Chapter 110

Arteritis

Michael Wall and James John Corbett

Arteritis causes headache by inflammation of dural and cerebral arteries. Arteritis is thought to be due to immune complex deposition in vessel walls. Of the many causes of arteritis, this chapter concentrates on giant cell arteritis (GCA), systemic lupus erythematosus (SLE), and primary central nervous system (CNS) vasculitis.

GIANT CELL ARTERITIS

International Headache Society (IHS) code and diagnosis: 6.4.1 Headache associated with giant cell arteritis

World Health Organization (WHO) code and diagnosis: G44.81 Headache associated with other vascular disorders

Short description: Giant cell arteritis (GCA) is a polysymptomatic disease of the elderly characterized by granulomatous inflammation of aortic origin vessels. Prominent symptoms are headache and other cranial pains, jaw claudication, visual loss, hip and shoulder girdle stiffness, and constitutional symptoms.

Other terms: Temporal arteritis, Horton's disease, cranial arteritis

Ali ibn Isâ first described GCA in the 10th century when he noted heat and inflammation in the temporalis muscles associated with loss of sight (50). Hutchinson in 1890 described a man who had symmetric, painful red streaks on his head that prevented him from wearing his hat; he ascribed the disorder to the pressure of the hat on the temples (28). In 1932, Horton and colleagues reported on two patients with a characteristic clinical presentation for GCA. They performed the first temporal artery biopsies that showed the well-known pathologic findings (26). Jennings in 1938 emphasized the blinding ocular complications and the associated musculoskeletal symptoms now known as *polymyalgia rheumatica* (PMR) (29).

EPIDEMIOLOGY

The incidence of GCA is 3 per 100,000 per year in Rochester, Minnesota (16), and 9 per 100,000 per year in Göteborg, Sweden (4). GCA was found in 1.7% of 889 postmortem examinations (1). The incidence of GCA rises dramatically with increasing age after age 50, from 17.4 per 100,000 (27) to 22 per 100,000 (42); it is nine times as frequent in the ninth decade as the sixth (4). The mean age at diagnosis is about 70 years. GCA rarely is reported in patients younger than 50 years, but the diagnosis in these cases is seldom confirmed (24). GCA is rare in Asians and African Americans and is most common in northern geographic areas, especially in persons of British or Scandinavian heritage (34). GCA is two to four times more common in women than in men (39).

Ninet and colleagues summarized data on a potential genetic basis for GCA and concluded that a predisposition is probable because of the higher frequency in Caucasians and reports of familial forms (familial cases appear to be uncommon) (38). Also, an association with human leukocyte antigen (HLA) DR4 antigen was suggested (38).

PATHOLOGY

The presence of granulomatous arteritis is the *sine qua non* for the diagnosis of GCA. Histologic features usually include (a) patchy, granulomatous inflammation involving the vessel media with lymphocytes predominating and the presence of epithelioid cells and histiocytes that, unlike giant cells that often are seen, are necessary for the diagnosis; (b) fragmentation of the internal elastic lamina; (c) occlusion of the vessel lumen with thrombus or marked subintimal edema and cellular proliferation; and (d) areas of subintimal fibromuscular hyperplasia with lymphocytic and plasma cell infiltration of the adventitia, but their presence is nondiagnostic (2).

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-110 Olesen- 2057G GRBT050-Olesen-v6.cls August 17, 2005 1:43

"Skip" areas of vessel pathology are common and represent a major cause of false-negative biopsies; thus, a segment of artery of at least 1 inch should be obtained and serial sectioned at least every 1 mm throughout its length. Direct immunofluorescence microscopy using antibodies to immunoglobulin (Ig) G, IgM, IgA, complement, and fibrinogen is usually abnormal but is not more sensitive than light microscopy (48). Humoral immunity is abnormal with the presence of circulating immune complexes in the serum and deposition of immunoglobulins in arteries. Cellular immunity also appears to be abnormal with decreased OKT 8 in the blood. Activation of CD4+ T cells in the adventitia is indicative of antigen–antibody reactivity, but it is unclear whether the antigen is of internal or external origin.

At autopsy, the superficial temporal, posterior ciliary, ophthalmic, and vertebral arteries are often involved (49), which parallels the amount of elastic tissue in the media and adventitia of the arteries of the head and neck. The internal and external carotid, central retinal, and anterior ciliary arteries are less commonly involved. Involvement of arteries after they penetrate the dura is rare. The pathologic process is similar to that of Takayasu arteritis, which led to the suggestion that Takayasu arteritis may be a related or biphasic manifestation of a similar pathogenic process.

CLINICAL FEATURES

The IHS diagnostic criteria for GCA (Revised International Classification for Headache Disorders [ICHD-II]) are as follows:

A. One or more of the following:
   1. Swollen and tender scalp artery (usually superficial temporal artery)
   2. Elevated red blood cell sedimentation rate
   3. Disappearance of headache within 48 hours of steroid therapy
B. Temporal artery biopsy demonstrating GCA.
C. Headache as a new symptom or of a new type occurs in close temporal relation to onset of GCA.

SYMPTOMS

GCA is expressed in numerous ways (Table 110-1). Headache, jaw claudication, throat pain, and other head and neck pains are usually present. Jaw claudication or neck pain markedly increases the likelihood of a positive biopsy (18). Constitutional symptoms, nontender shoulder and hip girdle aching and stiffness, diplopia, and hair loss may be present before the occurrence of visual loss. Although postmortem studies usually show involvement of the vertebral artery, stroke is uncommon. Patients uncommonly present with few or no symptoms, a condition that is called *occult giant cell arteritis*. In this form, the clinical presentation is purely visual (anterior ischemic optic neuropathy, ocular motor palsies, or central retinal artery occlusion), with no systemic symptoms. It is agreed that occult GCA is due to failure to recognize symptoms by either patient or physician (23).

