Juvenile dermatomyositis: review and update of the pathogenesis and treatment

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ABSTRACT

Juvenile dermatomyositis (JDM) is an autoimmune disease characterized by systemic vasculopathy. Its main manifestations include symmetrical proximal muscle weakness, elevated serum muscle enzymes and cutaneous lesions, among which the heliotrope and Gottron's papules are pathognomonic. Early recognition and prompt therapy allow better prognosis and prevent the development of calcinosis. Although the treatment is based on glucocorticoids, the more commonly associated immunosuppressors include methotrexate, azathioprine, cyclosporine, and cyclophosphamide, depending on the severity of disease. The use of immunobiologicals for refractory cases remains under investigation, but the results are controversial or inexpressive. In this review, we highlight recent updates on the pathogenesis and treatment of JDM.

Keywords: juvenile dermatomyositis, inflammatory myopathy, autoimmune myositis, pathogenesis, tumor necrosis factor alpha inhibitor.

INTRODUCTION

Juvenile dermatomyositis (JDM) is an inflammatory myopathy, of which etiology is probably autoimmune, with an onset before the age of 18 years. It differs from the adult disease by the higher incidence of vasculopathy, proliferation of the intima of small vessels, thrombosis or infarctions,[1] and by the smaller frequency of autoantibodies. The mean time for the diagnosis is 12 months.

Among childhood inflammatory myopathies, it is the most frequent, although it is less common than in adults. It has an incidence of two to three cases/million children/year in the general population. American studies reveal a prevalence of 65.1% in Caucasians; 14.2% in Hispanics; and 11.4% in African-Americans.[2] The female gender predominates. The pattern of involvement is bimodal, with a higher incidence between 2 and 5 years of age and in adolescence, between 12 and 13 years of age.[1]

In general, the prognosis of JDM is good regarding education and capacitation for work, but it usually requires prolonged treatment that delays the development of children and adolescents.[1]

Etiology

Although its etiology is still unknown, several hypotheses have been postulated. Several cases are related to the presence of class II major histocompatibility complex (MHC) (for example, HLA-DQA1*0501 – especially in Hispanics and African-Americans, and DMA*0103; DMB*0102; and DQA1*0301).[1,2-5] Recently, DRBI*0301 was listed as the one with the greatest relative importance in JDM in Caucasians. On the other hand, the alleles DQA1*0201, *0101, and *0102[4] have been described as protective. There are those who defend the role of microchimerism. To this date, some authors have observed a higher frequency of microchimerism in mothers with HLA-DQA1*0501; however, other authors have not confirmed this finding.[1,6]

Note that some cases if JDM are related to the inheritance of genes that are great producers of tumor necrosis factor-α

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(TNF-α 308A), being characterized by more severe and prolonged disease. Those patients have higher levels of trambospondin-1, a factor that promotes the proliferation of vascular smooth muscle. However, the presence of the allele TNF-α 238AG seems to be a protective factor for JDM.[1,7-9] Genetic polymorphisms of interleukin-1 (IL-1) also influence the development of this disease. The presence of the genes IL-1α +4845TT and IL-β +3953T is related to JDM and can indicate the severity of the disease, while the allele IL-1α +4845G behaves as a protective factor in Caucasians.[8]

Infectious factors could be involved via a mechanism of molecular mimicry with epitopes of the heavy chain of myosin. Some studies have implicated vaccines, such as hepatitis B, viral triple vaccine, typhoid fever, and cholera, in the development of the disease.[1] Manlhiot *et al*.[10] recorded 71% of signs and symptoms consistent with infection present up to three months before the onset of inflammatory myopathy and 80% of them in the airways. Environmental factors, such as drugs and ultraviolet light, also seem to play a role in the etiology of JDM.[1]

Pathogenesis

It is difficult to establish which event initiates and which one perpetuates the inflammatory process in JDM.[3] Vasculopathy is its main characteristic and it affects organs and tissues, being mediated by both humoral and cellular immunity, in addition to innate immunity. The mechanism of the lesion could be by true vasculitis, with necrosis or leukocytoclasia, or by vasculopathy, leading to tissue ischemia and infarction.[1] The duration of the inflammation is also related to the higher expression of anti-angiogenic factors (especially tenomodulin), leading to vascular remodelation.[11]

