Diagnosis and management of polymyalgia rheumatica

GERALD TRACEY

Polymyalgia rheumatica (PMR) can be a disabling condition, but the diagnosis is often delayed because many other conditions can mimic it. This article describes the recommended investigations and treatments for PMR, and discusses the GP’s role in management.

Polymyalgia rheumatica (PMR) is a common inflammatory condition that generally affects people over the age of 50 years. It can cause profound muscle stiffness (particularly in the early morning) and pain affecting the proximal muscles of the shoulders, neck and hip girdle. Some of the earliest reports of PMR describe a sudden onset of proximal muscle weakness, stiffness, malaise and low-grade fever.

Although the name ‘myalgia’ implies a problem with the muscles, PMR is thought to affect the periarticular surfaces. Muscle biopsies in PMR patients are essentially normal, while imaging studies have discovered that the inflammation lies in the proximal (subdeltoid, subacromial and glenohumeral) joints and hip joints. The prevalence of PMR increases with age and it affects females to males in a ratio of 3:1. PMR can be a disabling condition and affect morbidity and mortality, especially in the context of long-term glucocorticoid use. A diagnosis of PMR is often delayed, with the failure to diagnose potentially resulting in prolonged hospitalisation and extensive investigations.

Epidemiology

PMR overlaps considerably with the condition giant cell arteritis (GCA), with up to half of the patients with GCA complaining of symptoms consistent with PMR. Both conditions have been found to be associated with human leukocyte antigen (HLA)-DR 4. T helper (Th)-17 cells are decreased and regulatory T cells (Tregs) downregulated. Interestingly, interleukin (IL)-6 levels are elevated, accounting for the systemic symptoms experienced (IL-6 blockade is being targeted as a possible therapy). The production of adrenal hormones is decreased in patients with active PMR.

The exact causes of PMR are currently unknown, though the greatest risk factor for GCA/PMR is age. Seasonal variation has been documented and it has been noted that PMR often presents in a cyclical pattern – that is, with many patients...
presenting around the same time. It is for this reason that environmental factors have been considered as a potential cause; however, definitive evidence of causation is lacking. There is also an increase in incidence of GCA with latitude in the northern hemisphere.²

Due to the cyclical nature of GCA/PMR, infections have been long suspected, although the exact organisms involved have been difficult to pin down.² Fluctuations of GCA/PMR have supported an association with Mycoplasma pneumoniae, parvovirus B19, and Chlamydia pneumoniae.⁴ Many theories have been postulated, with one interesting study noting an association between increases in geomagnetic activity (solar cycles) and spikes in GCA cases.⁵

Clinical presentation
Patients will often describe a fairly abrupt onset of symptoms with profound muscle stiffness and pain. Classically, the symptoms are predominant in the morning and get better as the day goes on. ‘Gelling’ of the joints often occurs, which is when a patient describes stiffness associated with immobility.

Patients may complain of difficulty getting out of bed, out of a chair, turning over in bed, getting dressed or abducting the shoulders. All patients with symptoms of PMR should be asked about GCA-type symptoms, which can occur at any time in the disease process; for example, headache, jaw pain/claudication, scalp tenderness, beading or tenderness along the temporal artery and new visual disturbance (diplopia, amaurosis fugax). If GCA is suspected then an investigation of this should take precedence over PMR because of the risk of permanent visual loss if inadequately treated.

Investigations
The diagnosis of PMR is largely a clinical one. However, it is important to also consider and exclude other possible diagnoses that mimic the condition. The British Society for Rheumatology and British Health Professionals in Rheumatology (BSR/BHPR) clinical guidelines recommend several baseline investigations (see Table 1).⁶ These should include inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and plasma viscosity (PV). Creatinine kinase (CK) should be checked as myositis may mimic PMR. A bone profile, which includes alkaline phosphatase (ALP), vitamin D and calcium, should be taken. Very low vitamin D levels can cause significant myalgia while raised serum calcium or ALP could suggest malignancy. An isolated raised ALP could also suggest Paget’s disease.

If a person has significant shoulder or hip pain, or is presenting with unilateral joint symptoms, investigation with plain-film X-rays should be considered (see Table 2). In the elderly population, rotator cuff tendinopathy is common and can be picked up on X-ray or imaging (ultrasound or MRI). If there is a predominance of systemic symptoms (fever, weight loss, fatigue), the clinician may need to consider whether cross-sectional imaging is indicated (CT thorax, abdomen, pelvis), especially in the context of an atypical history or failure to respond to glucocorticoids. Normal inflammatory markers should make a clinician strongly reconsider the diagnosis and if in any doubt, seek specialist opinion. Normal or very high inflammatory markers along with inadequate response to glucocorticoid therapy would warrant referral to a specialist.

