

Giant cell arteritis: recent advances and guidelines for management

B. Dasgupta, N. Hassan

Bhaskar Dasgupta, MD, FRCP, Consultant Rheumatologist, Honorary Professor, Essex University; Nada Hassan MB, MRCP, Specialist Registrar in Rheumatology, Department of Rheumatology, Southend University Hospital, Prittlewell Chase, Westcliff-on-Sea, Essex, UK.

Please address correspondence to: Prof B. Dasgupta, Consultant Rheumatologist, Southend University Hospital, Prittlewell Chase, Westcliff-on-Sea, Essex, SS0 0RY, UK.

E-mail: Bhaskar.Dasgupta@southend.nhs.uk

© Copyright CLINICAL AND

EXPERIMENTAL RHEUMATOLOGY 2007.

Key words: Giant cell arteritis, epidemiology, temporal artery biopsy, diagnosis, treatment, ultrasonography.

ABSTRACT

This article reviews some of the recent work in epidemiology and pathology of giant cell arteritis (GCA), with particular regard to the immuno-histochemical findings in temporal artery biopsy (TAB) specimens. The diagnostic as well as prognostic role of biopsy histology is discussed. The role of novel imaging techniques e.g. duplex ultrasonography and FDG-PET scanning in diagnosis and staging of disease extent is reviewed. Existing evidence on the treatment is also discussed to propose guidelines on management of GCA.

Introduction

Giant cell arteritis (GCA) is an inflammatory rheumatic disease closely related to polymyalgia rheumatica, predominantly seen in the elderly, and is characterized by vasculitis of large and medium sized vessels.

Epidemiology

A major risk factor is age, with cases under the age of fifty being rare. Female sex also predisposes to developing GCA with a 2.5-3 fold relative risk. Both GCA and PMR are common in Caucasians, but rare in Asians and Blacks. The incidence has been estimated in over the 50s at 7/100,000 in Italy, 17.8/100,000 in Olmsted County, USA and 30/100,000 in Denmark (1). A recent investigation of time trends, geographical variation, and seasonality in the incidence in the United Kingdom from an analysis of computerized general practice medical records showed that the age adjusted incidence rate of GCA was 2.2/10 000 person-years (2). Both PMR and GCA were more common in the south than in the north of the UK, and both were more commonly diagnosed in the summer months.

Pathogenesis

The pathology of GCA is characterised by transmural inflammatory cell infiltration with giant cell formation, intimal hyperplasia and luminal occlusion (1). Tissue ischaemia is a direct consequence of intimal hyperplasia, which seems dependent on neovascularisation. Inflammation promotes the ex-

pression of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) (3). Higher levels of interferon- γ and interleukin-1 β expression contribute to the intimal hyperplasia and correlate with ischaemic outcomes.

A recent study on neovascularisation showed apparently isolated rings of new microvessels in the intima (4). The new microvessels in the inflamed arterial wall may be formed not only by the branching of adventitial capillaries, but also by the recruitment of vascular stem cells.

A histological scoring system using a standardised score for general inflammation, presence of giant cells, intimal proliferation, fibrinous exudate and neovascularisation showed that intimal proliferation produced maximum inter and intra-observer reliability (5). A histology study of 30 patients suggests that severity of intimal hyperplasia increases the likelihood of neuro-ophthalmic complications (6).

Diagnosis and disease assessment of GCA

The American College of Rheumatology classification criteria for the diagnosis of giant cell arteritis are well established (Table I) (7). For purposes of classification, a patient shall be said to have giant cell (temporal) arteritis if at least 3 of these 5 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%

Clinical clues associated with TAB positivity in suspected GCA (8)

Historical features that increase the likelihood of TAB positivity are jaw claudication; positive LR 4.2 (2.8-6.2), diplopia positive LR 3.4 (1.3-8.6). Physical findings that increase the likelihood of TAB positivity are TA beading [positive LR 4.6 (1.1-18.4), prominence +LR 4.3; 2.1-8.9), tenderness +LR 2.6; 1.9-3.7)].