No autoantigen has been definitively associated with the development of inflammation in JDM. However, it has been recently shown that the thermal shock protein Hsp60 seemingly exerts a regulatory effect on specific T lymphocytes in children with the disease and that it would be related to the production of TNF-α, IL-1β, and IL-10; note that the induction of the latter is associated with clinical remission.[12]

The participation of cellular immunity is relevant. In fact, in patients with dermatomyositis (DM), the perivascular distribution of T lymphocytes CD4+ and B lymphocytes in the affected muscle has been observed, unlike PM, in which T lymphocyte CD8+-mediated inflammation of the endomysium is seen. It has been supposed that the main mechanism of the muscular and vascular lesion would be induced by the complement cascade, while T lymphocytes CD4+ and B lymphocytes would produce immunoglobulins and myocytes would increase the production of class I and II MHC.[1,3,13] It is known that the activation of the complement promotes the release of cytokines and promotes vascular lesion. In JDM, a smaller expression of CD59 is seen in the sarcolemma. The binding of CD59 to C8 and C9 incorporated into the membrane attack complex (MAC) blocks polymerization and interrupts the formation of the complex. This would facilitate the local activation of the MAC – more exactly, in blood vessels and muscular fibers – in patients with JDM and, consequently, promote vascular lesion and muscular ischemia.[14] Moreover, apoptosis of muscle cells in JDM is mediated by the activation of two proteins: TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) and FASL (FAS ligand protein) and the severity of the disease seems to be connected to a greater period without treatment.[15]

As for soluble adhesion molecules that promote recruitment of inflammatory cells, an increase in ICAM-1 is seen in capillaries and perimysium of large vessels and, occasionally, in their endomysium and higher clinical and laboratorial activity is observed in JDM related to its higher serum levels. VCAM-1 is increased in the perimysium of large vessels, but with an irregular distribution, being associated to the inflammatory infiltrates.[16]

The expression of class I MHC is low in the normal musculature, while in patients with JDM there is an excess of its heavy chain, verified in a phase anterior to the development of inflammation.[13,17] It triggers type I interferon (IFN)-induced inflammatory response. In fact, genes inducible by IFN type I and its products are correlated with the activity of the disease in DM and JDM, in the analysis of both the serum and peripheral blood leukocytes. Interferon causes inappropriate increase in the expression of MHC-I and induces proinflammatory cytokines and chemokines (IL-5, IFN- γ) and maybe participating in the initiation of the inflammatory process, as its activity is directly correlated to a higher elevation of serum muscle enzymes and inversely with the time of non-treated disease.[18] Plasmacytoid dendritic cells, which regulate both the innate and acquired immune response, especially against virus, were equally identified in inflammatory infiltrates of JDM patients; they would lead to an increase in the production of IFN and they would be actively involved in disease progression by modulating the function of T lymphocytes in muscular blood vessels, participating in the initiation and maintenance of the characteristic autoimmune inflammatory lesions.[3,11,19,20]

Diagnosis

For the diagnosis of JDM, the traditional criteria of Bohan and Peter, shown in Table 1,[21,22] are used, considering the age of onset below 18 years.

Table 1
Bohan and Peter Diagnostic Criteria[21,22]

A	Proximal and symmetrical muscle weakness of the pelvic and scapular girdle, anterior flexors of the neck, progressing for weeks to months, with or without dysphagia or involvement of reparatory muscles.
B	Elevation of the serum levels of skeletal muscle enzymes: creatine phosphokinase, aspartate aminotransferase, lactate dehydrogenase, and aldolase.
C	Electromyography characteristic of myopathy (short and small motor units, fibrillations, positive pointy waves, insertional irritability and repetitive high-frequency firing).
D	Muscle biopsy showing necrosis, phagocytosis, regeneration, perifascicular atrophy, perivascular inflammatory exudate.
E	Typical cutaneous changes: • heliotrope with periorbital edema and violaceous erythema; • Gottron's sign: vasculitis in the elbow, metacarpophalangeal, and proximal iterphalangeal joints.