TABLE 110-1 Cranial Symptoms of Giant Cell Arteritis

Symptoms	*Temporal Arteritis and PMR*	*Temporal Arteritis*	*Total*
Headache	23	20	43
Diffuse headache	3	5	8
Unilateral temporal headache	4	2	6
Bilateral temporal headache	10	13	23
Forehead pain	4	1	5
Occipital pain	2	1	3
Neck pain	9	13	22
Ear pain	8	4	12
Throat pain	4	4	8
Jaw claudication	4	0	4
Severe scalp tenderness	1	2	3
Facial pain	1	0	1
Eye pain	1	0	1
Gum pain	0	1	1

PMR, polymyalgia rheumatica.
From the study of (5), $n = 95$.

Hutchinson's original patient had headache that worsened when he wore a hat and had scalp ischemia with gangrene. Headache is present in up to 90% of patients and often localized to one or both temporal regions or the forehead, but it may be holocranial, spare the temple, or occur in any location (44). The pain is constant in about half of patients and intermittent in the other half (44). The pain is often described as throbbing (44) or superficial and burning with a superimposed lancinating quality (4), but it may be a boring sensation (30); its intensity ranges from mild to severe (4). The headache may be a relatively minor feature in the background of generalized aches and pains of PMR. It may be so far in the background as to be recognized only by its absence after therapy is started. Head soreness and cutaneous allodynia (increased sensitivity to touch, brushing, combing, etc.), which are unusual features of other types of headache, are important complaints of patients with GCA. With severe granulomatous inflammation, frank scalp necrosis can occur (Fig. 110-1).

The visual loss in GCA may be transient (*amaurosis fugax*), unilateral, or bilateral (19). When visual loss is permanent, it is due to granulomatous inflammation of the posterior ciliary arteries with anterior ischemic optic neuropathy (AION). Jaw or masticatory claudication is almost pathognomonic; it does not occur with atherosclerosis.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-110 Olesen- 2057G GRBT050-Olesen-v6.cls August 17, 2005 1:43

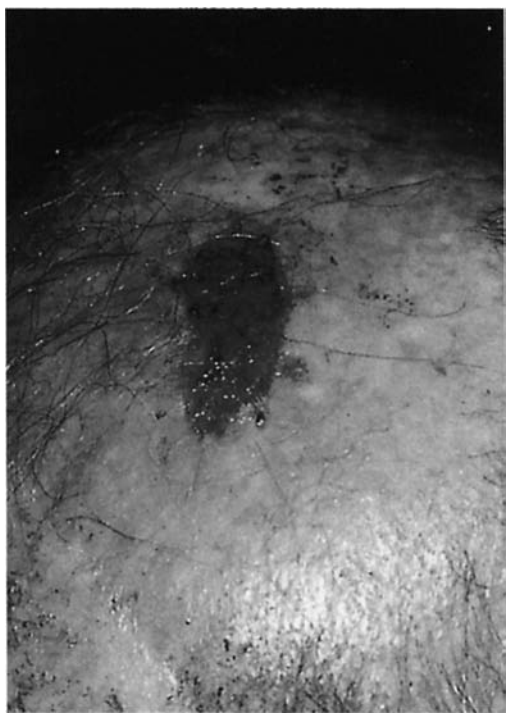

FIGURE 110-1. Scalp necrosis in a case of giant cell arteritis. (Courtesy of Mr. Roger Hitchings, Moorefields Eye Hospital.)

The pain produced by chewing is an aching cramp in the jaw or the temporalis muscle and should be differentiated from temporomandibular joint disease, which is preauricular (anterior to the tragus) and often occurs immediately upon chewing. Tongue pain or infarction of the tongue also can occur.

PMR is a syndrome of synovial inflammation that accompanies many cases of GCA. Biopsy of the synovium shows nonspecific inflammatory changes without granulomatous arteritis. Patients have chronic stiffness of the shoulder girdles with common involvement of the sternoclavicular joint. Thickened synovium can be palpated in the sternoclavicular joint in about 40% of patients. The hip girdle is less commonly affected. The pain and stiffness are especially prominent in the morning. Proximal muscle pain may occur, but muscle biopsies are normal; the pain is thought to be referred from joints, tendons, and ligaments.

At least 20% of patients (possibly many more) with GCA have a PMR-like prodrome (15). About half of patients with PMR later develop GCA; about one fourth have serious visual or neurologic complications (30). Patients with PMR may have positive temporal artery biopsies but, according to some investigators, if they do not have any symptoms of GCA, they appear to be at low risk for visual loss. Also, low-dose corticosteroids do not protect PMR patients from developing GCA. A number of questions remain regarding the relationship of GCA and PMR, largely because of the lack of large, long-duration, prospective studies.

SIGNS

Many GCA signs are visual. Patients with AION characteristically develop pale, swollen optic discs (Fig. 110-2) with accompanying blinding visual loss. Diplopia, when present, is likely due to ischemia of the extraocular muscles (3) as a result of involvement of muscular branches of the anterior ciliary arteries. Ischemia of the third, fourth, or sixth cranial nerves probably also occurs but is rare (19). Prominent (Fig. 110-3) tender, nonpulsatile, noncompressible, or beaded temporal arteries may be present, but the artery may be normal to palpation.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A typical clinical course or characteristic temporal artery biopsy establishes the diagnosis of GCA. Biopsies should show interruption of the internal elastic membrane with infiltration of mononuclear cells in the arterial wall. The presence of giant cells is not required.

