BANGLADESH J CHILD HEALTH 2009; VOL 33 (2): 59-65

Review Article

Juvenile Dermatomyositis: An Update

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Introduction

Juvenile idiopathic inflammatory myopathies (JIIM) are rare conditions which are probably autoimmune in nature[1]. Childhood myositis is relatively more homogeneous than adult myositis. Juvenile dermatomyositis (JDM) is the most common paediatric inflammatory myopathy. It is a systemic vasculopathy with characteristic cutaneous findings and focal areas of myositis resulting in progressive proximal muscle weakness[2]. Other paediatric inflammatory myopathies are: fewer cases of polymyositis, amyopathic dermatomyositis, overlap myositis and inclusion body myositis[1].

JDM is a multi-system disease of uncertain aetiology that results in non-suppurative inflammation of striated muscles and skin[3]. It differs from the adult form of dermatomyositis by much higher incidence of vasculitis, often with intimal proliferation of small blood vessels, thrombosis, and sometimes infarction, which can involve gastrointestinal tract and myocardium as well[1,4,5]. Early in the course it is characterized by immune complex vasculitis of varying severity and later by development of calcinosis[3,4,6].

Historical overview

The clinical presentation of dermatomyositis was described by four different investigators in 1887[3,6]. Those four investigators were Hepp P, Jackson H, Wagner E and Unverricht H. Unverricht best described the cutaneous and muscular manifestations of the disease, introducing the term dermotomyositis.

Distinctive features of JDM were not known in detail until many years[7,8]. Pearson in 1966 recognized the uniqueness of childhood dermatomyositis and separated the childhood disease from that occuring in adults[3]. Sullivan et al in 1972 and 1977 emphasized the importance of an adequately high dose and long therapeutic course of glucocorticoids for better outcome of JDM[7,8].

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Epidemiology

The incidence of JDM in different states of USA ranged from 2.5 to 4.1 per million children, with an average annual incidence rate of 3.2 per million children below the age of 17 years[1,2,9]. It is apparently similar for all racial groups[2].

The average age of onset is 6.7 years. Children with disease onset before 7 years of age may have a milder course[2]. Girls are usually affected more often than boys. The sex ratio varies widely in different reported studies ranging from 1:1 in Singapore to 5:1 in Britain[10]. In general 16 to 20 percent of all the patients with dermatomyositis have their disease onset in childhood[3].

Aetio-pathogenesis

The aetiology and pathogenesis of JDM is not yet clearly known. But it is considered as an autoimmune disease and results from an angiopathy[1,3,11]. Many potential pathogenic mechanisms are suggested, including a genetic pre-disposition. The role of triggering factors, such as infectious agents and the role of complements and soluble adhesion molecules have also been suggested[1,3,12]. Like other auto-immune diseases, JDM probably results from interactions with environmental agents in a genetically predisposed child.

Disease susceptibility appears to be associated with the class II HLA antigen DQA1*0501, which is found in more than 80% of JDM children in the United States. A chronic disease course requiring prolonged immuno-suppressive therapy and increased frequency of pathologic calcifications is usually associated with a substitution of an A for G in the -308 promoter region of the gene for TNF-α[2].

An immune complex mediated vasculitis may be an important initiating or perpetuating event in JDM[13]. Complement activation and immune complex deposition in vessel walls of skeletal muscles are demonstrated in both childhood and adult dermatomyositis, although the frequency and intensity of deposition were more pronounced in children[3]. Elevated plasma levels of factor VIII- related antigen, fibrinopeptide A and C_3 provide additional evidence of endothelial cell injury that may be immue-complex induced.

The main pathological feature of JDM is the vasculopathy affecting small arteries and veins[6]. The distinctive pathologic lesions involve the striated muscles, skin, subcutaneous tissue and gastro-intestinal tract[3,6]. The earliest changes in the muscles are seen on electron microscopy. These changes include endothelial cell damage with swelling, cell necrosis and regeneration. On light microscopy, these changes may be seen as prominence of endothelium, with later intimal hyperplasia. As endothelial cell changes develop, the more obvious findings like inflammatory cells infiltrating the blood vessels of the perimysium and extending into the endomysium can also be seen. The cells are initially polymorphonuclear leukocytes, but later on lymphocytes, histocytes and plasma cells are also found. Following this, fibrin thrombus formation and occlusion of the blood vessels occur. The severity of clinical disease may or may not be correlated with the intensity of microscopical findings[3].

