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Polymyalgia rheumatica: pathogenesis and management

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What is polymyalgia rheumatica?

Polymyalgia rheumatica (PMR) is an inflammatory musculoskeletal disorder, with a lifetime risk of 2.4% for women and 1.7% for men.[1] Its cause is unknown, but ultrasound and magnetic resonance imaging (MRI) studies reveal extra-capsular inflammation, such as bursitis, in addition to synovitis.[2] PMR classically responds very well to systemic glucocorticoids.

PMR, if undiagnosed, has devastating effects: patients typically cannot get out of, or even turn over in, bed. The catastrophic effects on physical functioning and quality of life are reversed by treatment.[3] Rapid diagnosis is therefore essential.

Diagnosis of PMR can be challenging. The classical history consists of profound pain and stiffness affecting the neck, shoulder and hip areas. Symptoms are maximal in the morning and improve throughout the day. Physical examination may be unremarkable but may give clues to mimics of PMR (such as malignancy, deep seated infection or other inflammatory illness).[4] Inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and plasma viscosity (PV) are typically elevated.

Reflecting the difficulty in diagnosis, multiple sets of diagnostic criteria for PMR have been produced, none with perfect performance. Recent provisional criteria incorporate optional ultrasound features;[5] it should be emphasised that these are classification criteria (disease-defining) and have not yet been validated as diagnostic criteria.

Relationship to giant cell arteritis

There is a well-known association between PMR and giant cell arteritis (GCA). Many patients with GCA also have polymyalgic symptoms and some patients with PMR subsequently develop GCA.[6] A subset of patients with PMR may have subclinical GCA.[7] There is some discussion as to whether PMR and GCA are separate disease entities or two conditions on a single pathophysiological spectrum. For the practising clinician it is important to realise that PMR and GCA are treated with different doses of glucocorticoids and that treatment of GCA is a medical emergency, whereas the immediate priority with PMR is to exclude other conditions before starting treatment. The subset of PMR patients that later develop GCA tend to have higher inflammatory markers and particular *HLA-DRB1* alleles (a subclass of the human leukocyte antigen [HLA]) and so receive a higher than usual dose of glucocorticoids at PMR onset.[6] Indeed, studies of GCA consistently reveal an association with *HLA-DRB1*04* alleles, whereas no consistent HLA association of PMR has been found. At present PMR may be best viewed as a clinical syndrome with heterogeneous aetiology, overlapping with GCA in only a minority of cases.

Relationship to ageing

By far the strongest risk factor for PMR is increasing age. PMR is virtually unheard of in those under 50 years old and incidence of the disease becomes more common with each decade, with a peak incidence around 75 years. The reason for this is unclear. Ageing of the immune system (immunosenescence), ageing of the tissues and ageing of neurohumoral regulatory systems may all be involved. Based on the clustering of cases in space and time, it has been proposed that PMR may be triggered by infection in some cases. This could lead to persistent inflammation on a background of chronic low-grade inflammation secondary to decline in adaptive immunity and a compensatory increase in innate immune mechanisms. Neurohumoral mechanisms may also be involved.

Diagnosis

Diagnosis of PMR involves recognising the clinical syndrome of PMR and excluding common differential diagnoses. This has been conceptualised as a 'stepped approach'.[8]

The clinical syndrome of PMR consists of pain and stiffness that is typically worst in the early hours of the morning or on waking, and tends to improve over the course of the day. The neck, shoulder and hip areas are classically affected first. Inflammatory markers are typically elevated and anaemia of inflammation may be present. If any of these features are missing then particular efforts should be made to search for other diagnoses prior to considering glucocorticoid treatment. 'PMR with a normal ESR' has been described; in these cases it is may be useful to check CRP levels.