A 77-year-old woman presented with a 2-week history of temporal headache, fever, myalgias, fatigue, and anorexia. Erythrocyte sedimentation rate (ESR) was 125 mm per hour. At surgery, the left temporal artery was thickened. The first biopsy specimen (Fig. 110-4) showed evidence of resolution: so-called healed arteritis. A contralateral biopsy on the other side demonstrated an area of granulomatous inflammation adjacent to normal artery (Fig. 110-5).

Bengtsson and Malmvall propose that biopsy-negative patients with GCA are identified by at least one of the

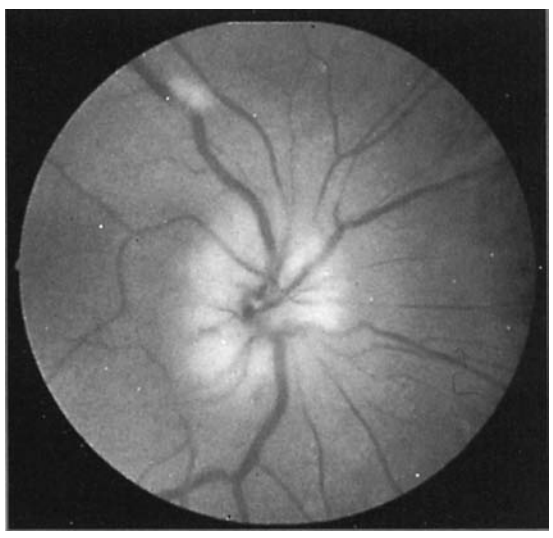

FIGURE 110-2. Pallid disk edema in giant cell arteritis. When this much pallor is present associated with disk edema in a case of anterior ischemic optic neuropathy, one should consider giant cell arteritis as a cause. (Courtesy of Sohon S. Hayreh, MD, PhD.)

FIGURE 110-3. Prominent temporal artery in a case of giant cell arteritis.

following characteristic symptoms and signs: temporal ache, scalp tenderness, jaw claudication, features of AION, or abnormal temporal arteries (4). In addition, an ESR above 40 mm per hour (Westergren) and an age of 50 years or more are required, as is rapid and lasting relief of symptoms after institution of corticosteroid therapy.

It is well established that the temporal artery may be uninvolved despite GCA lesions elsewhere in the arterial

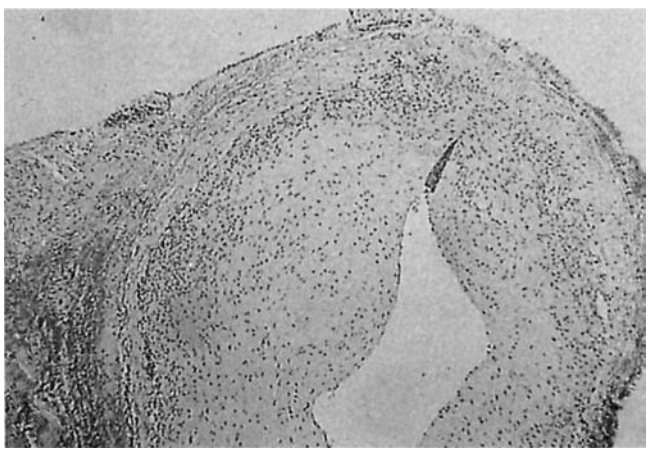

FIGURE 110-4. Pathologic changes of giant cell arteritis. A normal temporal artery is present with granulomatous inflammation present in a branch of the artery (example of skip areas). The high magnification view (**B**) shows transmural inflammation consistent with arteritis. (Courtesy of Robert Folberg, Educational Resources Group, Department of Ophthalmology, University of Iowa.)

system (46). It is equally well known that the changes can appear interspersed with normal arterial segments (Fig. 110-4), the so-called skip lesions. Therefore, a second biopsy on the opposite side may be rewarding (13,18). The differential diagnosis of headache in the elderly patient includes GCA, brain tumor, carcinomatous meningitis, and aneurysm. Most other types of vasculitis that present with headache have other organ systems affected and have no association with PMR. Characteristic findings on temporal artery biopsy clearly distinguish GCA.

Patients presenting with AION may have a "nonarteritic" type. Cranial pain, diplopia, or amaurosis fugax are not present, and no constitutional symptoms are noted. Patients usually have systemic arterial hypertension or

