Polymyalgia rheumatica and giant cell arteritis

Polymyalgia rheumatica and giant cell arteritis are the commonest inflammatory rheumatic conditions seen in the elderly. This review focuses on the diagnostic processes and complications of disease and treatment; and the safe management of these conditions with careful consideration of balance between benefits and long-term risks of glucocorticosteroid therapy.

Giant cell arteritis (GCA) is the commonest of the primary systemic vasculitides. The clinical significance of this condition relates to involvement of the ophthalmic artery, leading to neuro-ophthalmic complications. Polymyalgia rheumatica (PMR) presents with shoulder and/or pelvic girdle pain and stiffness. Both these conditions are associated with significant morbidity in the elderly population because of the disease and the long-term complications associated with steroid treatment. The conditions are common in Caucasians of northern European descent and are rare among Asians and African-Americans. They occur more commonly in women and are almost never seen in people aged less than 50 years. The annual incidence rate of GCA varies in different studies from 9.3 to 27 per 100 000 persons aged 50 years and older. The age adjusted incidence of PMR in England is 8.4 per 10 000 person-years (Smeeth et al, 2006).

Pathology

GCA involves the large and medium-sized vessels and in particular the aorta and its branches. Involvement of the superficial temporal artery is common (and hence the other name of temporal arteritis for this condition) and clinically useful for performing arterial biopsy. GCA is histologically characterized by chronic inflammation of the vessel wall with varying amounts of lymphocytes, histiocytes and multinucleated giant cells. The arterial inflammation is not uniform and 'skip phenomenon' is common. PMR involves synovitis of the glenohumeral and hip joints, subacromial bursa, and bicipital tendinitis.

Clinical features

Giant cell arteritis

Headache is the main symptom in more than two-thirds of the patients. It is usually sudden in onset, severe and predominantly temporal in location but occasionally may be occipital or even non-localized. The temporal artery may be thickened, tender, red and non-pulsatile. Scalp tenderness, either localized or diffuse, may be present. Jaw claudication is a specific diagnostic symptom and may indicate impending ischaemic complications. Low-grade fever may be seen and patients may present with pyrexia of unknown origin.

Visual symptoms include transient and permanent visual loss, diplopia and ptosis. Fundus examination during the early stage may show slight pallor and oedema of the optic disc and scattered cotton-wool exudates. Anterior ischaemic optic neuropathy may quickly follow. Upper cranial nerve involvement is occasionally seen. Nuenninghoff et al (2003) have shown that aortic (usually thoracic aorta) aneurysms and/or dissection can occur in up to 27% of patients with GCA.

Polymyalgia rheumatica

Arthralgias and myalgias usually develop abruptly and involve proximal parts of extremities. Shoulder girdle pain and morning stiffness are the predominant features at the onset in almost all of the patients. The symptoms may be unilateral initially but soon become bilateral. On formal objective testing, muscle strength is usually preserved. Systemic features like fever, malaise, anorexia, fatigue and weight loss may occur in up to a third of patients. Although the symptoms are predominantly proximal, peripheral involvement may also occur. This often takes the form of transient synovitis of knees, wrists and sternoclavicular joints. Patients experience significant disability with activities of daily living associated with poor quality of life.

Relationship between GCA and PMR

Polymyalgia is reported in 40–60% of patients with GCA and as part of the initial GCA symptom complex in 20–40%. Between 10 and 15% of patients with PMR without clinical symptoms of GCA have been documented to have abnormal temporal artery biopsy. PMR may occur before, simultaneously, or after GCA.

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Table 1. American College of Rheumatology criteria for the classification of giant cell arteritis

Presence of three or more of the following:
Age greater than or equal to 50 years at the time of disease onset
Localized headache of new onset
Tenderness or decreased pulsations of the temporal artery
Erythrocyte sedimentation rate greater than 50 mm/h (Westergren method)
Necrotizing arteritis with mononuclear cell infiltrate or granulomatous inflammation with multinucleated giant cells in the arterial biopsy

From Hunder et al (1990)

Diagnosis of GCA

The American College of Rheumatology (ACR) classification criteria (*Table 1*) are helpful but temporal artery biopsy remains the gold standard for diagnosis.

Diagnosis of PMR

Various diagnostic criteria are currently in use (*Table 2*).

The main symptoms of PMR (pain and stiffness in the girdle areas and neck) can occur in many other conditions, particularly rheumatoid arthritis, infection and neoplasia. Clues for a possible non-PMR diagnosis are summarized in *Table 3*.

