Neurol Sci (2005) 26:S134–S137
DOI 10.1007/s10072-005-0426-5

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Headache in giant cell arteritis and other arteritides

Abstract Giant cell arteritis remains the most common systemic vasculitis in patients over the age of 50. Headache is the most common symptom, but is not invariably present. The headache may take almost any form, and may resemble any of the primary headaches, even cluster. Prompt diagnosis is important to prevent the well known serious complications. Accurate diagnosis allows appropriate therapy. Other forms of vasculitis may also cause headaches so correct diagnosis is essential as therapies may differ.

Key words Arteritis • Giant cell • Vasculitis • Horton's disease

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Giant cell arteritis (GCA), also known as cranial arteritis, temporal arteritis and Horton's disease has probably been present for centuries. There is a suggestive description in a lost text by Ali ibn Isâ from the 10th century describing a man with heat/inflammation of the temporalis muscle and loss of sight [1]. Hutchinson [2] in 1890 published a case of a man with painful inflamed temporal arteries, which prevented him from wearing his hat. The disease was finally clearly defined by Horton et al. [3] in 1932.

While this disease is best known for headache, the 1932 report described 2 cases neither of which had headache. The patients had fever, weakness, anorexia, weight loss, anaemia, mild leukocytosis and tender temporal arteries. Symptoms had been present for 4–6 weeks. Temporal artery biopsy revealed chronic periarteritis and arteritis with granulomas in the adventitia, round cells in the media and in the adventitia of the vasa vasorum. Haemorrhage was present in the media and the intima was thickened. The lumen was partially occluded by thrombi. The authors noted that the history, clinical course and pathology were different than periarteritis nodosum and thrombo-angiitis obliterans. They concluded "it is apparently a focal localisation of some unknown systemic disease" [3].

By 1937 headache had been recognised as a prominent symptom, and by 1938 Jennings had emphasised the risk of visual loss [4, 5]. Steroids were not available until 1949, so unfortunately the natural history of the illness was well described [6]. In 1972 Dalessio again noted the difference from periarteritis and lupus, but also noted the pathology was indistinguishable from Takayasu's arteritis [7]. He referred to the work of Dr. Eng Tang at Scripps clinic, suggesting GCA was an immunologic vasculitis.

GCA commonly occurs in patients over the age of 50, with an erythrocyte sedimentation rate (ESR) over 50 mm/h. It is more common in Caucasians, at higher latitudes, in females, and particularly seems to affect Scandinavians and the British [8]. The prevalence in those over 50 years of age is 133/100 000 [9]. It may be under-

diagnosed, having been found in 1.7% of a consecutive autopsy series [9]. It is the most common primary systemic vasculitis in the elderly [10].

Headache in GCA is the initial symptom in 48% of patients, and is eventually found in 90%, making it the most common manifestation [11]. It may be any type of headache, constant or intermittent, and may mimic tension-type headache, migraine or even cluster [4, 12]. It may be of variable location and severity. This is also true for headache due to other arteritides, which makes accurate diagnosis essential. The headache of GCA usually subsides promptly with initiation of steroid therapy. Other symptoms includes tender temporal artery in 69%, jaw claudication in 67%, polymyalgia rheumatica (PMR) in 48%, weight loss in 55%, fever in 21% (and GCA may present as a fever of unknown origin), absent temporal artery pulse in 40%, visual symptoms in 40%, peripheral joint pain in 21%, tongue claudication in 7%, pain on swallowing in 7% and limb claudication in 5% [9, 13]. Jaw and dental symptoms have caused diagnostic confusion [14].

Other physical findings and symptoms in GCA include signs of temporal artery inflammation (erythema, tenderness, nodularity, thickening, diminished pulsation). It has been noted that the headache of GCA often resolves upon temporal artery biopsy [15]. One-third of patients may have arterial bruits and/or diminished peripheral pulses. Involvement of the aorta may lead to aortic aneurysm, dissection, aortic regurgitation and even aortic rupture. A partial Horner's syndrome may be found, as may a tender carotid artery. Rarely there may be tongue or scalp necrosis. Other findings include neuropathy, vertigo, tremor, tinnitus, myopathy, seizures, anosmia, myelopathy, stupor and coma [9, 16].

The best known dreaded complications of GCA include blindness and stroke (more often involving the posterior circulation/vertebral arteries). When there is ocular involvement without any systemic symptoms/signs the presentation is known as occult GCA. The ophthalmologic complications of GCA include amaurosis fugax (14%), visual loss, diplopia, ptosis, formed visual hallucinations, orbital bruits and acute ocular hypotony [17]. Intraocular vessels, as intracranial vessels, are not involved as they lack an internal elastic lamina. In the pre-steroid era, blindness occurred in up to 60% of patients in some series. Involvement of the posterior ciliary arteries is more frequent than the central retinal artery. Sudden blindness as a presenting symptom is rare. Twenty-five per cent of patients manifesting ophthalmoplegia may go on to blindness if untreated. Fixed visual loss does not improve, and blindness may occur despite the initiation of steroids. If it occurs, the second eye is often affected within 2 weeks; it rarely occurs beyond 2 months [17]. Patients with blindness are also at increased risk of stroke. Bilateral occipitotemporal infarction may occur, resulting in Anton's syndrome, which may explain some reports of blind patients not being particularly concerned about their deficits.

The aetiology of GCA remains unknown. It is known that viruses can induce vasculitic syndromes. Candidate agents in GCA include parvovirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, EBV, RSV, HSV, measles, CMV and parainfluenza virus [18].

