The idiopathic inflammatory myopathies (IIMs) – comprising polymyositis, dermatomyositis and inclusion body myositis – are a rare group of disorders characterised by muscle inflammation. This article discusses the causes, symptoms, assessment and treatment of these disorders, and the GP’s role in management.

The idiopathic inflammatory myopathies (IIMs) are a rare group of heterogeneous diseases that are characterised by the presence of muscle inflammation, ie myositis, and are associated with significant disability and mortality. A wide spectrum of extramuscular (internal organ) involvement is also observed, and this is responsible for much of the pain, disability and mortality associated with these diseases.

The IIMs consist of polymyositis, dermatomyositis and inclusion body myositis. The term ‘myositis’ and IIMs are often used interchangeably; however, myositis is a non-specific term that indicates the presence of muscle tissue inflammation and can occur secondary to a wide range of other causes including (but not limited to) infection, trauma and metabolic/inherited conditions. The causes of an elevated creatine kinase with and without muscle involvement/weakness are presented in Table 1.

The purpose of this review is to describe the clinical spectrum of disease observed within patients with IIMs, including the key underlying mechanisms/causes of disease, an initial approach to management and assessment (including first- and second-line drug treatments, where appropriate), and the role of the GP, including in facilitating the early diagnosis of IIMs.

### Causes

Although great advancements have been made in understanding the aetiopathogenesis of the IIMs in the past few decades, the definite mechanisms to date remain incompletely understood. There is a complex interaction between environmental factors in a genetically primed individual. The autoimmune response differs depending on the type of IIM. In dermatomyositis, the presence of autoantibodies leads to subsequent complement activation and is largely driven by a humoral-mediated immune response. In contrast, polymyositis and inclusion body myositis are driven by a CD8+ cytotoxic T cell response. As with many autoimmune rheumatological conditions, genes within the

<table>
<thead>
<tr>
<th>Muscle involvement</th>
<th>Origin</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised creatine kinase with muscle weakness</td>
<td>Infection</td>
<td>Viral: influenza, hepatitis B, coxsackie</td>
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<tr>
<td></td>
<td></td>
<td>Bacterial: staphylococcus, streptococcus, leprosy</td>
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<td></td>
<td></td>
<td>Parasites: toxoplasma, trichiella, schistosoma, cysticercus</td>
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<td></td>
<td>Endocrine</td>
<td>Acromegaly</td>
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<td></td>
<td></td>
<td>Hypothyroidism</td>
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<td></td>
<td></td>
<td>Hyperthyroidism (rare)</td>
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<td></td>
<td></td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular</td>
<td>Neuromuscular junction disorders: myaesthenia gravis, Lambert-Eaton myaesthetic syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuropathic disorders: Guillain-Barré syndrome, motor neurone disease</td>
</tr>
<tr>
<td></td>
<td>Drug/toxin</td>
<td>Lipid-lowering agents: HMG-CoA reductase inhibitors (statins)</td>
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<td></td>
<td></td>
<td>Anti-malarial: hydroxychloroquine</td>
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<td></td>
<td></td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
<td>Crush injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mechanical fall</td>
</tr>
<tr>
<td>Raised creatine kinase without muscle weakness</td>
<td>Drug/toxin</td>
<td>Lipid-lowering agents: statins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Prolonged/unaccustomed exercise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macro-CK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased muscle mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Convulsions</td>
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</tbody>
</table>

Table 1. Causes of elevated creatine kinase with and without muscle involvement/weakness (this is not an exhaustive list)
major histocompatibility complex (MHC) region have been found to be significantly associated with dermatomyositis, which suggest other genetic loci play a significant role.\textsuperscript{2,3} It is likely that environmental factors have a significant impact on the course of the disease. No definitive association between infection and IIMs has been found to date, although infectious agents, in particular viral infections, are important causes of (often acute and self-limiting) myositis.\textsuperscript{2} Smoking is independently associated with poor outcomes.\textsuperscript{4}