Criteria for DM	
Definitive	Three criteria (A, B, C or D) + E
Probable	Two criteria (A, B, C or D) + E
Possible	One criterion (A, B, C or D) + E

Anamnesis and physical examination should be meticulous. Complementary examinations help the diagnosis and the evolution follow-up of the affected child. Muscle enzymes (aldolase, creatine phosphokinase, aspartate aminotransferase, and lactate dehydrogenase), inflammatory tests, autoantibodies, electroneuromyography, and muscle biopsy are included. Immunohistochemical evaluation of MHC-I in muscle biopsies is useful in the diagnosis of DM in the adult, even in cases in which inflammation is not seen and it is of value in PM, although its absence does not rule out this diagnosis. However, it should be emphasized that MHC-I is not, or it is little expressed in other muscle diseases with inflammatory infiltrates (usually only close to the center of inflammation).[16]

When involvement of other organs is suspected, chest X-ray or CT scan, pulmonary function tests with flows, volumes and carbon monoxide diffusion, electrocardiogram and investigation of the gastrointestinal tract can be useful.[1]

Capillaroscopy helps the diagnosis and follow-up of more severe cases of JDM and the correlation with cutaneous signs, but not with muscular signs, suggests a different pathophysiological mechanism between both vasculopathies. Moreover, a greater regeneration of capillaries is observed in patients with less time without treatment.

Recently, the role of the MRI of the proximal musculature, especially T2 sequences with suppression of fat and STIR, to evaluate the extension and inflammatory activity of the affected musculature, making the edematous areas stand out, has been recognized. There are those who defend its use in substitution to muscle biopsy or as a means to provide a better place so it will be more valuable, therefore allowing adequate disgnosis.[24,25]

Clinical picture

Constitutional symptoms, such as fever, fatigue, indisposition, anorexia, weight loss, retarded growth, and irritability, both at the onset and during the evolution of the disease, are frequent.[1]

Muscle-skeletal manifestations

Weakness can affect the whole musculature; however, it is more evident in the pelvic and scapular girdle and anterior flexors of the neck and trunk. Involved muscles are painful, swollen, and rigid. Pharyngeal, hypopharyngeal, or palatal involvement, causing dysphonia, dysphagia, nasalized speech, and regurgitation of liquids through the nose can be seen in 25% of the patients.[1]

Arthralgias are mild and transitory. Some children can present with non-erosive arthritis, which develops early, in the first six months, affecting knees, wrists, elbows, and proximal interphalangeal joints. In 67% of the cases, the involvement is oligoarticular, and in 33%, polyarticular. As a rule, it improves after treatment with glucocorticoids (GC). Tenosynovitis and nodules in the flexor aspect of muscles can be seen, and flexion contractures are common.[1]

Additionally, children with JDM have osteopenia and even established osteoporosis. Indeed, on diagnosis, an elevated RANKL/osteoprotegerin ratio is seen, resulting in an increase in the number of osteoclasts and, consequently, greater bone resorption. Thus, early diagnosis and treatment help prevent greater bone loss.[26]

Cutaneous manifestations

Erythema is characteristic and up to 80% of the children develop it before, concomitantly, or after the myopathy. Heliotrope rash is a purple-red or violet erythema seen around the eyes, especially in the upper eyelids, usually associated with periorbital edema. Gottron's papules are erythematous, desquamative lesions seen on the extensor surface of the fingers, especially the metacarpophalangeal and proximal interphalangeal joints. The same patterns of lesion, known as Gottron's sign, can be identified in elbows, knees, and ankles.[1,27]