Temporal artery biopsy remains the gold standard for the diagnosis of GCA. It helps exclude other arteritides as diagnoses. Beyond this, other arteritides have characteristic presentations. For example, primary angiitis of the CNS has headache as a prominent symptom, but also has multiple strokes and a CSF pleocytosis with a lack of systemic manifestations. Wegener's granulomatosis tends to affect the respiratory tracts and kidneys. Polyarteritis nodosum is also a multisystem arteritis but affects small and medium-sized vessels. The headache of lupus is controversial, but the diagnosis can be made based on serology and clinical presentation [19]. In GCA, the temporal artery biopsy reveals intimal proliferation with luminal stenosis, disruption of the internal elastic lamina by a mononuclear cell infiltrate, invasion and necrosis of the media by mononuclear cells, intravascular thrombosis, and sometimes giant cells with granulomata (not required). Patchy involvement of the arteries leads to the notorious "skip lesions". Three stages of pathologic activity are known: acute/necrotising, granulomatous and regenerative (media fibrosed) [20].

In the pathogenesis of GCA, Th1 lymphocytes recognise antigens which leads to γ interferon (γIFN) production. In turn, macrophages produce interleukin-1 (IL-1, endogenous pyrogen), IL-6, TGFβ, NOS, TNF-α and matrix metalloproteinases (MMP). MMP cause smooth muscle cells to migrate to the vascular lumen. γIFN is crucial for the development of giant cells and granulomata. Giant cells release PDGF and VEGF, which lead to intimal hyperplasia and neoangiogensis [20].

An individual's particular cytokine profile may determine the constitutional symptoms and ischaemia such as fever, weight loss and malaise [21]. IL-6 is a pro-inflammatory cytokine important in the induction of the acute phase response. Interestingly, aspirin suppresses γIFN, while indomethacin does not (and NSAIDs are typically ineffective in GCA) [22, 23]. Therapies for GCA include agents that non-selectively and selectively suppress the immune and vascular responses.

The 1990 Classification of the American College of Rheumatology for GCA are 94% sensitive and 91% specific [24]. They include: age>50, ESR>50, headache of new onset, temporal artery abnormality (tender or Ø pulse), positive temporal artery biopsy. Not all must be present, only three, so the necessity of a temporal artery biopsy has been called into question if other features are present. When considering the diagnosis of GCA, it is prudent to rule out other arteritides, occult infection and malignancy.

Laboratory evaluation in GCA is useful. IL-6 induces the acute phase response so ESR is usually increased, as is C-reactive protein (C-RP). ESR may be normal in 1%–2% of GCA; C-RP may be as sensitive and perhaps more specific [18]. They both tend to be less elevated in occult GCA. Anaemia is seen in 2/3 of patients, leukocytosis in 38%, and abnormal liver chemistries, thrombocytosis and lymphocytosis may also be encountered [25]. ESR normalises with effective therapy, while elevated von Willebrand's factor (due to endothelial dysfunction) and IL-6 remain elevated [18, 20, 25].

Ultrasonography may assist in selecting the site for temporal artery biopsy, demonstrating a hypoechoic halo around the involved lumen [18]. An adequate sample should be taken, with serial sections performed by the pathologist. The false negative rate on bilateral biopsies is probably less than 5%. Ideally therapy with steroids is begun immediately upon suspecting the diagnosis, and the sample should be taken within 1–2 weeks [4]. Positive biopsies have been reported after long periods from the initiation of treatment [26]. Histopathology is not a predictor of clinical outcome [9].

F-18-deoxyglucose PET scanning may show uptake in large thoracic arteries such as the aorta, subclavians or carotids. This is 98% specific for GCA/PMR. However, the sensitivity is only 56% [18]. MRI may show synovitis and bursitis.

In treating GCA, there is no real alternative to corticosteroids. Prednisone, at a dose of approximately 40–80 mg/day, is begun. The dose is gradually reduced following both symptoms and ESR. Symptoms of PMR may appear as the dose is reduced. Relapses are uncommon as long as the prednisone dose is above 7.5 mg/day [4, 9, 18]. Treatment suppresses symptoms but does not shorten the disease duration (IL-6 and von Willebrand's fail to normalise) [18]. GCA is usually a self-limited process, ending after 2–3 years. Alternate day steroids are ineffective, as are NSAIDs [18]. Side effects from therapy are common and include vertebral compression fracture, aseptic necrosis of joints, infection, diabetes mellitus, peptic ulceration, congestive heart failure, cataracts, myopathy and psychosis [27]. GI protective measures, calcium, vitamin D and biphosphonates are usually indicated.

Steroid resistance, implying the need for doses of prednisone >15–20 mg/day beyond 3–6 months after initiation of therapy is seen in perhaps 20% of patients with GCA [20, 28]. For these patients other treatment options need to be considered. Both methotrexate and azathioprine have been advocated albeit with little evidence [18, 20, 25, 29]. Cyclosporine has been ineffective. Dapsone has been abandoned due to serious haematologic side effects [30]. There are also anecdotal reports on hydroxychloroquine, cyclophosphamide and trimethoprim/sulphamethoxazole.

As already stated, the lesions in GCA are driven by Th1 lymphocytes and macrophages and are rich in pro-inflammatory cytokines such as IL-1, TNF-α and γIFN. Because anti-TNF-α therapy in rheumatoid arthritis has been effective, inflixamab (a monoclonal antibody directed against TNF-α) has been reported as a potential treatment in steroid-resistant GCA [31]. Similarly, etanercept (the fusion protein of the extracellular ligand binding portion of the p75 TNF receptor and the Fc portion of IgG1) has been utilised [32]. Interestingly, thalidomide has anti-TNF-α activity, although to date it has not been investigated for this purpose.

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