It is likely that there is a complex interaction between genetic predisposition and environmental factors. For example, the presence of the HLA-DRB1*03:01 allele in combination with smoking has been reported to significantly increase the risk of interstitial lung disease and polymyositis.\textsuperscript{5} Of interest, the prevalence of dermatomyositis decreases the further away from the equator,\textsuperscript{6} and this may be explained by exposure to UV light.\textsuperscript{8} Furthermore, an association has been reported between the latitude-dependent development of dermatomyositis and myositis-specific (anti-Mi-2 and anti-TIF1-γ) antibodies.\textsuperscript{7,8}

### Which patient groups are most susceptible?

The IIMs are very rare, and therefore extensive national and international collaboration has been required to establish significant cohorts of patients to perform high-quality research studies. In a systematic review that included 46 articles (published between 1966 to 2013), the incidence of the IIMs ranged between 1.16 and 19 per million per year and the prevalence ranged between 2.4 and 33.8 per 100,000.\textsuperscript{6} Although the IIMs can affect patients of any age, including children, the peak age of onset is reported to be between 45 and 60 years.\textsuperscript{1} Diagnostic delay is not uncommon in the IIMs.\textsuperscript{6} Akin to many rheumatological/autoimmune-based diseases, the IIMs have a female predominance in the order of 2:1,\textsuperscript{6} apart from inclusion body myositis, which is twice as common in men.\textsuperscript{1}

<table>
<thead>
<tr>
<th>Organ/system</th>
<th>Clinical manifestation</th>
<th>Potential treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>Arthralgia/arthritis (eg associated with anti-synthetase syndrome)</td>
<td>Oral prednisolone&lt;br&gt;DMARDs (eg methotrexate)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Interstitial lung disease (especially with anti-synthetase syndrome)&lt;br&gt;Aspiration pneumonia</td>
<td>Oral prednisolone&lt;br&gt;Intravenous methylprednisolone&lt;br&gt;Cyclophosphamide&lt;br&gt;Oral or intravenous antibiotic</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Oesophageal dysmotility&lt;br&gt;Intestinal perforation</td>
<td>Proton-pump inhibitor&lt;br&gt;Urgent surgical assessment</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Dysrhythmias&lt;br&gt;Congestive heart failure</td>
<td>Usual treatment (eg beta-blocker)&lt;br&gt;Usual treatment (eg ACE inhibitor and/or diuretic)</td>
</tr>
<tr>
<td>Vascular</td>
<td>Skin ulceration&lt;br&gt;Raynaud’s phenomenon</td>
<td>Tissue viability team&lt;br&gt;Prompt treatment of infection&lt;br&gt;Vascular surgical assessment&lt;br&gt;Conservative measures&lt;br&gt;Drug therapies including oral vasodilators</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Rash (dermatomyositis)</td>
<td>Topical steroid&lt;br&gt;Other systemic immunosuppression</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Osteoporosis&lt;br&gt;Avascular necrosis&lt;br&gt;Corticosteroid-induced myopathy&lt;br&gt;Corticosteroid-induced diabetes</td>
<td>Oral calcium/vitamin D supplementation&lt;br&gt;Bisphosphonate (eg alendronic acid)&lt;br&gt;Assess bone density (eg DEXA)&lt;br&gt;Prompt recognition&lt;br&gt;Urgent orthopaedic assessment&lt;br&gt;Judicious use of steroid-sparing immunosuppression (eg methotrexate)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Wide range of possible solid-tumour and haematological malignancies</td>
<td>Investigate appropriately including screening&lt;br&gt;Refer to appropriate speciality/oncology</td>
</tr>
</tbody>
</table>

DMARD: disease-modifying anti-rheumatic drug

Table 2. The organ-based and potential treatment-related complications in idiopathic inflammatory myopathies. NB. this is not an exhaustive list and is intended to give an overview of potential complications and treatments. Adapted from West S, 2015\textsuperscript{14}
**Signs and symptoms**

Disease and treatment-related organ-based complications are presented in Table 2. Below, we describe the presentation of disease subsets and then organ-based complications.

**Polymyositis and dermatomyositis**

The IIMs typically present as progressive muscle weakness (e.g., over weeks). However, this can also be very rapid in nature, presenting as an acute medical emergency, including failure of the respiratory muscles. The typical picture is of profound proximal muscle group weakness, making activities such as standing from a sitting position and walking upstairs difficult. The difference between polymyositis and dermatomyositis lies in the involvement of the skin, which is absent in the former.