It is important to point out that vasculitic lesions, calcinosis and lipodystrophy are more common in children than in adults, being more prevalent in those with the TNF- α 308A allele.[6,27,18] Calcinosis affects 30 to 70% of patients, especially in elbows and knees. It develops in up to a mean of 3.4 years after the onset of the disease and results from the accumulation of hydroxyapatite after release of mitochondrial calcium by the damaged muscle, leading to mineralization. It is common in late phases of the disease, in sites of trauma, in more severe cases and in situations in which treatment was delayed.[1]

Lipodystrophy, the symmetrical, slow and progressive loss of subcutaneous fat, is seen more often in girls and it is associated to hirsutism, acanthosis nigricans, hepatomegaly, steatohepatitis, menstrual irregularities, elevation of serum levels of testosterone, diabetes mellitus, glucose intolerance (insulin resistance), and hypertriglyceridemia.[1,6,27,29]

Different autoantibodies seem to be related to distinct cutaneous manifestations. When present in JDM patients, anti-M2 is associated with heliotrope and Gottron's papules and usually, with a monocyclic course of the disease and good response to treatment[6]. The recently identified anti-p140 (renamed CADM-140 – clinically amyopathic dermatomyositis) is related, in adults, to the amyopathic onset of the disease and in the juvenile type, to the presence of calcinosis.[6,10] The presence of anti-p155/140 is associated with cutaneous ulcers, subcutaneous edema, erythroderma and generalized lipodystrophy.[6,31]

Other clinical manifestations

Dysphagia and esophageal dysmotility are common and can be identified in approximately 40% of children with JDM, considerably increasing the risk of bronchoaspiration.[3] On the other hand, primary pulmonary involvement is less frequent than in adults.[1] Symptoms are due, more commonly, to weakness of respiratory muscles or chronic aspiration. Pericarditis and myocarditis can be seen, and, rarely, cardiac tamponade.[32]

Clinical follow-up

Several clinical and laboratory parameters can be used in the follow-up of JDM patients, such as global evaluation by the physician, patient, and/or patients, using the visual analogue or the Likert scales, in which fixed levels of answers are used (for example: I disagree completely, disagree, indifferent, agree, agree completely). At each appointment, at least two different muscle enzymes, in addition to the acute phase tests, should be analyzed.

Muscle strength is measured and compared using standardized tests. The Childhood Myositis Assessment Scale (CMAS) includes fourteen activities that evaluate axial and proximal limb musculature. This scale is observational and based on performance and it evaluates functionality, strength, and endurance, *i.e.*, the capacity to perform activities of low and medium intensity for a prolonged time. Its reference is the result of performance of those activities by healthy children.[24,34-37] The Manual Muscle Testing (MMT) includes seven proximal and five distal muscle groups bilaterally and it only evaluates muscle strength. The Childhood Health Assessment Questionnaire (CHAQ) analyses the functional capacity of children, regardless of the baseline disease. This instrument has also been validated specifically for children with JDM. The traditional questionnaire should be answered by parents or legal guardians (children ages 2 to 19 years), but a version which patients themselves can answer (ages 8 to 19 years), similar to the traditional HAQ of adults, does exist.[17] Only the CHAQ has been validated to the Portuguese language.[38] Global disease activity, which includes cutaneous and muscular manifestations, can be evaluated by the DAS, Disease Activity Score,[39] and by the MDAA, Myositis Disease Activity Assessment.[40] Health status and quality of life can be verified by questionnaires, such as the SF-36 (Short Form Health Survery-36),[37] and by the HRQOL (Health-Related Quality of Life) by using the CHQ (Childhood Health Quality), which consists of 50 questions that should be answered by the parents, validated for patients 5 to 18 years of age.[41]

To evaluate the skin involvement, in addition to the aforementioned tools, which include cutaneous and muscular involvement, the CAT, Cutaneous Assessment Tool,[42] consisting of 21 items, allows the analysis of the cutaneous activity and damage (for example: Gottron's papules, heliotrope rash, facial erythema, shawl sign, among others), evaluating the activity and hyper- or hypopigmentation. Due to the complexity and delay in filling it out, the CAT was reduced to a simplified alternative score that encompasses different categories, and "yes" or "no" answers are considered. Its results are similar to the complete test. In the pediatric population, the CDASI – Cutaneous Dermatomyositis Disease Area and Severity Index – and the DSSI – Dermatomyositis Skin Severity Index – can also be used.[6,42-45]