Features that reduce the likelihood of TAB positivity: absence of TA abnormality, negative LR 0.53 (0.38- 0.75); normal ESR suggests much less likelihood of disease, LR for abnormal ESR 0.2; 0.08-0.51).

Table I. Classification criteria for GCA (traditional format).

Criterion	Definition
1. Age at disease onset \geq 50 years	Development of symptoms or findings beginning at age 50 or older.
2. New headache	New onset of or new type of localised pain in the head.
3. Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation unrelated to arteriosclerosis of cervical arteries.
4. Elevated erythrocyte sedimentation rate	Erythrocyte sedimentation rate \geq 50 mm/hour by the Westergren method.
5. Abnormal artery biopsy	Biopsy specimen with the artery showing vasculitis characterised by prominence of mononuclear cell infiltration or granulocyte inflammation, usually with multinucleated giant cells.

*For purposes of classification, a patient with vasculitis shall be said to have giant cell (temporal arteritis) if at least 3 of these 5 criteria are present.

Large vessel GCA

Nueninghoff *et al.* have reported the incidence and predictors of large-artery complication in a population-based study over 50 years (9). They found 46 incident cases i.e. 27% of a 168 patient cohort (1950-1999) with 30 (18%) cases of aortic aneurysm/aortic dissection (18 thoracic, 9 aortic dissection), 21 (15%) large artery stenosis [15 (9%) cervical and 6 (4%) subclavian/brachial]. Thoracic aortic dissection was associated with marked increase in mortality. It is important to monitor for bruits and asymmetry of pulses and blood pressure in GCA.

Temporal artery biopsy

Do we need to do a TAB?

Temporal artery biopsy remains the gold standard for diagnosis, and provides prognostic information. Early TAB in all patients is desirable in all cases (1), preferably within a week of starting steroids. There are reports that TAB may remain positive for 14-28 days following the initiation of steroids.

How long should it be?

Biopsy specimens should be a minimum of 1 cm in length, ideally 2 cm or more. Contra-lateral biopsies are not required unless the size of the original biopsy specimen was sub-optimal. The need to examine the specimen at multiple levels is controversial.

Does a +ve TAB link to the clinical picture?

Biopsy positivity correlates with jaw

claudication, abnormal temporal artery on examination, constitutional symptoms, vision loss (10). Severity of intimal hyperplasia is associated with increasing neuro-ophthalmic complications (6).

Duplex ultrasonography

Duplex ultrasonography is a useful approach for detecting characteristic edematous wall swellings - 'halo' sign, in active GCA (positive up to 16 days post steroid therapy) and for assessing vasculitis of the axillary arteries with sensitivity 83% and specificity 96% compared to TAB positivity (11). In addition, this modality can also be used to investigate the axillary and subclavian arteries in large vessel arteritis.

Fleuro deoxy glucose – positron emission tomography

Blockmans *et al.*, in a study of 35 patients with GCA, described vascular FDG uptake at diagnosis, in 29 patients (83%) in the subclavian, aorta and up to the femoral arteries (12). FDG uptake in the shoulders at diagnosis correlated significantly with the presence of polymyalgia rheumatica ($P = 0.005$). This modality appears to be a very promising imaging modality for evaluation of disease activity and extent in GCA.

MRI

FDG PET and MRI in the diagnosis of aortitis are comparable, but FDG imaging identified more vascular regions involved in the inflammatory process

than did MRI (13). FDG PET is more reliable than MRI in monitoring disease activity during immunosuppressive therapy.

Initial treatment in GCA (14)

There are no RCTs comparing different initial oral steroid doses. There are a few trials comparing oral versus IV followed by oral steroids. There are several observational studies. The initial dose favoured is around 40 - 60 mg prednisolone daily, with a few suggesting 1mg/k (1). It is the timing of steroid treatment rather than the dose of steroids that is suggested as the important issue. Some observational reports mention using IV steroids in patients with evolving visual symptoms or amaurosis fugax (250mg-1 gram/ day for 3 days) followed by oral steroids to prevent visual deterioration. There is no evidence that IV steroid use results in visual improvement in patients with established visual loss. Aspirin use is recommended unless contraindicated (15). Acetylsalicylate has also shown *in vitro* to reduce interferon-gamma secretion by a cyclo-oxygenase independent mechanism.