Other features at presentation may support alternative diagnoses. Although weight loss, fever and synovitis/tenosynovitis have all been described in PMR, they should raise a suspicion of malignancy, of deep-seated or disseminated infection (such as endocarditis or osteomyelitis) or of inflammatory arthritides such as rheumatoid arthritis (RA), spondyloarthropathy or crystal arthropathy.[9,10]

Even in apparently classical PMR, it is advisable to perform a complete physical investigation and basic laboratory investigations including tests for full blood count (FBC), urea and electrolytes (U+E), liver function tests (LFT), calcium, creatinine kinase (CK), thyroid stimulating hormone (TSH) and immunoglobulins to screen for other medical conditions.[8]

Initial treatment

Once a clinical diagnosis of PMR has been made, treatment is commenced:[11] 15mg prednisolone daily is typically used. Clinical response does not confirm the diagnosis as many other inflammatory conditions also respond to glucocorticoids.[5] However, failure to respond within a few days to 15–20 mg prednisolone daily should raise suspicions of other conditions and the diagnosis should be reconsidered. Also, patients with PMR may be left with some pain and stiffness despite glucocorticoid therapy,[3,5] which may perhaps relate to comorbid osteoarthritis in older patients.

Ongoing treatment

After the initial symptomatic response to glucocorticoids, the dose is gradually reduced. A typical regimen is reduction by 2.5 mg prednisolone every 2–4 weeks, until reaching 10 mg daily, and then by 1 mg per month until cessation or until symptoms flare. Some patients need a slower reduction of 0.5 mg per month. Tapering of glucocorticoid dose should be guided by clinical symptoms, not by inflammatory markers; thus recording relevant patient-reported outcomes[12] represents good practice. In the case of symptom flare, returning to the previous effective dose is usually sufficient. If GCA supervenes, treatment should be as for de novo GCA with high-dose glucocorticoids.

At present there does not seem to be any alternative to glucocorticoid therapy. Oral prednisolone/prednisone is currently used for almost all patients, but alternatives include periodic intramuscular methylprednisolone.[13]

There is little evidence to justify the use of steroid-sparing drugs in PMR. Methotrexate[14–16] and azathioprine[17] have been proposed, but one study[15] gave negative results and methotrexate does not seem to lead to a substantial reduction in glucocorticoid-related adverse events.[18] The difficulty with interpreting the evidence is the clinical heterogeneity of PMR and ascertainment issues of each case. It may be that the weak effect of methotrexate in some studies is due to patients with apparent PMR actually having RA, which usually responds well to methotrexate. However this theory is speculative. A similar argument applies to the small number of patients for whom biologic drugs have been tried, with mixed results.

Comorbidity

At the time of diagnosis of PMR it is important to assess patients for comorbidities and to continue to monitor patients during the course of treatment. Given the strong association with GCA, patients should be alerted to possible GCA symptoms (eg headache, scalp tenderness, jaw claudication, visual symptoms), but there is no need for a temporal artery biopsy if there are no clinical features of GCA. It is also important to remember that glucocorticoids can cause adverse effects in elderly people.[19] When committing patients to long-term glucocorticoid treatment, there should be an assessment of conditions that may be caused, or exacerbated, by glucocorticoids, including osteoporosis, diabetes, hypertension, vascular disease, increased body weight and peripheral oedema.[20] These conditions should then be monitored during the course of the patient's treatment. Co-prescription of gastric and bone protection (at least calcium and vitamin D supplements) is advisable throughout the period of treatment with steroids.

Prognosis

It is important to keep an open mind about diagnosis, at least for the first year of treatment, as other conditions may take time to declare themselves. PMR itself is usually seen as a self-limiting disorder and the expectation is that glucocorticoid therapy can be gradually withdrawn and ultimately stopped. However, many patients relapse as the glucocorticoid dose is reduced, particularly those with higher inflammatory markers pre-treatment. Typically, half of all patients still require treatment 2 years after diagnosis.[6] Because patients with PMR almost invariably receive glucocorticoids it is difficult to determine whether subsequent adverse events are due to the PMR, to the glucocorticoids, or both. When prospectively monitored, a high rate of adverse events has been noted.[3] Patients should be involved in decisions about their treatment, as the balance between the risk of relapse and the risk of treatment-related complications may be different for each individual.

