Juvenile dermatomyositis

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Abstract

Juvenile dermatomyositis (JDM) is a rare but important autoimmune paediatric disease. The main clinical features are proximal muscle weakness and skin rashes or other skin manifestations, but multiple organ systems can also be involved. Diagnosis is made using the 1975 Bohan and Peter diagnostic criteria (a gold standard for clinical trials) or by revised criteria from 2006 based on an international consensus survey process. Optimal treatment requires a multidisciplinary approach, and is based on immunosuppression combined with intensive physiotherapy. Initially medical treatment involves intravenous and oral corticosteroids with adjuvant disease modifying anti-rheumatic drugs (DMARDs) and later biologic therapy. Randomised controlled trials are limited due to the low incidence but consensus on treatment has been agreed and is shown in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) protocol. Without treatment, mortality can be high but with early diagnosis and treatment the prognosis is good, with a third achieving full remission, a third having a cyclic, relapsing and remitting course and the remainder having an ulcerative chronic course.

Keywords biologic therapy; disease modifying anti-rheumatic drugs (DMARDs); juvenile dermatomyositis; muscle disease; paediatric rheumatology; physiotherapy; skin disease

Overview

Juvenile dermatomyositis (JDM) is a chronic autoimmune condition that presents before the age of 16-year-old. It primarily affects the skin and muscles but can also affect other organs such as the joints, gastro-intestinal system, lungs and heart. It is characterised by proximal muscle weakness, impairment of muscle function due to inflammation, and skin involvement.

Epidemiology

JDM is a rare disease with a global incidence ranging from 1.9 to 4.1 cases per million children per year. In the United Kingdom (UK) the reported incidence is 3.2 cases per million children per year. There have been reports of some differences in incidence between racial groups but other studies have not found this difference. There is however a consistent female predominance with an approximate ratio of 2.3:1 females to males.

The mean age of diagnosis is 7 years and it is most commonly described in the 4–10 year old age group. About a quarter present before the age of five and it is thought that a young age of onset may be associated with a poorer prognosis.

The aetiology of JDM is largely unknown. It is thought to be the result of an environmental effect on hosts with genetic susceptibility.

In retrospective studies a high proportion of children have a clinical history consistent with an infection prior to onset leading to the hypothesis that there is an infectious trigger, the majority of these are respiratory infections but Coxsackie virus, parvovirus and echovirus, *Toxoplasma* and *Borrelia* have also been implicated. Exposure to UV light has also been implicated in triggering disease onset especially in the subset of patients positive for p155/140 transcriptional intermediary factor 1-gamma (TIF1-gamma) autoantibodies. The hypothesis for this is that sunlight might upregulate interferon type 1 cytokines which in turn upregulate the tripartite motif family of proteins leading to an autoantibody response.

There is often a family history of autoimmune disease especially type 1 diabetes and systemic lupus erythematous.

The genetic predisposition to JDM is complex and polygenetic. It is thought that each genetic association has a moderate effect on the risk of acquiring JDM. It is likely that both innate and adaptive immunity are involved in the disease process. Allelic variations associated with increased risk of JDM include HLA-B*08, DRB1*0301 and DQA1*0501. The Genome-Wide Association Study (GWAS) of adult and juvenile dermatomyositis confirmed the major histocompatibility complex (MHC) as the major genetic region associated with dermatomyositis and indicated that dermatomyositis shares non-MHC genetic features with other autoimmune diseases.

Pathology

Macroscopic

Muscle oedema can be seen in the proximal region of the affected muscles.

Microscopic

Muscle biopsies of affected patients can demonstrate either inflammatory, vascular or muscle fibre changes. One of the earliest changes present in muscle biopsies is increased expression in MHC I. It is thought that this overexpression of MHC class I in muscle cells can lead to an activation of the endoplasmic reticulum stress response which is pro-inflammatory and can lead to muscle damage.

Clinical presentation

Clinical features

The main features at diagnosis are proximal muscle weakness and skin manifestations specific to JDM including a heliotrope rash (Figure 1) and Gottron's papules over extensor surfaces and the small joints of the hand (Figure 2). These skin manifestations

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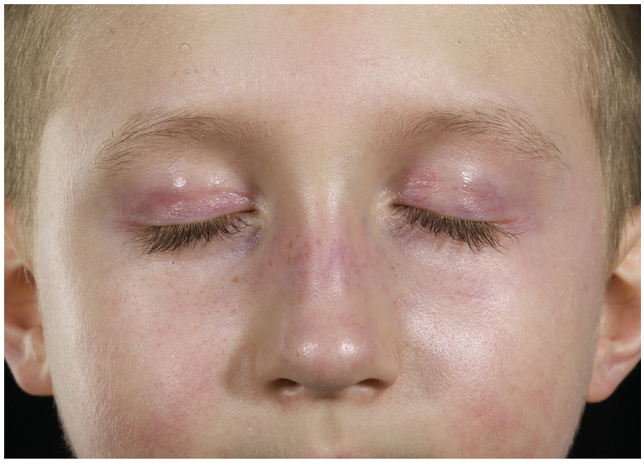