Disease modifying drugs in GCA

Methotrexate has been tried in 4 RCTs with varying results. Hoffman *et al.* reported in a study of 98 patients over 12 months no difference in relapses, GCA related morbidity, steroid dosage, treatment toxicity between methotrexate and placebo (16). However Jover *et al.*, in 42 patients over 24 months showed a significant decrease in steroid dosage and relapses with methotrexate compared to placebo (17). Azathioprine, cyclosporin, dapsone and hydroxychloroquine have also been used as steroid sparing agents with reports of limited benefits. Rituximab has been reported successful in a single case. There are 5 case reports of successful anti TNF use in resistant GCA, (3 infliximab and 2 etanercept) although a recent phase II study was ended prematurely when an interim analysis did not show any benefit (18). There appears to be a great unmet need for well-designed studies of novel biological therapies in GCA.

Summary of management guidelines for GCA (based upon recommendations from THE BRITISH SOCIETY FOR RHEUMATOLOGY GUIDELINES GROUP)

Referral

Urgent referral is suggested for all patients with GCA for specialist evaluation and urgent temporal artery biopsy.

Management principles

Immediate initiation of steroid treatment without delay after clinical suspicion of GCA – either fulfilling $\geq 3/5$ ACR criteria or historical features of GCA associated impending neuro-ophthalmic complications e.g. jaw claudication, amaurosis fugax, other visual symptoms.

Urgent referral to a physician with interest in GCA, e.g. rheumatologist/ ophthalmologist.

Obtain an urgent temporal artery biopsy. Perform indicated laboratory investigations listed above.

Initial treatment

Uncomplicated GCA (without jaw/ tongue claudication, visual symptoms): prednisolone 40 mg daily until resolution of symptoms and lab abnormalities.

Complicated GCA: evolving visual loss or history of amaurosis fugax: IV 500 mg – 1 gm daily for 3 days.

Established vision loss (prevent contra-lateral eye involvement): 60 mg prednisolone daily.

Add low dose aspirin 75 mg daily if there are no contraindications.

Add bisphosphonates and calcium vitamin D supplementation.

Consider proton pump inhibitors.

Steroid reduction

Principle

Steroid reduction should be considered only in the absence of clinical symptoms, signs and lab abnormalities suggestive of active diseases. The initial steroid dose should not be tapered too quickly (initial dose for 3-4 weeks) since earlier taper increases the risk of relapse. However, it is important to use the minimum effective dose for controlling disease activity.

Suggested tapering regimen (this may vary depending on many other factors): 40-60mg prednisolone continued for 2-4 weeks (until resolution of symptoms and lab abnormalities), then dose is reduced by 10 mg every 2 weeks to 20mg, then by 2.5mg every 2 weeks to 10 mg, and then by 1mg every month, provided there is no relapse.

Relapses

Patients should be monitored for relapses which may be indicated by a rise in ESR > 40 mm/Hr, plus at least one symptom or sign of GCA (not attributable to other causes) including classic polymyalgia rheumatica-like symptoms, headache or scalp pain/tenderness, new ischemic retinopathy, optic neuropathy, or visual loss, tongue/jaw pain and/or claudication, extremity claudication, thickness, tenderness, or ulcers or nodules over the temporal or occipital arteries, angiographic abnormalities compatible with vasculitis of the aorta and/or its primary branches, transient cerebral ischemia or stroke (31).

Treatment of relapse

Headaches: treat with the previous higher steroid dosage.

Headaches and jaw claudication: treat with 40mg prednisolone daily.

Eye symptoms: treat with either 60mg prednisolone or IV methyl prednisolone.

Large vessel GCA (prominent systemic symptoms, limb claudication, persistent high inflammatory markers): investigate with PET/ MRI /CT. Consider treatment using systemic vasculitis protocols.

Consider early introduction of methotrexate/alternative DMARDS.