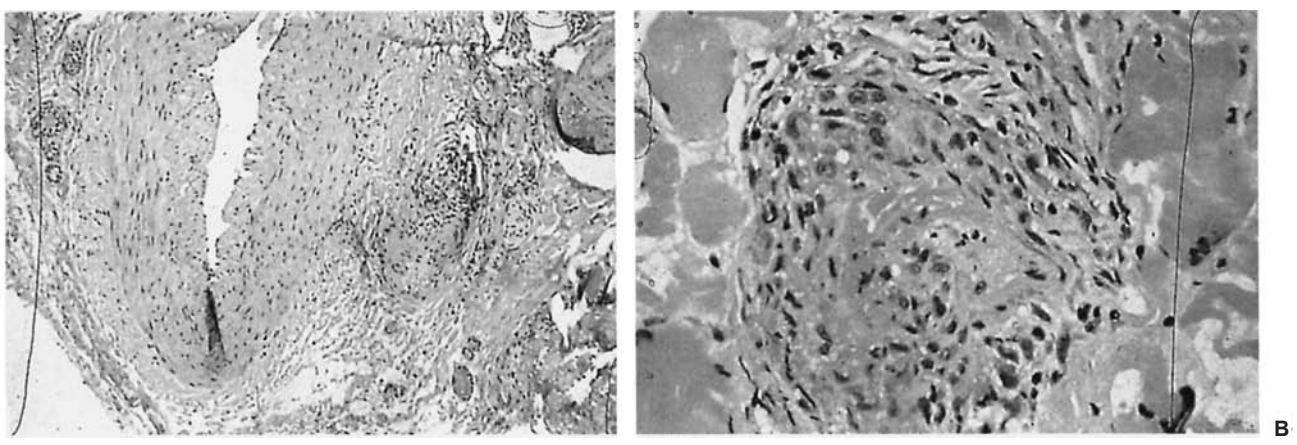

FIGURE 110-5. Healed arteritis. There is asymmetric intimal thickening with concomitant focal disruption and scarring of the media. (Courtesy of Robert Folberg, Educational Resources Group, Department of Ophthalmology, University of Iowa.)

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-110 Olesen- 2057G GRBT050-Olesen-v6.cls August 17, 2005 1:43

diabetes mellitus and have a small or absent optic cup in the uninvolved eye. ESR and C-reactive protein (CRP) are normal in nonarteritic ischemic optic neuropathy.

Elevation of ESR, although highly suggestive of GCA in elderly patients with new-onset headache and constitutional symptoms, may be encountered in other conditions. Age, monoclonal gammopathies, polyclonal hyperglobulinemias, hyperfibrinogenemia, connective-tissue diseases, leukemias, lymphomas, carcinomas, and sarcomas all cause elevation of ESR with values exceeding 100 mm per hour. Also, this rate also may be exceeded in collagenoses, acute bacterial infections, portal or biliary cirrhosis, and ulcerative colitis.

LABORATORY FINDINGS

An elevated ESR is the most frequent laboratory finding for the diagnosis of GCA. ESR is a measure of the size and number of red blood cell aggregations. The more the red cells adhere to each other, the higher the sedimentation rate, because large-volume masses sediment faster than small ones. Factors that increase the sedimentation rate are fibrinogen, globulins (especially A and B), pregnancy, hypercholesterolemia, macrocytosis, and anemia. Thus, the ESR must be corrected for anemia (Wintrobe, not Westergren).

The mean ESR during the acute phase of GCA is 91 mm per hour, greater than 50 mm per hour in 89% and more than 100 mm per hour in 41% (4). ESR may be normal in about 1 to 2% of GCA cases (4,19). ESR decreases with corticosteroid therapy and is used by some as a management guide. Relapses may occur with a normal ESR, and resolution of the disease can occur with a mildly to moderately elevated rate (about 40 mm per hour).

Other useful abnormalities include elevated acute-phase reactants, such as CRP and von Willebrand factor, fibrinogen, and anemia of chronic disease as well as abnormal liver function studies. Also, thrombocytosis, leukocytosis, lymphocytosis, and elevation of α-, $\alpha 2$-, β-, and γ-globulins occur. Serum haptoglobin may rise, as may total complement, C3, and C4.

The normal values for the Westergren sedimentation rate are less than 10 mm per hour in men and less than 20 mm per hour in women. In patients aged over 60, many use 40 mm per hour as indicative of disease.

CRP, an acute-phase plasma protein, may be more specific for detecting inflammation. It is not elevated by anemia, altered red blood cell morphology, or the level of a number of plasma proteins. C-reactive protein in our experience is a more useful parameter than ESR for the diagnosis of GCA and monitoring disease activity. CRP is as sensitive but more specific than ESR and may better correlate with symptoms (17,18). CRP may be elevated in GCA when ESR is normal (17,18). In the extensive experience with CGA of Hayreh and colleagues, active GCA was not seen without an elevated CRP (18).

PROGNOSIS

Many cases of GCA are chronic and need treatment for years. Recurrences also have been noted years later. The time between the first symptom and subsequent visual loss varies, usually weeks to several months but occasionally longer. The time between visual loss in the first eye and loss in the second one is usually within the first week and nearly always within a month; uncommonly it is longer than 2 months. It appears that after first-eye involvement, if the second eye is to be involved, it will nearly always be within 2 months (29,32). Visual loss in the second eye can occur despite therapy with large doses of steroids, usually within 5 days of treatment initiation (22).

A retrospective study of 32 consecutive patients with GCA who had AION or central retinal artery occlusion–related visual loss and who were treated with high-dose steroids showed improvement in visual acuity in only 13% (11). Similiarly, Hayreh and colleagues (22) found improvement of acuity and central visual field in only 4% and they correctly pointed out that improvement in acuity alone may simply be due to learning to eccentrically fixate.

Another study indicated that 5 of 13 patients developed visual loss while treated with salicylates alone during the headache phase of GCA (43), as compared to none of the 10 patients who received steroids. Finally, Palm reported that 14 of 16 untreated cases became blind bilaterally as opposed to 1 of 8 treated with steroids (40).

GCA does not shorten life span, but side effects of corticosteroids can be fatal, especially in elderly patients.

MANAGEMENT

The headache of GCA responds rapidly to treatment with steroids. High and, sometimes, megadoses (1 g methylprednisolone twice daily), are recommended. Megadoses are used in patients who have unilateral visual loss of less than 1 week's duration or episodes of amaurosis.