Diagnostic uncertainty and a stepped diagnostic approach for PMR

Many clinicians use response to steroids as the main defining feature of both PMR and GCA, but this encourages diagnostic error since steroids are potent anti-inflammatory agents which can mask symptoms. At the Third International Conference on PMR/GCA, which took place in Cambridge, UK, in July 2005 an international consensus effort was initiated in developing classification criteria for the polymyalgic syndrome. This is being sponsored by the ACR. The consensus committee has endorsed the following stepped approach for the diagnosis of PMR (Dasgupta et al, 2006):

- Inclusion criteria, including the 'core' criteria, i.e. symmetrical, proximal limb girdle pain associated with morning stiffness
- Exclude mimics, particularly active infection, neoplasia, inflammatory arthropathies and connective tissue diseases
- Prescribe the standard low dose of steroids and assess the response: at least 75% reduction in the clinical symptoms within a week followed by resolution of the inflammatory response.

Investigations

The minimum laboratory data set suggested for the evaluation of PMR is:

- Full blood count
- Urea and electrolytes
- Liver function tests
- Erythrocyte sedimentation rate or C-reactive protein
- Dipstick urinalysis
- Thyroid-stimulating hormone
- Serum electrophoresis
- Creatinine kinase
- Rheumatoid factor and possibly anti-nuclear antibody.

Table 2. Diagnostic criteria for polymyalgia rheumatica

Criteria	Chaung et al (1982)	Healey (1984)	Bird et al (1979)	Jones and Hazleman (1981)
Age	≥50 years	≥50 years	≥65 years	≥50 years
Bilateral aching of neck, shoulders, pelvic girdle	Any two	Any two	Shoulder pain and/or stiffness	Shoulder and pelvic girdle pain without weakness
Morning stiffness ≥1 h	Yes	Yes	Yes	Yes
Duration of symptoms	≥1 month	≥1 month	2 weeks	≥2 months (unless treated)
ESR	≥40 mm/h	≥40 mm/h	≥40 mm/h	ESR ≥30 mm/hr or CRP ≥6 mg/ml
Depression and/loss of weight	Not relevant	Not relevant	Relevant and recognized criteria	Not relevant
Exclusion of other diagnosis	Required	Required	Not required	Required
Rapid response to prednisolone (≤20 mg/day)	Not required	Required	Not required	Required
Other features	None	None	Bilateral upper arm tenderness	None
Diagnosis	All criteria need to be fulfilled	All criteria need to be fulfilled	Any 3 or 1 plus positive temporal artery biopsy	All criteria need to be fulfilled

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

Table 3. Clues to a non-polymyalgia rheumatica diagnosis

Age of onset ≤50 years
Chronic onset
Absence of upper limb involvement
Absence of inflammatory stiffness
Normal erythrocyte sedimentation rate and C-reactive protein
Incomplete response to 1 mg/day of prednisolone

Imaging

Chest X-ray is useful in identifying a non-PMR diagnosis, for example a pancoast tumour. Ultrasonography in PMR may show a gleno-humoral effusion and/or subacromial bursitis in a significant number of patients (Coari et al, 1999). Halo sign around the lumen of the temporal artery may be demonstrated on colour duplex ultrasonography. Angiography is useful to document large vessel vasculitis in the form of stenotic areas, occlusions and collaterals in some patients. Positron emission tomography using fluorodeoxyglucose has been shown to be a very useful non-invasive technique to evaluate large vessel arteritis (Blockmans et al, 1999). Vascular imaging with magnetic resonance imaging/computed tomography shows promise in demonstrating vessel wall abnormalities such as oedema and contrast uptake.

Temporal artery biopsy

Temporal artery biopsy remains the gold standard for the diagnosis of GCA and hence every attempt must be made to obtain the biopsy in a suspected case of GCA. The chances of getting a positive diagnostic biopsy will be higher, if:

- Performed within 2 weeks of the initiation of steroid therapy
- The length of the arterial biopsy segment is at least 3 cm
- The biopsy is performed by a trained surgeon with experience in temporal artery biopsy.

Treatment

Corticosteroids are the mainstay of drug therapy for both PMR and GCA. One of the common pitfalls in the management of these conditions is the usage of an initial high dose of steroids combined with rapid tapering of the dose, which leads to frequent relapses. Suggested steroid treatment schedules for PMR and GCA are summarized (*Table 4*).