Due to so many parameters and in order to facilitate the follow-up of children with JDM, recently, the international PRINTO group – Pediatric Rheumatology International Trials Organization – reviewed the measures indicated to evaluate the treatment of the disease and recommended the following: 1) global disease assessment by the physician; 2) evaluation

of muscle strength; 3) global assessment of disease activity; 4) global well-being assessment by the parents; 5) functional capacity; and 6) health-related quality of life. All those have discriminative capacity, internal consistency, good validity and are easy to use.[46]

It should be emphasized, at this stage of life, the importance of sequential growth and development assessment of children and adolescents with this disease and weight and height, the presence of regular menses and Tanner pubertal staging should always be a part of medical consultations.

TREATMENT

It is important to establish the duration of the symptoms before the diagnosis, when programming the treatment of a child with JDM.[47]

The use of oral GC, at 2 mg/kg/day, until achieving a maximal daily dose of 80 mg, is recommended. For children with suspected mesenteric vasculopathy, intravenous pulse therapy with methylprednisolone, 30 mg/kg/dose, up to a maximal dose of 1 g/dose, is recommended, as intestinal absorption may be hindered. Patients with dysphagia, dysphonia and severe pulmonary involvement are possible candidates for intravenous therapy.[1,3,48] In Canada, Feldman *et al*., from the Hospital for Sick Children in Toronto, recommends oral prednisone taken three times a day for approximately six weeks.[1] If the disease shows signs of control, then the prednisone is switched to two times a day, followed by once a day, withdrawing 10% of the dose every two weeks. If the patient decompensates, pulse therapy with methylprednisolone can be used. Kim *et al*.[49] suggest that an aggressive treatment to obtain rapid control of muscle weakness and inflammation significantly improves the prognosis and reduces the risk of complications related to the disease. Their therapeutic schedule recommends three pulses of methylprednisolone, 30 mg.kg/day for three days followed by the weekly addition of 2 mg/kg/day of oral prednisone, in addition to weekly methotrexate, until total remission is achieved, when gradual withdrawal of the GC is initiated. If the objective is not achieved within three months, cyclosporin or intravenous gamma globulin (IVIG) is added. With this approach, more than half of the children achieved prolonged remission and were free of the medication 38 months after the onset of JDM. Azathioprine and hydroxychloroquine can also be used, with positive response, especially in marked cutaneous involvement. More recently, good results have been observed with mycophenolate mofetil.[3]

Oral or subcutaneous methotrexate (at a mean dose of 15 mg/m^2/week) or intravenous cyclophosphamide can be used as baseline drugs depending on the initial severity of the disease. These drugs should be initiated up to four weeks after the onset of the disease to decrease the risk of calcinosis and fracture. For more severe and refractory cases, with predominance of cutaneous ulcers, cyclophosphamide has shown good results, without evidence of short-term toxicity.[1,50,51]

The use of cyclosporin is based on findings of efficiency in series of cases; however, an assay comparing isolated GC and its association with methotrexate or cyclosporine is ongoing.[3] Another series of cases of refractory JDM showed good response of cutaneous manifestations with tacrolimus; although cutaneous remission has not been achieved, an improvement of myalgia and normalization of muscle enzymes, however, without gain in muscle strength, possibly due to the severity, chronicity and failure of the prior treatment, has been seen.[52]