Followup of patients with GCA includes serial Westergren ESR and CRP. Because there is diurnal variation of the ESR, it is useful to have blood drawn at the same time of the day at each return visit. Patients must be asked specifically about steroid side effects, and visual and masticatory symptoms should be reviewed. Ideally, ESR and CRP should fall and stay low, and symptoms should improve. Steroids then can be tapered gradually over 6 to 12 months (21). If ESR increases by more than 10 mm per hour, if the CRP becomes abnormal, or if symptoms reappear, the dose of steroids should be increased and then

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-110 Olesen- 2057G GRBT050-Olesen-v6.cls August 17, 2005 1:43

gradually tapered again. Steroid reduction responses vary; it is common for patients to be on low doses of steroids for years.

Because of the high incidence of complications of steroid use in older populations, various cytotoxic agents have been tried. Methotrexate was shown to reduce disease activity in one randomized, double-blind placebo-controlled trial (31) but failed in another (25). Also, case reports suggest that tumor necrosis factor blockers may be a promising area for GCA treatment (7).

OTHER SYSTEMIC ARTERIDITIES: SYSTEMIC LUPUS ERYTHEMATOSUS

Definition of Other Systemic Arteritides

IHS code and diagnosis: 6.4.3 Headache attributed to secondary central nervous system (CNS)

WHO code and diagnosis: G44.812 Headache associated with other vascular disorders

Short description: Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease of unknown etiology. Like multiple sclerosis, it is characterized by exacerbations and remissions. The incidence of headache attributed to SLE is difficult to determine because of confounding factors such as headache frequency in the general population, presence of systemic arterial hypertension, increased intracranial pressure, and uremia.

EPIDEMIOLOGY

SLE occurs at any age, and women are affected three times as often as men. Most often, SLE begins between puberty and 40 years. In this age range, more than 90% are women. Blacks outnumber whites 3:1. The prevalence of SLE is 51 per 100,000; the incidence is 3 to 27 per 100,000 per year. In black women, the incidence is 1 per 245 per year (10). Central nervous system (CNS) involvement occurs in about 60% of patients. There is a slightly increased risk for those with family history of SLE. Also, there is about two-thirds concordance in identical twins (92% concordance for autoantibodies), but dizygotic twins are discordant (12). The frequency of SLE in first- and second-degree relatives is 5 to 12%. HLA-DR antigens have been shown to be associated with SLE cases.

PATHOLOGY

Small parenchymal and leptomeningeal vessels show fibrinoid and hyaline degeneration and endothelial proliferation with occlusion and perivascular lymphocytic infiltrations or microhemorrhages. Later, mononuclear infiltration with deposition of eosinophilic material and hematoxylin bodies (nuclear fragments) is found. There is immunoglobulin and complement deposition in vessels. The presence of inflammatory cells within blood vessels, a cardinal feature of vasculitis, is rare within the CNS in SLE cases, but perivascular inflammatory infiltrates are common (9,27).

CLINICAL FEATURES

The IHS diagnostic criteria for headache attributed to secondary CNS angiitis (ICHD-II) are as follows:

A. Any new persisting headache fulfilling criteria D and E.
B. Encephalic signs of any type (e.g., stroke, seizures, disorders of cognition or consciousness).
C. Evidence of systemic arteritis.
D. Headache develops in close temporal relation to encephalic signs.
E. Headache improves within 1 month of steroid and/or immunosuppressive treatment.

Symptoms of SLE are variable (Table 110-2) and initially are commonly nonspecific. Neurologic manifestations of SLE can be focal or diffuse and include seizures, cranial nerve palsies, long-tract signs, movement disorders, pseudotumor cerebri, meningitis, an encephalopathy or dementialike picture, psychosis, and headache. Headache occurs in one third of patients with CNS

TABLE 110-2 Common Clinical Abnormalities in Patients With Systemic Lupus Erythematosus Rounded to the Nearest 10%

	Approximate Abnormality Frequency (%)
Constitutional	
Fatigue	90
Fever	80
Weight loss, anorexia	60
Musculoskeletal	
Arthritis, arthralgia	90
Myalgia, myositis	30
Central nervous system	
Personality disorders	50
Seizures	20
Psychoses	20
Stroke or long-tract signs	10
Migraine headaches	10

From (46) Petri M, Rheinschmidt M, Whiting-O'Keefe Q, et al. The frequency of lupus anticoagulant in systemic lupus erythematous. *Ann Intern Med* 1987;106:524–531, with permission.

TABLE 110-3 American Rheumatologic Association Diagnostic Criteria for Systemic Lupus Erythematosus[a]

Malar rash
Discoid rash
Photosensitivity
Arthritis without deformity
Serositis (pleuritis or pericarditis)
Oral or nasopharyngeal ulceration
Kidney disease (proteinuria, cellular casts)
CNS manifestations (seizures or psychosis)
Hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
Positive LE prep or anti-DNA antibody, or anti-Sm antibody or false-positive serologic test of syphilis
Antinuclear antibody

CNS, central nervous system; LE, lupus erythematosus.
[a]The presence of 4 or more of the 11 criteria is required.
From (52) Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–1277, with permission.

involvement (35) and can mimic migraine with hemicrania pain and fortification scotoma (32,43).

The American Rheumatologic Association criteria are found in Table 110-3 (43). SLE should be suspected if any of these findings are present and unexplained.

LABORATORY FINDINGS

There is no single test diagnostic for SLE. High titers of antinuclear antibodies are 95% sensitive and 86% specific. A battery of tests of specifically reactive antigens are most useful (e.g., Sm, SS-A, SS-B, native DNA—Table 110-4). Patients with antibodies to Ro (SS-A) or La (SS-B) have a higher incidence of sicca syndrome, muscle disease, and lung disease with little or no renal disease. Also, anti-Ro is associated with skin lesions and heart block. Anti-DNA antibodies are thought to cause damage by forming antigen–antibody complexes in the circulation with deposition in various organs. Antiribosomal protein antibodies are present in about 12% of SLE patients; their presence appears to be highly correlated with lupus psychosis (37). The SLE cell is found in about 80% of patients. Anemia and leukopenia are common, and ESR is usually elevated (37).