Differential diagnosis
Malignancy
Malignancy is the one diagnosis that should be always considered. It can present with systemic symptoms similar to PMR – that is, weight loss, fatigue, fever and bony pain. The diagnosis might be further clouded by a partial response to glucocorticoids. For men, it can be worthwhile assessing urinary symptoms and investigating whether there are any symptoms of prostatism (urinary frequency, nocturia, incomplete voiding, poor stream, post-micturition voiding). Rectal examination and prostate specific antigen (PSA) testing may be warranted. Multiple myeloma is also a mimic and tends to affect a similar age population. Anaemia, raised calcium, raised ESR and renal impairment should alert to this possibility. Serum protein electrophoresis, serum free light chain and urinary Bence-Jones protein testing are needed for further evaluation.

Infection
Infection needs to be ruled out prior to considering glucocorticoid therapy. A full assessment is needed with particular focus on common infection sites such as the respiratory tract (chest X-ray) and the urinary tract (dipstick testing). Other rarer mimics could include Infective endocarditis, septic arthritis or viral infections.

Vasculitides
Vasculitides should be considered, especially if a patient has other associated symptoms. Nasal symptoms (nose bleeds or polyps), sinusitis, haemoptysis and ear, nose and throat (ENT) symptoms can be suggestive of granulomatosis with polyangiitis (GPA), formerly known as Wegener’s granulomatosis. Respiratory symptoms, shortness of breath, wheeziness and a raised eosinophil count could raise the possibility of eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome. Patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides can often have

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Table 1. Baseline investigations for suspected polymyalgia rheumatica (PMR)⁶

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<thead>
<tr>
<th>Test</th>
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<tr>
<td>Erythrocyte sedimentation rate (ESR)/ C-reactive protein CRP</td>
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<tr>
<td>Urea and electrolytes</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Full blood count</td>
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<tr>
<td>Liver function tests</td>
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<tr>
<td>Bone profile (calcium, phosphate, alkaline phosphatase, vitamin D)</td>
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<tr>
<td>Serum protein electrophoresis</td>
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<tr>
<td>Chest X-ray</td>
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<tr>
<td>Urine dipstick</td>
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<td>Creatinine kinase</td>
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Table 2. Plain-film X-ray findings in polymyalgia rheumatica and related conditions

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Polymyalgia rheumatica (PMR)</td>
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<tr>
<td>Differential diagnosis</td>
</tr>
<tr>
<td>Malignancy</td>
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<tr>
<td>Infectious diseases</td>
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<td>Vasculitides</td>
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PMR-type symptoms. If there is a suggestion of any of these conditions or ANCA positivity then specialist advice should be sought.

Inflammatory arthritis

Inflammatory arthritis can present with PMR-type onset symptoms, sometimes called late-onset rheumatoid arthritis or polymyalgic-onset rheumatoid arthritis. These patients might be difficult to wean off glucocorticoids or have predominant articular symptoms.

Treatments and guidelines

The mainstay of treatment is glucocorticoids. PMR is classically a glucocorticoid-responsive condition. The BSR/BHPR issued guidelines in 2010 (due for update later this year), while the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) guidelines were updated in 2015.

First-line treatment options

The BSR/BHPR recommend a standard starting dose of prednisolone 15mg. Patients should expect a greater than 70% improvement in symptoms within a week and normalisation of inflammatory markers within four weeks. If the response is less than this, alternative diagnoses should be considered.

A patient’s response to glucocorticoids and total treatment duration is highly variable so treatment may need to be tailored to the patient’s needs. The BSR/BHPR has outlined a suggested tapering regimen: prednisolone 15mg daily for three weeks, 12.5mg for three weeks, 10mg for four to six weeks, then reduce by 1mg every four to eight weeks or alternate day reductions (eg 10mg/7.5mg on alternate days). If a patient relapses with symptoms suggestive of PMR, it is suggested that they go to the pre-relapse dosage and once symptoms have abated another tapering attempt can be made. If the tapering of glucocorticoids is proving difficult, referral to specialist care is recommended.