Intravenous gamma globulin can be indicated in cases of recurrence and incomplete response to the initial treatment. Some defend its use of GC-sparing drug. The exact action mechanism is unknown; however, among the explanations are (a) modulation of pathogenic autoantibodies; (b) inhibition of complement activation and formation of MAC; (c) modulation of the activation of Fc receptors; (d) down-regulation of pathogenic cytokines and adhesion molecules; (e) suppression of the function of T cells; and (f) interference with antigen recognition[53]. In Canada, The group of Feldman *et al*. recommends the dose of 2 mg/kg per infusion (maximal dose of 70 mg) every two weeks in a total of five doses, always associated to a second agent, such as azathioprine, methotrexate, or cyclophosphamide.[1] In case of improvement, monthly IVIG is maintained up to one year, followed by spacing the doses, initially to every six weeks, followed by every eight weeks, until every 12 weeks. In patients who tolerate well every twelve weeks without symptoms, the infusion can be discontinued with low risk of recurrence. A good response has also been reported in JDM with predominance of cutaneous involvement.[53]

Unfortunately, control of calcinosis remains a constant challenge in the treatment of JDM. Its best prevention is the early diagnosis and control of the disease with fast introduction of adequate treatment.

The use of immunobiologicals has been reported in small series of cases with conflicting results or extrapolating from the experience with adult inflammatory myopathies. Its rationale is based on the role of TNF-α in the pathogenesis of JDM. In children with JDM, Riley *et al*. reported five patients treated with infliximab, initially at the dose of 3 mg/kg, with improvement of global assessment, by the physician, of the CMAS, CHAQ, articular mobility, and, in some cases,

improvement of calcinosis.[54] Among us, one study evaluating the use of anti-TNF-α in rheumatic diseases with childhood onset, reported the experience of four patients with JDM, refractory to immunosuppressive therapy. Ages ranged from 6 to 22 years. The four patients initially received infliximab: one patient showed good response, another, partial response, and in two, therapeutic response was obtained only after the drug was switched to etanercept. However, patients did not achieve remission.[55] As for anti-CD20 – rituximab – very few cases of JDM have been reported. In a series of four cases, one achieved prolonged remission (26 months after three doses); two obtained partial response and the dose of GC could be reduced; in another, worsening of the disease was observed.[56]

Note that in addition to treatment, it is necessary to rehabilitate the child with JDM as soon as possible. In active disease, exercise parameters are reduced when compared to patients in remission.[57] Therefore, physical therapy, physical training and rehabilitation should be started early, maintained throughout the treatment and reinforced after full recovery, in an attempt to maintain muscle strength.[58]

Prognosis

Juvenile dermatomyositis is a rare and potentially severe disease, of which early diagnosis and adequate treatment can change the course of the disease.[1] At the end of the phase of growth, 31% of the children with JDM will be situated in one standard deviation (SD) and 16% two SD below the predictive height. The scores of the CHAQ at the onset, female gender, continuous course and presence of calcinosis at any time are predictive factors of worse prognosis.[59]

The disease can show three patterns: monocyclic, polycyclic, and continuous. Huber *et al*.[59] demonstrated that 37% of the patients have a monocyclic course and the remaining showed a polycyclic or continuous course. Those with monocyclic disease achieve remission after a mean of two years of disease activity. Recently, Stringer *et al*.[60] also recorded 37% of children with JDM with monocyclic course and 60% with persistent disease. In those, the presence of capillaroscopic changes and persistence of cutaneous erythema after six months of evolution were associated with a longer time to achieve remission.

Serologically, anti-p155/140 autoantibodies are common, and can identify patients with potentially more severe disease, as well as predict the clinical course and prognosis.[31,61] However, in the last 40 years, a change in the percentage of children who develop persistent disease in spite of the treatment has not been observed. Before GC, 1/3 developed spontaneous cure, 1/3 died and the remaining developed severe sequelae and dysfunctions.

It is important to stress that JDM patients have significant reduction in their quality of life, assessed by the HRQOL, when compared with healthy children, especially physically-related aspects, indicating that prevention of functional damage is one of the most important objectives when instituting treatment[44]. However, note that mortality decreases from 33% to less than 2% with introduction of adequate treatment.[3]

CONCLUSION

Juvenile dermatomyositis remains a great challenge for all professional involved in its management. Early diagnosis and the fast institution of adequate therapy are fundamental determinants to achieve good results and quality of life for the affected child.

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