Figure 1 Violaceous or heliotrope hue over the eyelids.

can often be mistaken for eczema or psoriasis and consequently treated as such, thus delaying the diagnosis particularly if they are thought of in isolation and not in conjunction with the muscle signs. Other skin manifestations include lipoatrophy, ulceration, calcinosis and nailfold changes. The majority of children will also have other symptoms at presentation; these include pyrexia, malaise and fatigue, anorexia, weight loss, irritability and other general symptoms such as headaches, mouth ulcers or alopecia.

It is important to perform a thorough systemic examination as JDM can affect multiple organs:

- Gastro-intestinal tract: dysphagia, abdominal pain, persistent diarrhoea, melaena indicating vasculitis of the bowel
- Joints: arthritis, contractures
- Cardiac: non-specific tachycardia, hypertension, heart murmurs, cardiomegaly, pericarditis
- Pulmonary: aspiration secondary to dysphagia, interstitial lung disease

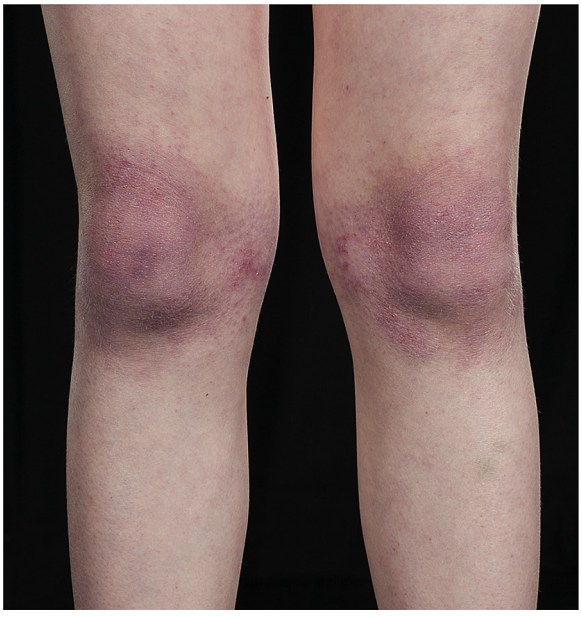

Figure 2 Gottron's papules over extensor surfaces.

- Eyes: glaucoma or cataracts
- Other: dysphonia

Severe clinical features

Ectopic calcification in skin and muscles is a severe cutaneous manifestation of JDM and this affects approximately 22–26% of patients. Risk factors for calcinosis are having untreated disease for a prolonged period, younger age of onset of JDM and the presence of various autoantibodies. Calcinosis can cause skin ulceration, nerve entrapment and contractures. It is most prevalent in pressure areas. It is now thought not just to be a manifestation of damage, but also indicates continuing disease activity and is an important cause of morbidity in JDM, contributing to long-term disability. Other severe skin manifestations include lipoatrophy or scarring due to ulceration in 30–40%.

Course of disease

The presenting features and the course of disease are variable. This heterogeneity in such a rare disease makes prediction of the course of disease and outcomes difficult. The course of disease can be divided into discrete groups of patients depending on the duration of disease activity. JDM can be monophasic, polyphasic or chronic. A cohort study in Canada showed a median time to remission of 4.67 years.

Predictors of disease severity

Identification of predictors of disease severity would allow for an early aggressive approach to treatment in those patients at risk. Some studies have shown that an early onset of disease is predictive of a poorer outcome but other studies found no difference. Cohort studies (retrospective and prospective) to determine predictors of severity and course of disease have shown differing results. One study showed presence of rash at 3 months and presence of nailfold abnormalities at 6 months predicts a longer time to remission, whilst another showed that female gender, negative Gower's sign at disease onset and positive photosensitivity were predictors of achieving complete clinical remission.

High levels of circulating T cells expressing CXCR5 have been shown in JDM, this may account for autoantibodies associated with JDM, with the hypothesis that these CXCR5 positive T cells support the differentiation of naïve B cells into antibody producing cells.

In adult dermatomyositis there are a few well described serological features, less is known about JDM but autoantibodies, both myositis specific antibodies (MSA) and myositis associated antibodies (MAA) have been described. Approximately 70% of children with JDM have one or more MSA or MAA. The frequency of these autoantibodies varies by ethnicity, but gives very helpful information regarding a patient's disease associations and consequently disease course.

Diagnosis

Diagnostic criteria

The initial diagnostic criteria were from Bohan and Peter in 1975 and include:

- characteristic rash
- systemic proximal muscle weakness
- elevated serum muscle enzymes: creatine kinase (CK), transaminases, lactate dehydrogenase (LDH) and aldose