Measures of process and adherence to guidelines

Minimum dataset recorded: clinical features, e.g. headaches, jaw claudication, visual symptoms, temporal artery abnormalities, limb claudication and bruits, proximal pain and stiffness. TAB and other relevant investigations. Initial steroid dose and taper.

Monitoring frequency: 0, 1, 4, 8, 12 weeks then 3, 6, 9, 12 months in the first year.

Bone protection: Co-prescription of calcium, vitamin D and bisphosphonates, DXA - as required.

References

- PENN H, DASGUPTA B: Giant cell arteritis. *Autoimmunity Reviews* 2003; 2: 199-203.
- SMEETH L, COOK C, HALL AJ: Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. *Ann Rheum Dis* 2006; 65: 1093-8.
- WEYAND CM, GORONZY JJ: Arterial wall injury in giant cell arteritis. *Arthritis Rheum* 1999; 42: 844-53.
- NORDBORG C, LARSSON K, NORDBORG E: Stereological study of neovascularisation in temporal arteritis. *J Rheumatol* 2006; 33: 2020-5.
- BHARADWAJ A, DASGUPTA B, WOLFE K, NORDBORG E, NORDBORG C: Difficulties in the development of histological scoring of inflamed temporal arteries in giant cell arteritis. *Rheumatology (Oxford)* 2005; 44: 1579-80.
- MAKKUNI D, BHARADWAJ A, WOLFE K, HUTCHINGS A, DASGUPTA B: Is intimal hyperplasia a marker for neuro-ophthalmic complications in GCA? *Arthritis Rheum* (under review).
- HUNDER GG, BLOCH DA, MICHAEL BA *et al.*: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990; 33: 1122.
- SMETANA GW, SHMERLING RH: Does this patient have temporal arteritis? *JAMA* 2002; 287: 92-101.
- NUENNINGHOFF DM, HUNDER GG, CHRISTIANSON TJ, MCCLELLAND RL, MATTESON EL: Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis in a population-based study over 50 years. *Arthritis Rheum* 2003; 48: 3522-31.
- ARASHVAND K, ALEXANDER WLA, WOLFE K, DASGUPTA B: Eye involvement in GCA: experience from a single centre. *Arthritis Rheum* 2006; 54: S762.
- SCHMIDT WA: Technology Insight: the role of color and power Doppler ultrasonography in rheumatology. *Nature Clinical Practice Rheumatology* 2007; 3: 35-42; quiz 59.
- BLOCKMANS D, DE CEUNINCK L, VANDER-SCHUEREN S, KNOCKAERT D, MORTELMANS L, BOBBAERS H: Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum* 2006; 55: 131-7.
- MELLER J, STRUTZ F, SIEFKER U *et al.*: Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. *European Journal of Nuclear Medicine & Molecular Imaging* 2003; 30: 730-6.
- KYLE V, HAZLEMAN BL: Treatment of polymyalgia rheumatica and giant cell arteritis II: relation between steroid dose and steroid associated side effects. *Ann Rheum Dis* 1989; 48: 662-6.
- NESHER G, BERKUN Y, MATES M, BARAS M, RUBINOW A, SONNENBLICK M: Low-dose

- aspirin and prevention of cranial ischemic complications in giant cell arteritis. *Arthritis Rheum* 2004; 50:1332-7.
16. HOFFMAN GS, CID MC, HELLMANN DB *et al.*: A multi-center, randomised, double blind, placebo controlled trial of adjuvant methotrexate treatment for giant cell arteri-
- tis. *Arthritis Rheum* 2002; 46: 1309-18.
17. JOVER JA, HETRANDEZ-GARCIA C, MORADO IC *et al.*: Combined treatment of giant cell arteritis with methotrexate and prednisolone: a randomised, double blind, placebo-controlled trial. *Annals Int Med* 2001; 134: 106-14.
18. HOFFMAN GS, CID MC, WEYAND CM *et al.*: for THE INFLIXIMAB - GCA STUDY GROUP: Phase II study of the safety and efficacy of infliximab in giant cell arteritis: a 22 week interim analysis. *Rheumatology (Oxford)* 2005; 44: 18.