**Inclusion body myositis**

This subtype of IIM has a characteristic presentation compared to both polymyositis and dermatomyositis. Although both proximal and distal muscle groups can be involved, there is notable involvement of the finger flexor tendons and weakness of the thigh muscles. It is very important to distinguish polymyositis and dermatomyositis from inclusion body myositis as the latter is a relentless disease with no known disease-modifying therapy, including no response to immunosuppressive therapy.

**Juvenile IIM**

Juvenile dermatomyositis is the most common form of juvenile IIM, with a presentation that is largely similar to adult dermatomyositis. A particular, and often very challenging, manifestation of the disease in the paediatric population is calcinosis – the deposition of calcium within the skin and subcutaneous tissues. This can cause significant morbidity including from extensive ‘sheet-like’ deposition in the abdominal wall, cutaneous ulceration and/or superadded infection (which should be promptly treated).

**Anti-synthetase syndrome**

This is a specific clinical syndrome that is associated with antibodies directed toward the tRNA synthetases (e.g., anti-Jo-1) and consists of fever, arthritis (non-erosive), mechanic’s hands, interstitial lung disease and Raynaud’s phenomenon.

**Skin involvement**

Skin involvement in the IIMs is characteristic of dermatomyositis. Examples include Gottron’s papules (raised erythematous lesions, commonly distributed over the extensor aspect of the hands and digits), the heliotrope rash (a violaceous or dusky red discolouration over the eyelids, with or without periorbital oedema), mechanic’s hands (scaly, flaking, cracked skin on lateral and palmar aspect of digits), the ‘V’ sign (a violaceous, erythematous rash in the ‘V area’ of the neck), and the shawl sign (a violaceous, erythematous rash, distributed over the shoulders, upper back and neck). Examples of the ‘V’ and shawl sign are shown in Figures 1 and 2, respectively. Occasionally, the rash may predate the diagnosis of muscle disease by months or even years, which is termed ‘clinically amyopathic dermatomyositis’.

**Cardiorespiratory involvement**

Cardiorespiratory involvement is an important cause of morbidity and mortality in patients with IIMs, and is often subclinical. Cardiac involvement includes (but is not limited to) heart failure, conduction system abnormalities and myocarditis. A range of respiratory conditions can be observed in the IIMs, including interstitial lung disease and respiratory muscle weakness. An example of imaging of interstitial lung disease is presented in Figure 3.

**Gastrointestinal involvement**

Gastrointestinal involvement is not uncommonly recognised. Subjective swallowing problems are common and can result from severe weakness of the tongue, pharyngeal muscles and lower oesophagus, which can result in aspiration pneumonia. Patients may experience significant dyspepsia, which can be due to treatment (over prolonged periods) with high-dose oral steroid therapy. Lower gastrointestinal symptoms can result from abnormal GI motility.

**Cancer**

The risk of cancer is increased in patients with IIMs. Patients of both sexes with dermatomyositis have been found to have a relative risk of 4.66 compared with the general population, in
Clinical assessment and investigation

A diagnosis of IIMs should be considered in patients presenting with insidious or more acute forms onset of symmetrical muscle weakness. The diagnosis of IIM is supported through targeted investigations.

As in all aspects of medicine, a full medical history and clinical examination is indicated in all patients with IIMs. It is important for clinicians to be aware of classification criteria, which can act as an aide memoire in the assessment of patients with a possible IIM. Several decades ago, Bohan and Peter proposed classification criteria (see Table 3) for polymyositis and dermatomyositis, which are still widely used in clinical practice. More recently, classification criteria for IIMs have been developed as the result of a joint EULAR/ACR initiative.14