Key points

- **Polymyalgia rheumatica (PMR) is a treatable, inflammatory musculoskeletal disease mostly affecting those over 50 years of age**
- **Diagnosis of PMR can be difficult and is primarily based on the history of the patient plus consideration of alternative diagnoses including infection, malignancy and other musculoskeletal disorders**
- **It is important to check inflammatory markers prior to treatment. If either the symptoms or inflammatory markers do not respond rapidly to 15–20 mg prednisolone daily, the diagnosis of PMR should be reconsidered**
- **Patients with PMR should be alerted to possible giant cell arteritis (GCA) symptoms, including what they should do if they develop any of these symptoms**
- **Patients treated for PMR should be monitored for adverse effects of long-term glucocorticoids**

KEY WORDS: Polymyalgia rheumatica (PMR), pathogenesis, management, giant cell arteritis (GCA)

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Treatment of hyperuricaemia and gout

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Introduction

Gout is the most prevalent inflammatory arthritis, affecting 1.4% of adults in the UK.[1] Chronic elevation of serum uric acid (SUA), or hyperuricaemia, is required for gout to develop. Risk factors for hyperuricaemia and gout are summarised in Box 1. When the SUA level increases above the physiological saturation threshold, monosodium urate (MSU) crystals precipitate in and around peripheral joints. After a prolonged period of asymptomatic hyperuricaemia, gout typically presents clinically as an acute attack of excruciating joint pain, swelling and tenderness, commonly affecting the first metatarsophalangeal joint. Attacks characteristically resolve over 2–3 weeks, but most patients subsequently experience recurrent attacks involving other joints and can develop joint damage and clinically apparent subcutaneous MSU crystal concretions (tophi) (Fig 1). Treatment aims to first relieve the severe pain and inflammation of acute gout and then to reduce the SUA level sufficiently to prevent crystal formation and to dissolve existing crystals, thereby preventing further attacks and irreversible joint damage.

Box 1. Risk factors for hyperuricaemia and gout.[1]

- Male gender
- Family history and/or genetic factors
- Metabolic syndrome
- Hypertension
- Insulin resistance
- Obesity
- Dietary factors (increased risk)
  - alcohol (particularly beer)
  - purine-rich foods (red meat and seafood)
  - fructose and sugar-sweetened soft drinks
- Dietary factors (reduced risk)
  - cherries
  - vitamin C
  - dairy products
  - coffee
- Medication
  - diuretics (loops and thiazides)
  - ciclosporin
  - pyrazinamide
  - ethambutol
- Impaired renal function
- Osteoarthritis (gout only)
- Chronic lead poisoning
- Myeloproliferative disorders

Management of acute gout

Treatment of acute gout aims to provide rapid relief of pain and inflammation. The affected joint should be rested and the application of local ice-packs can safely reduce pain and swelling.[2] Pharmacological options are oral non-steroidal anti-inflammatory drugs (NSAIDs), oral colchicine and corticosteroids.[3,4] Although no individual NSAID appears superior to another, any quick-acting NSAID can be used at the full dose together with a proton pump inhibitor. Indometacin is best avoided in view of frequent gastrointestinal, central nervous system and cardiovascular adverse effects. Until recently, oral colchicine was often used in high doses, which frequently led to severe diarrhoea, nausea or vomiting.[5] However, current advice is to use a lower dose of 500 µg two to four times daily, which remains effective and is better tolerated.[3,4,6,7]

The single most effective treatment for acute gout is combined joint aspiration (immediately reducing intra-articular pressure and severe pain) and injection of intra-articular corticosteroid. This is particularly appropriate when NSAIDs and colchicine are contra-indicated or poorly tolerated and enables a definitive diagnosis by synovial fluid MSU crystal identification. Intramuscular or oral corticosteroids (eg prednisolone 20 mg daily) are effective alternatives when NSAIDs and colchicine are not appropriate, when attacks are oligo- and/or polyarticular or when monoarticular attacks occur at sites that are not amenable to aspiration (eg mid-foot joints).

Long-term management

Once the acute attack has resolved, long-term management aims to reduce the level of SUA below the saturation point,