TABLE 110-4 Diagnostic Criteria for Primary Central Nervous System Vasculitis

Clinical pattern of headaches and multifocal neurologic deficits for at least 6 months unless the onset is with a severe deficit
Cerebral angiography showing areas of segmental arterial narrowing
No evidence of systemic inflammation, infection, or vasculitis
Leptomeningeal or parenchymal biopsy characterized by vascular inflammation and exclusion of alternate diagnoses (infection, atherosclerosis, and neoplasia)

From (41) Moore PM. Diagnosis and management of isolated angiitis of the central nervous system. *Neurology* 1989;39:167–173, with permission.

PROGNOSIS

With treatment, organ system function can be preserved for prolonged periods in many cases.

Management

Therapy for SLE is beyond the scope of this text. Corticosteroids and immunosuppressives (azathioprine and cyclophosphamide) are commonly used. Plasmapheresis may be useful. SLE patients treated with nonsteroidal antiinflammatory agents may develop rebound headaches (47); this headache should not be confused with the headache of arteritis.

PRIMARY CENTRAL NERVOUS SYSTEM ANGIITIS

IHS code and diagnosis: 6.4.2 Headache attributed to primary central nervous system (CNS) angiitis
WHO code and diagnosis: G44.812 Headache associated with other vascular disorders
Short description: Primary CNS angiitis is a noninfectious recurrent angiopathy confined to the CNS. It is usually fatal if untreated. Patients are adults and they usually present with headache and recurrent stroke.
Other terms: Granulomatous angiitis, isolated angiitis of the nervous system, primary CNS vasculitis

EPIDEMIOLOGY

Patients with primary CNS angiitis are aged 3 to 78 years (mean, 49 years) (14). Men and women are equally affected. There is no apparent genetic predisposition.

PATHOPHYSIOLOGY

The cause of primary CNS angiitis is unknown. Particles like mycoplasma were observed in two necropsies (44). Also, viral-like particles have been seen (44) but those can be found in the normal human brain. Interestingly, turkeys infected with *Mycoplasma gallisepticum* can develop a primary CNS angiitislike picture.

Finally, the presence of granulomas and the absence of antibodies or immune complexes in the vessel walls suggest that primary CNS angiitis is a disorder of cell-medicated immunity (36).

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-110 Olesen- 2057G GRBT050-Olesen-v6.cls August 17, 2005 1:43

PATHOLOGY

There is segmental necrotizing granulomatous involvement of vessel walls with a predilection for small blood vessels. Inflammatory infiltrates are present with varying degrees of granuloma formation. The inflammation is characterized by the presence of mononucleocytes, polymorphonucleocytes, epithelioid-appearing histiocytes, and multinucleated giant cells with granulomas. Leptomeningeal vessels more often are involved than parenchymal vessels. Any vessel of the brain or spinal cord can be involved. Any portion of the vessel wall can be affected, but the media appears to be less involved than the adventitia or intima. Granulomatous angiitis is a variable finding, hence the more appropriate term *primary CNS angiitis*.

CLINICAL FEATURES

The IHS diagnostic criteria for headache attributed to primary CNS angiitis (ICHD-II) are as follows:

A. Any new persisting headache fulfilling criteria D and E.
B. Encephalic signs of any type (e.g., stroke, seizures, disorders of cognition or consciousness).
C. CNS angiitis proven by cerebral or meningeal biopsy or suspected on angiographic signs in the absence of systemic arteritis.
D. Headache develops in close temporal relation to encephalic signs.
E. Headache improves within 1 month of steroid and/or immunosuppressive treatment.

The most common presenting symptom of primary CNS angiitis is headache, which occurs in about two thirds of cases and is usually severe (33). Headaches can be generalized or localized and are usually pulsatile (8). Their onset may be acute, or progression may be stepwise. Patients may present with a low-grade fever, weight loss, confusion, or visual loss, or have an apoplectic onset. Although encephalopathy is present in about half, focal or multifocal neurologic deficits develop in more than 90% of patients (8). Nonconstitutional symptoms of arthritis or skin involvement are absent. Seizures occur in one-third. Mental symptoms occur in two thirds and often predominate. Patients with spinal cord involvement may present with back pain.

On examination, patients can have diffuse signs of encephalopathy or more focal signs of stroke. Signs of generalized increased intracranial pressure (i.e., papilledema with resultant visual loss and sixth-nerve palsies) may be present. Meningismus is occasionally present. Myelopathy is a less common finding.

Moore proposed specific diagnostic criteria for primary CNS angiitis (Table 110-4) (36). Unfortunately, a biopsy is only diagnostic in about three quarters of patients because of patchy involvement.

The differential diagnosis of primary CNS angiitis includes the many types of vasculitis that can affect the CNS. Polyarteritis nodosa commonly affects the peripheral nervous system, but CNS involvement is rare. Rheumatoid vasculitis and lupus are differentiated by systemic involvement and laboratory abnormalities of collagen vascular disease. Lymphomatoid granulomatosis is characterized by infiltration of lymphoid and plasmacytoid cells with granulomatous inflammation. It primarily involves the lungs but may involve the skin, kidneys, and CNS. It has some aspects of a lymphoproliferative disease and is usually fatal. The chest radiography almost always shows bilateral infiltrates. Malignant angioendotheliosis is another rare fatal disease characterized by malignant cell deposition in small vessels in several organs. It may be a variant of lymphoma.