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symmetrical proximal muscle weakness</td>
<td>All of items 1–4 (definite polymyositis)</td>
</tr>
<tr>
<td>2. Elevation of skeletal muscle enzymes</td>
<td>3 of items 1–4 (probable polymyositis)</td>
</tr>
<tr>
<td>3. Typical electromyographic features of myositis</td>
<td>2 of items 1–4 (possible polymyositis)</td>
</tr>
<tr>
<td>4. Muscle biopsy abnormalities typical of myositis</td>
<td>Item 5 plus 3 of items 1–4 (definite dermatomyositis)</td>
</tr>
<tr>
<td>5. Typical skin rash of dermatomyositis (eg heliotrope rash and Gottron’s papules)</td>
<td>Item 5 plus 2 of items 1–4 (probable dermatomyositis)</td>
</tr>
</tbody>
</table>

Table 3. Diagnostic criteria for polymyositis and dermatomyositis, as proposed by Bohan and Peter19,20

Extramuscular features/disease should be actively sought. These include (but are not limited to) fevers, weight loss, shortness of breath, rashes, inflammatory arthritis and/or Raynaud’s phenomenon. Other aspects of the patient’s history that should enquired about include medications that could cause muscle pathology (eg statins or long-term corticosteroids), a social history (eg occupation or smoking) and any family history (eg of myopathy or autoimmune rheumatic diseases).

A full neuromuscular examination should be performed. It is crucial to characterise muscle involvement, including formal manual muscle assessment of the upper and lower limbs and axial spine (eg hip flexors) to define the distribution (eg proximal vs distal). This should be performed with reference to the wide expression of disease observed in patients with IIMs, including extramuscular disease, and possible localised/associated signs of cancer. This could include examination of the breast, rectum, prostate and testes along with measurement of prostate-specific antigen.2 Further imaging, including of the ovaries in women, and computerised tomography should be considered, as appropriate. Localising symptoms and signs should be investigated along standard lines.

Supportive investigations include an elevated creatine kinase; however, other tests that could indicate myositis include lactate dehydrogenase, alanine transaminase, aspartate aminotransferase and aldolase. There is increasing evidence that cardiac troponin T (but not troponin I) is potentially elevated in patients with IIMs from peripheral muscle inflammation/regeneration.15 However, raised cardiac troponin T is usually a marker of myocardial injury, and therefore GPs should exclude cardiac pathology in the context of it being raised. Muscle biopsy allows examination to confirm the diagnosis of IIMs and exclude other potential causes of myositis. Electromyography abnormalities are non-specific and may only be found in the acute phase of the disease (eg fibrillations).1 Magnetic resonance imaging
(see Figure 4) is increasingly being used in patients with IIMs and can help to differentiate between active disease (eg muscle oedema) and damage (eg replacement with fatty tissue). Myositis-specific antibodies (eg anti-Jo-1) and myositis-associated antibodies (eg anti-Ro) can help inform both the diagnosis and prognosis (see Figure 5). Respiratory investigations may include (but are not limited to) a chest computerised tomography scan and pulmonary function testing (eg looking for evidence of interstitial lung disease).

**First- and second-line treatment options**

There is a paucity of randomised controlled trials of pharmacological treatments for the IIMs owing to the rarity of these conditions. In general, the current treatment of IIMs consists of steroid therapy in the acute phase, which is weaned over time, with the introduction of a steroid-sparing agent. Depending on severity, a high-dose steroid is initiated and maintained for around four to six weeks at the full dose. Oral prednisolone is commenced at a daily dose of, for example, 0.5–1mg/kg and for more severe disease intravenous methylprednisolone is utilised. The dose is subsequently tapered based upon clinical response as assessed clinically by improvement in muscle strength, and supported through investigations (eg improvement in creatine kinase).

Patients are often prescribed steroid-sparing agents. Commonly used examples include methotrexate, azathioprine and mycophenolate mofetil. In refractory disease (eg recurrent flares of muscle disease activity), further treatment options include rituximab (an anti-CD20 monoclonal antibody that depletes B cells) and intravenous immunoglobulin. Patients’ bone health

**Figure 4.** Muscle magnetic resonance imaging (MRI) in myositis: thigh MRI from the same patient presented in Figure 3. There is widespread oedema (which appears white) with bilateral symmetrical involvement of the extensor muscles.

