of the transverse section of superficial temporal artery with features of giant cell arteritis. There is a slit-like lumen (black arrow) due to intimal swelling, with disruption of the internal elastic lamina (*) and scattered, multinucleated giant cells (white arrow). See color plate.

Uncommon Causes of Stroke, 2nd edition, ed. Louis R. Caplan. Published by Cambridge University Press.

Figure 2.2 High-powered view of disrupted internal elastic lamina (white arrow), with multinucleated giant cell (black arrow). See color plate.

per 100 000 in those aged over 50 years (Machado *et al.*, 1988). Incidence increases with age and peaks between 70 and 80 years of age. Women are at least twice as often affected (Salvarani *et al.*, 2002). Prevalence is higher in those of Scandinavian and Northern European descent (Franzen *et al.*, 1992; Hunder, 2002).

Headache is the most common symptom (Goodman, 1979). Headache is often severe and associated with scalp tenderness, usually in the region of the temporal arteries. Hence the patient may have scalp pain when brushing the hair, or even resting his or her head on a pillow. However, the headache pattern is often atypical, and the diagnosis should be considered in any elderly patient presenting with headache (Huston *et al.*, 1978). Jaw claudication, meanwhile, is the most specific nonneurological feature of the condition and is due to involvement of the facial artery (Goodman, 1979; Smetana and Shmerling, 2002). Other clinical manifestations, also due to arteritis of external carotid artery branches, can include scalp, skin, and tongue necrosis (Figure 2.3; Table 2.1). Examination of the temporal arteries, typically reveals tenderness, and the temporal arteries may become firm, nodular, and pulseless (Salvarani *et al.*, 2002). The occipital arteries are also often involved and can show similar abnormalities in response to palpation.

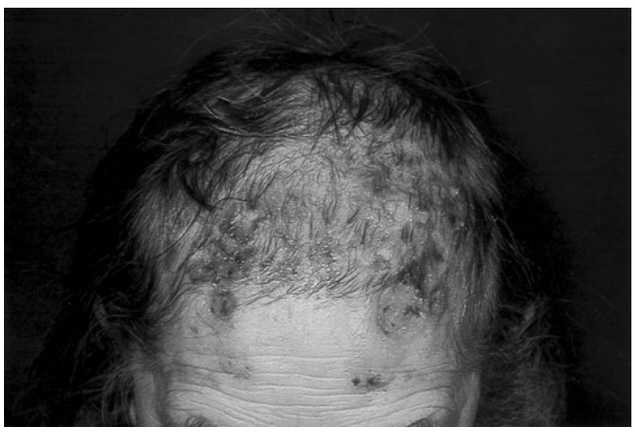

Figure 2.3 Extensive scalp necrosis in a patient with biopsy-proven temporal arteritis. See color plate.

Table 2.1 Cardinal symptoms of temporal arteritis

Headache
Polymyalgia rheumatica syndrome
Jaw claudication
Constitutional symptoms (anorexia, weight loss, malaise)
Scalp necrosis
Ischemic optic neuropathy
Stroke

Systemic symptoms can include fever, malaise, and anorexia with weight loss. These features are especially common in patients with coexisting polymyalgia rheumatica (PMR), but can be conspicuously absent. A low-grade fever can occur and may even reach 40°C. In fact, temporal arteritis is a classical cause of "pyrexia of unknown origin" in the elderly (Calamia and Hunder, 1981).

The relationship between temporal arteritis and PMR is complex. Many experts consider both to be different spectrums of the same disease (Salvarani *et al.*, 2002). About 50% of patients with temporal arteritis will also have PMR (Calamia and Hunder, 1981). Suggestive symptoms include shoulder and, less commonly, hip girdle pain. As a result, a classical complaint is difficulty hanging out the wash on a clothesline. MRI studies have implicated not only synovitis but also periarticular bursitis and tenosynovitis (Pavlica *et al.*, 2000). IT is interesting to note that only 20% of patients with PMR are said to have temporal arteritis (Franzen *et al.*, 1992; Pavlica *et al.*, 2000). However, PET studies have suggested that the rate of subclinical temporal arteritis may be significantly higher than 20% (Blockmans *et al.*, 2000). The clinical significance of these findings is yet to be determined. Currently, the usual practice is to biopsy only those patients with PMR who also have features of temporal arteritis.

Neurological and neuro-ophthalmological manifestations

Neurological complications are common in patients with temporal arteritis (Table 2.2). Caselli *et al.* (1988) reported a series of 166 consecutive patients with biopsy-proven temporal arteritis and found that approximately 30% had neurological features (Caselli *et al.*, 1988) Peripheral nervous system involvement can include mononeuropathy and peripheral polyneuropathy (Caselli *et al.*, 1984). Labyrinth dysfunction and hearing loss occur frequently (Amor-Dorado *et al.*, 2003). Numbness of the tongue can be attributed to ischemia of the lingual nerve. Neuropsychiatric manifestations, such as depression, are also well-recognized (Caselli *et al.*, 1988; Goodman, 1979). Stroke often leads to devastating consequences.

Neuro-ophthalmological manifestations are frequent. In Caselli's series, over 20% of patients with biopsy proven temporal arteritis developed ocular symptoms including amaurosis fugax, scintillating scotoma and diplopia and 8% suffered permanent visual loss (Caselli *et al.*, 1988). Other series have reported far higher rates (Reich *et al.*, 1990). The usual cause of blindness is anterior ischemic optic neuropathy (AION) (Reich *et al.*, 1990).