GCA rarely affects arteries after they penetrate the dura. Some of the reported cases with intracranial involvement actually may be cases of primary CNS vasculitis. Temporal artery biopsy is negative in isolated primary CNS angiitis.

Infectious angiitis (herpes zoster) and the vasculitis associated with Hodgkin disease, although histologically similar, are distinguished by a lack of systemic involvement. In the case of zoster, there is, of course, a preceding infection. Sarcoidosis can be differentiated by its nodular-enhancing lesions involving the base of the brain, noncaseating granulomata, and system involvement. Wegener granulomatosis is a necrotizing granulomatous vasculitis and is differentiated by its common involvement of the upper and lower respiratory tracts and kidney (glomerulonephritis). Less commonly, the orbit, skin, and CNS are involved. Lyme disease and syphilis yield characteristic abnormal serologic tests; involvement outside the CNS is common. Headache and upper-extremity claudication may be prominent features of Takayasu (pulseless) disease, an obliterative arteritis of the aorta and medium-sized arteries that primarily affects young women.

LABORATORY FINDINGS

ESR is usually normal or mildly elevated in primary CNS angiitis, and rarely markedly elevated. In one review, mean ESR was 27 mm per hour (range, 2 to 95) (14). A leukocytosis greater than 10,000/mm^3 without eosinophilia is present in one-half of cases. Lumbar puncture may show increased intracranial pressure. Cerebrospinal fluid (CSF) examination is often abnormal. An elevated protein (sometimes greater than 100 mg% occurs in three quarters with a mild lymphocytic pleocytosis, CSF cell count is seldom greater than 400 (6), and blood in CSF is observed in about

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-110 Olesen- 2057G GRBT050-Olesen-v6.cls August 17, 2005 1:43

one fourth of cases. CSF glucose is usually normal, but it can be less than 45 mg%. Although there may be elevation of CSF IgG, oligoclonal bands are absent.

The electroencephalogram (EEG) shows generalized or localized slowing. Neuroimaging is nonspecific with signs of multifocal ischemia; evidence of cerebral edema may be present. Laboratory findings of collagen vascular disease are notoriously absent. Cerebral arteriography is abnormal in about three-fourths of cases and has no pathognomonic features. It shows segmental arterial narrowing of medium-sized vessels (sausage pattern) in about half of the cases. Other findings are vascular occlusions, vascular shifts, vascular channels, and avascular areas. These "vasculitic" patterns, however, may be seen in atherosclerosis, heroin and amphetamine abuse, and infection. Cerebral angiography may be normal in spite of pathologic confirmation of the disease. Biopsy is abnormal in only three-fourths of patients studied because of patchy involvement (6). There is frequent involvement of leptomeninges.

Prognosis

The clinical course can be rapidly progressive over weeks or "smolder" for months. There may be a fluctuating course with periods of stability. If it goes untreated, primary CNS angiitis usually results in death within 3 years. Although no controlled trials of treatment have been reported, of the 26 survivors described in the literature, one third became asymptomatic with treatment and one-half had mild deficits (14). Patients with isolated focal deficits have a better prognosis than those with encephalopathy, thus implying a more diffuse process.

Management

Patients suspected of the diagnosis should have leptomeningeal and temporal tip biopsy that includes a longitudinally oriented surface vessel. When the diagnosis is confirmed, patients should be treated with a combination of prednisone 40 to 60 mg/day and cyclophosphamide 100 mg/day.