PMR can also be treated effectively with intramuscular depot methylprednisolone acetate (depomedrone) using a regimen of 120 mg every 3 weeks for the first 12 weeks and thereafter by monthly injections reducing by 20 mg every 12 weeks. Depomedrone has the advantage of a much lower cumulative dose compared with the oral steroids and associated with fewer side effects (Dasgupta et al, 1998).

If the symptoms relapse while the steroid dose is tapered, the dose can be increased to the previous higher dose rather than restarting at the initial dose; for example, if PMR symptoms recur when the prednisolone dose is reduced to 5 mg, then the dose can be increased to 6 or 7 mg rather than re-starting at 15 mg. Higher doses are needed for the relapse of arteritic symptoms.

Follow up

Close follow up is mandatory during the initial phase for assessment of the steroid response and disease activity, monitoring steroid dosage and adverse events, and recognizing emergence of alternative diagnoses. Most patients require treatment for a variable period from 18–24 months and some may need treatment for a more prolonged period, albeit with a smaller dose.

Table 4. Steroid treatment schedules

Polymyalgia rheumatica	Initiate therapy with 15 mg daily of prednisolone
	Continue the initial dose for 3 weeks and assess the response. The standard steroid response is at least 75% reduction in clinical symptoms within a week followed by resolution of the inflammatory markers
	If the patient responds, reduce the dose to 12.5 mg and continue it for a further 3 weeks then reduce to 10 mg
	Thereafter the dose is tapered by 1 mg per month depending on clinical and laboratory response
Giant cell arteritis	Prednisolone is initiated at variable doses of 40 mg/day for the symptoms of headache, and 60 mg/day if associated with visual symptoms and/or jaw claudication
	Consider using intravenous methylprednisolone for impending visual loss and involve the ophthalmologists early
	The initial high dose can be reduced to 40 mg after 3 weeks and to 20 mg after another 2–3 weeks depending on the clinical and acute phase response markers
	Taper the dose by 5 mg every 1–2 weeks until dose of 20 mg is reached
	Further reduction is by 2.5 mg every 2–4 weeks until 10 mg is reached
	Thereafter the dose is tapered by 1 mg per month depending on clinical and laboratory responses

Relapses can occur at any time during or after discontinuation of the therapy and hence, the need for long-term follow up.

Methotrexate can be used as a steroid-sparing agent in those who relapse frequently. Anecdotally other treatments such as azathioprine and anti-tumour necrosis factor therapy have been found to be useful in both PMR and GCA. However, a randomized controlled trial of infliximab did not show efficacy in the treatment of newly diagnosed GCA (Hoffman et al, 2005).

Bone protection

Glucocorticosteroid-induced osteoporosis is a serious problem and needs to be addressed from the start of steroid therapy especially in the elderly. Calcium and vitamin D supplements should be co-prescribed along with steroids. Individuals at high risk, for example those aged 65 years or over, those with a previous fragility fractures or other clinical risk factors, should be commenced on a bisphosphonate at the time of starting glucocorticoids. In these patients, measurement of bone density is not required. In other individuals, a dual energy X-ray absorptiometry scan is recommended and a T score of -1.5 or lower indicates the need for intervention with a bisphosphonate (Royal College of Physicians, 2003).

Conclusions

Both PMR and GCA are commonly prevalent disorders in the elderly leading to significant disability. There is a wide variation of practice in management of these conditions. Neuro-ophthalmic complications of GCA are common. Diagnostic uncertainty exists in PMR and a stepped approach is recommended. Steroid side-effects can be serious and hence every effort should be made to balance benefits *vs* risks. BJHM

Conflict of interest: none.

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KEY POINTS

- Every attempt must be made to obtain a temporal artery biopsy whenever giant cell arteritis is suspected.
- Do not delay the initiation of corticosteroid therapy while awaiting temporal artery biopsy in a suspected case of giant cell arteritis.
- The diagnostic evaluation of the polymyalgic syndrome should follow a stepped approach.
- The characteristic clinical response to low dose steroids in polymyalgia rheumatica is rapid, complete and sustained with regards to resolution of clinical symptoms and of the acute phase response.
- Early specialist referral criteria are: partial or non-response to low dose steroids, prominent systemic and 'red flag' symptoms, peripheral arthritis, and other atypical features.
- Initiate osteoporosis prophylaxis early to prevent the steroid induced bone loss.
- Steroid therapy is usually prolonged, hence accurate disease activity assessment is mandatory to balance benefits vs the long-term steroid-related complications.