**Figure 5.** Myositis autoantibodies and clinical associations. Reproduced with permission from Betteridge Z, 2016.

**Legend:**
- IBM = inclusion body myositis
- CTD = connective tissue disease
- SRP = signal recognition particle
- HMGCR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase
- TIF1 = transcription intermediary factor 1
- NXP2 = nuclear matrix protein 2
- MDA5 = melanoma differentiation-associated gene 5
- SAE = small ubiquitin-like modifier activating enzyme
- 5NT1A = cytosolic 5’nucleotidase 1A
- Mi-2 = nucleosome-remodelling deacetylase complex
- Jo-1 = histidyl tRNA synthetase
- PL7, threonyl tRNA synthetase
- PL12 = alanyl tRNA synthetase
- OJ = isoleucyl tRNA synthetases
- EJ = glycyl tRNA synthetase
- KS = asparaginyl tRNA synthetase
- Zo = phenylalanyl tRNA synthetase
- Ha = tyrosyl tRNA synthetase
- snRNP = small nuclear ribonucleic protein

IBM = inclusion body myositis; CTD = connective tissue disease; SRP = signal recognition particle; HMGCR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase; TIF1 = transcription intermediary factor 1; NXP2 = nuclear matrix protein 2; MDA5 = melanoma differentiation-associated gene 5; SAE = small ubiquitin-like modifier activating enzyme; 5NT1A = cytosolic 5’nucleotidase 1A; Mi-2 = nucleosome-remodelling deacetylase complex; Jo-1 = histidyl tRNA synthetase; PL7, threonyl tRNA synthetase; PL12 = alanyl tRNA synthetase; OJ = isoleucyl tRNA synthetases; EJ = glycyl tRNA synthetase; KS = asparaginyl tRNA synthetase; Zo = phenylalanyl tRNA synthetase; Ha = tyrosyl tRNA synthetase; snRNP = small nuclear ribonucleic protein
should be assessed (see Table 2) and concomitant oral calcium/vitamin D should be prescribed. Introduction of bone active therapy (eg an oral bisphosphonate) should also be considered.

The multidisciplinary team has a key role in the management of patients with IIMs throughout the course of their disease (eg physiotherapy and speech and language therapy). There is often a need for close working with organ-based specialists (eg specialists in respiratory medicine).

The role of the GP

GP s have an important role in the management of patients with IIMs throughout the course of the disease. Firstly, GPs should perform a comprehensive assessment of patients presenting with muscle weakness, with an awareness of the wide spectrum of disease observed in the IIMs. They must have an appreciation that the IIMs are rare diseases and consider all the other potential causes of the symptoms. Secondly, GPs need to be aware that patients may present very acutely unwell with severe muscle weakness and multi-organ involvement, potentially necessitating admission to critical care.27 Thirdly, GPs will be closely involved in the ongoing management of patients with IIMs, including prescribing and monitoring immunosuppressive therapy. Fourthly, GPs have a very important role in the assessment and management of common co-morbidities, such as dyspepsia, Raynaud’s phenomenon and bone disease. Finally, GPs are often the first point of contact for patients with IIMs and can have a unique and invaluable window into the detection and treatment of non-lethal complications (eg depression).

It is important to highlight that an important differential diagnosis of IIMs is polymyalgia rheumatica. However, although in both conditions there can be significant proximal limb girdle pain and stiffness, in IIMs, there is actual muscle weakness, GPs should refer any patient with suspected IIM and not just base referral upon an elevated creatine kinase. Referral processes may vary between centres; however, suspected IIM is usually referred to rheumatology.

Conclusion

The IIMs are a rare and heterogeneous group of diseases with a very high disease-related morbidity and mortality. The IIMs primarily affect skeletal muscle; however, a wide range of extra-muscular manifestations are also observed. Diagnosis is based upon the clinical presentation and exclusion of the other causes of myositis. Investigations are supportive and can help make the diagnosis and inform the prognosis. The mainstay of treatment is with steroid therapy, although other immunosuppressive drugs are also commonly used. The GP has a key role, including in the initial diagnosis of IIM by having a high index of clinical suspicion, as well as in the ongoing holistic management of this long-term and potentially life-threatening rheumatological condition.

References


Declaration of interests

None to declare.

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