REFERENCES

1. Ainsworth RW, Gresham GA, Balmforth GV. Pathological changes in temporal arteries removed from unselected cadavers. *J Clin Pathol* 1961;14:115–119.
2. Albert DM, Searl SS, Craft JL. Histologic and ultrastructural characteristics of temporal arteritis. *Ophthalmology* 1982;89:1111–1126.
3. Barricks ME, Traveisa DB, Glaser JG, et al. Ophthalmoplegia in cranial arteritis. *Brain* 1977;100:209–221.
4. Bengtsson B-Å, Malmvall BE. Giant cell arteritis. *Acta Med Scand* 1982;658:1–102.
5. Biller J, Adams HP. Noninfectious granulomatous angiitis of the central nervous system. In: Vinken PV, Bruyn GW, Klawans HL, eds. *Handbook of clinical neurology,* vol 2. Amsterdam: Elsevier, 1988:387–400.
6. Calabrese LH, Mallek JA. Primary angiitis of the central nervous system: report of eight new cases, review of the literature, and proposal for diagnostic criteria. *Medicine* 1987;67:20–39.
7. Cantini F, Niccoli L, Salvarani C, et al. Treatment of long-standing active giant cell arteritis with infliximab: report of four cases. *Arth Rheum* 2001;44(12):2933–2935.
8. Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system: prospective diagnostic and therapeutic experience. *Am J Med* 1983;74:97–105.
9. Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: a review of neuropathic findings in 57 cases 1955–1977. *Semin Arthritis Rheum* 1982;12:68–76.
10. Fessel MB. Systemic lupus erythematosus in the community. Incidence, prevalence, outcome and first symptoms: the high prevalence in black women. *Arch Intern Med* 1974;134:1027–1035.
11. Foroozan R, Deramo VA, Buono LM, et al. Recovery of visual function in patients with biopsy-proven giant cell arteritis. *Ophthalmology* 2003;110(3):539–542.
12. Goldstein R, Arnett FC. The genetics of rhematic disease in man: immunology of the rheumatic diseases. *Rheum Dis Clin North Am* 1987;13:487–510.
13. Hall SH, Hunder GG. Is temporal artery biopsy prudent? *Mayo Clin Proc* 1984;59:793–796.
14. Hankey GJ. Isolated angiitis/angiopathy of the central nervous system. *Cerebrovasc Dis* 1991;1:2–15.
15. Harrison MJH, Bevan AT. Early symptoms of temporal arteritis. *Lancet* 1967;2:638–640.
16. Hauser KA, Ferguson RH, Holley KE, et al. Temporal arteritis in Rochester, Minnesota, 1951–1967. *Mayo Clin Proc* 1971;46:597–602.
17. Hayreh SS. Ophthalmic features of giant cell arteritis. In: *Clinical rheumatology,* vol 5. 1991:431–459.
18. Hayreh SS, Podhajsky PA, Raman RI, et al. Giant cell arteritis: validity and reliability of various diagnostic criteria. *Am J Ophthalmol* 1997;123:285–296.
19. Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. *Am J Ophthalmol* 1998;125:509–520.
20. Hayreh SS, Zimmerman B. Management of giant cell arteritis. Our 27-year clinical study: new light on old controversies. *Ophthalmologica* 2003;217(4):239–259.
21. Hayreh SS, Zimmerman B, Kardon RH. Visual improvement with cortical therapy in giant cell arteritis. Report of a large study and review of literature [erratum appears in *Acta Ophthalmol Scand* 2002;80(6):688]. *Acta Ophthalmol Scand* 2002;80(4):355–367.
22. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;8:1–96.
23. Healy LA, Wilske KR. *The systemic symptoms of temporal arteritis*. New York: Grune and Stratton, 1978.
24. Hoffman GS, Cid MC, Hellman DB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002;46(5):1309–1318.
25. Horton BT, Magath TB, Brown GE. An undescribed form of arteritis of the temporal vessels. *Mayo Clin Proc* 1932;7:700–701.
26. Huston KA, Hunder GG, Lie JT, et al. Temporal arteritis: a 25-year epidemiologic clinical and pathologic study. *Ann Intern Med* 1978;88:162–167.
27. Hutchinson J. Disease of the arteries: on a peculiar form of thrombotic arteritis of the aged which is sometimes productive of gangrene. *Arch Surg* 1890;1:323–329.
28. Jennings GH. Arteritis of the temporal arteries. *Lancet* 1938;1:424–428.
29. Jones JG, Hazelman JL. Prognosis and management of polymyalgia rheumatica. *Ann Rheum Dis* 1981;40:1–5.
30. Jover JA, Hernandez-Garcia C, Morado IC, et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;134(2):106–114.
31. Keltner JL. Giant cell arteritis. *Ophthalmology* 1982;89:1101–1110.
32. Levine SR, Welch KMA. Antiphospholipid antibodies. *Ann Neurol* 1989;26:386–389.
33. Liang GC, Simkin PA, Hunder CC, et al. Familiar aggregation of

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-110 Olesen- 2057G GRBT050-Olesen-v6.cls August 17, 2005 1:43

polymyalgia rheumatica and giant cell arteritis. *Arthritis Rheum* 1974;17:19–24.
34. Maida E, Horvatits E. Neurological manifestations. In: Smolen JS, Zielinski, eds. *Systemic lupus erythematosus: clinical and experimental aspects*. Berlin: Springer-Verlag, 1987:251–269.
35. Moore PM. Diagnosis and management of isolated angiitis of the central nervous system. *Neurology* 1989;39:167–173.
36. Moskowitz N. Systemic lupus erythematosus of the central nervous system: I. Classification, epidemiology, pathology, diagnosis and therapy. *Mt Sinai J Med* 1988;55:147–152.
37. Ninet J, Gebuhrer L, Betuel H, et al. Immunogenetique de la maladie de Horton et de la pseudo-polyarthrite rhizomelique. *J Mal Vasc* 1989;14:128–136.
38. Nordborg E, Nordborg C. Giant cell arteritis: epidemiological clues to its pathogenesis and an update on its treatment. *Rheumatology* 2003;42(3):413–421.
39. Palm E. The ocular crisis of temporal arteritis syndrome (Horton). *Acta Ophthalmol* 1958;36:208–243.
40. Petri M, Rheinschmidt M, Whiting-O'Keefe Q, et al. The frequency of lupus anticoagulant in systemic lupus erythematosus. *Ann Intern Med* 1987;106:524–531.
41. Petursdottir V, Johansson H, Nordborg E, et al. The epidemiology of biopsy-proven giant cell arteritis: special reference to cyclic fluctuations. *Rheumatology* 1999;38:1208–1212.
42. Ross Russell RW. Giant cell arteritis: a review of 35 cases. *QJM* 1959;28:471–489.
43. Siva A. Vasculitis of the nervous system. *J Neurology* 2001;248:451–468.
44. Tam EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–1277.
45. Thielen KR, Wydicks EFM, Nichols DA. Giant cell (temporal) arteritis: involvement of the vertebral and internal carotid arteries. *Mayo Clin Proc* 1998;73:444–446.
46. Thomas L, Davidson M, McClusky RT. Studies of PPLO infections. I. The production of cerebral polyarteritis by *Mycoplasma gallisepticum* in turkeys. *J Exp Med* 1966;123:897–912.
47. Warner J. Diclofenac as a cause of rebound headache? *Headache* 2001;41(1):102–103.
48. Wells KK, Folberg R, Goeken JA, et al. Temporal artery biopsies. Correlation of light microscopy and immunofluorescence microscopy. *Ophthalmology* 1989;86:1058–1064.
49. Wilkinson IMS, Russell RWR. Arteries of the head and neck in giant cell arteritis. *Arch Neurol* 1972;27:378–391.