An alternative to oral prednisolone is intramuscular methyl-prednisolone. Although it is rarely used in clinical practice, in some instances it might be considered; for example, if a patient has problems swallowing tablets or issues with compliance. The initial dose is 120mg every three to four weeks, reducing by 20mg every two to three months.

Second-line treatment options

In secondary care, if there are frequent relapses (at least three) on tapering of glucocorticoids then a rheumatologist might consider the addition of a secondary agent. The disease-modifying antirheumatic drugs (DMARDs) methotrexate, azathioprine or leflunomide can all be used as steroid-sparing agents. However, before the addition of a DMARD, any alternative pathologies such as rotator cuff tendinopathy, secondary pain condition (eg fibromyalgia), or underlying inflammatory arthropathy, should be explored. There is limited evidence for the efficacy of DMARDs such as methotrexate in PMR with the best evidence for their use in early disease rather than in glucocorticoid-resistant cases (where it is recommended in the ACR/EULAR guidelines whereas the BSR recommends consideration of DMARDs after second relapse). TNF inhibitors have been used but are not recommended and trial data is not supportive of their use. Given the systemic nature of PMR, raised CRP and circulating IL-6 levels, IL-6 inhibition is one obvious target. The IL-6 antagonist tocilizumab or newer agents such as sarilumab could have a future role after demonstrating potential benefit. There is currently no NICE approval for the use of tocilizumab in polymyalgia rheumatica, though NICE TA518, published in April 2018, recommends tocilizumab as an option for relapsing or refractory GCA.

Role of the GP in management

GPs can diagnose and manage uncomplicated PMR. Any patient with an atypical presentation, inadequate response to glucocorticoids or difficulty weaning off them (remaining on glucocorticoids beyond two years) should be referred to secondary care.

At every visit, a patient should be assessed for symptoms or signs of GCA and any glucocorticoid-related side-effects. Up-to-date laboratory tests and inflammatory markers should be measured every three months. A sporadically raised inflammatory marker might not indicate a relapse and clinical correlation is needed.

Patients aged over 65 years or who have osteoporotic fracture risk factors should be offered bone protection with a bisphosphonate and calcium/vitamin D supplementation. Assessment of the patient’s fracture risk (using QFracture or FRAX) should be undertaken. A DEXA scan can be considered in low-risk patients who are likely to remain on glucocorticoids for more than three months. If T score <-1.5, a bisphosphonate is indicated while the patient is on glucocorticoids.

In 2017, the National Osteoporosis Guideline Group (NOGG) produced new guidelines for patients on glucocorticoid therapy. It recommended:

- Women and men age >70 years, with a previous fragility fracture, or taking high doses of glucocorticoids (>7.5mg daily prednisolone) should be considered for bone-protective therapy.
- In other individuals, fracture probability should be estimated using FRAX with adjustment for glucocorticoid dose.
- Bone-protective therapy should be started at the onset of glucocorticoid therapy in individuals at high risk of fracture.
- Alendronate and risedronate are first-line treatment options. Where these are contraindicated or not tolerated, zoledronic acid or teriparatide are alternative options.
- Bone-protective therapy may be appropriate in some premenopausal women and younger men, particularly in individuals with a previous history of fracture or receiving high doses of glucocorticoids.

Table 2. Other investigations to consider for suspected polymyalgia rheumatica (PMR)

- X-ray shoulders or hips
- CT thorax/abdomen/pelvis
- Rheumatoid factor (RF)
- Anticyclic citrullinated peptide (anti-CCP) antibodies
- Antinuclear antibodies (ANA)
When to refer

A GP should refer a patient to a specialist if there is any doubt regarding the diagnosis, for example if the patient is younger than 60 years and the history is atypical (see Table 3). Likewise, specialist help should be sought if a patient fails to respond adequately to glucocorticoids or develops articular symptoms. If there is any difficulty weaning the patient off glucocorticoids then secondary agents need to be considered. Referral to secondary care is also necessary if vasculitis (large vessel or ANCA-associated GCA) is suspected.

Conclusion

Although PMR is considered a benign condition, it can have profound implications for the patient and their quality of life. Much of the morbidity and mortality associated with PMR is related to long-term glucocorticoid exposure. Novel agents are now becoming available that will hopefully widen the scope of current treatment. If there are atypical features, or if the patient fails to respond to glucocorticoids, then specialist referral is warranted. However, it is important to be mindful of other conditions mimicking PMR, to minimise glucocorticoid exposure and to seek expert opinion in difficult cases.

References


Declaration of interests
None to declare.

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