Clinical manifestations

The onset of JDM is usually insidious with slowly increasing proximal muscle weakness[13]. Patients usually present with a combination of malaise, easy fatigue, muscle weakness, anorexia, fever and rash[3]. In young children, irritability and developmental regressions have been reported by the parents. There is great variation in the rapidity of evolution of the disease. Although insidious onset is common, acute onset occurs in approximately one third of children.The mean age of onset of JDM is about 7 years, ranging from the first year of life to 16 years. Girls are affected twice as frequently as boys[6].

Musculo skeletal manifestations:

JDM is characterized by weakness, which probably affects all muscle groups, but most obvious in the limb-girdle musculature, the anterior neck flexors, and the trunk muscles[1]. The affected muscles occasionally may be tender, oedematous or indurated. Gower's and Trendelenberg's signs are typical early findings on examination. Distal muscle weakness is found in severely affected children. About 10 percent of patients, who are very severely affected, have pharyngeal, hypopharyngeal and palatal muscles weakness. They usually present with difficulty in swallowing, dysphonia, nasal speech and regurgitation of liquids through the nose[1].

Some children with JDM have arthralgia or subtle arthritis that is transient, non-deforming, non-erosive and sometimes accompanied by tenosynovitis or flexor nodules[14]. Flexion contractures are common and they are the effects of muscle inflammation rather than synovitis. In the presence of significant arthritis, an overlap syndrome should be considered.

Cutaneous manifestations: The rash seen in JDM is the hall mark of the disease and is present in all cases[15]. The cutaneous abnormalities become evident in the first few weeks after the onset of muscle weakness[3]. But occasionally, dermatitis is the first manifestation of the disease. The three most typical cutaneous manifestations of early JDM are: heliotrope eyelid rash, Gottron's papules and periungual erythema with capillary loop abnormalities. The classic heliotrope dermatitis occurs over the upper eyelids as a violaceous, reddish purple discolouration often associated with a malar rash. Oedema of the eyelids and face often accompanies this heliotrope dermatitis.

Gottron's papules are sometimes also called collodion patches[16]. They are flat-topped, violaceous or red papules, which can be scaly. These Gottron's papules are commonly found over the extensor aspect of the knuckles, elbows, knees and the medial malleoli. Lately the lesions may develop an atrophic white center with telengiectasia. The rash usually spares the inter-phalengeal spaces. Severe skin ulceration, which may be related to vasculitis can also occur[6].

Abnormalities of the periungual skin and capillary bed are typical of JDM and are part of the systemic vasculopathy. The periungual skin is often intensely erythematous and careful examination may document the presence of nail fold telengiectasis.

Calcinosis: Dystrophic calcinocis is one of the hallmark sequelae of juvenile dermatomyositis. Despite recent progress in the therapy, calcification is still reported in 30% to 70% of patients in various series[4,17,18]. Cutaneous calcifications are often located on the elbows, knees and other acral parts but can be located anywhere[1]. Calcinosis is seen as crusted papules or plaques around joints or as non-healing sores. Sometimes, the calcified material is extruded through the skin as a white cheesy exudate, leaving behind a dry pitted scar[4]. Muscle calcification results in contractures or severe muscular pain. The mechanism of calcinosis is thought to be dystrophic. Damaged muscles release mitochondrial calcium into matrix vesicles that promote mineralization.

Calcinosis lesions are rarely present at diagnosis but are usually found later during the course of the disease[15,19]. Calcinosis may occur as superficial lumps, deep tumorous deposits around joints or plates along fascial planes.Lesions may have a widespread exoskeleton distribution as well. Delayed treatment and severe disease are risk factors for development of calcinosis[19,20].

Gastrointestinal involvement: Decreased oesophageal motility may lead to difficulty in handling secretions[4]. Involvement of the masseter can lead to difficulty in chewing. Vusculitis occurs in a few cases, usually soon after disease onset. It signifies a poor prognosis and sometimes rapidly leads to death[3]. Vasculitis is characterized by diffuse abdominal pain, pancreatitis, maelena, haematemsis, and even perforation, representing diffuse lesions in the mucosa of the gastrointestinal tract.

Cardiac involvement: Abnormalities in ECG are seen in more than 50 percent children with JDM. Myocarditis most commonly leads to asymptomatic conduction abnormalities. These resolve when disease activity subsides[4].

Pulmonary involvement: Lung manifestations are found much less often than in adult myositis. Respiratory weakness and decreased ventillatory capacity may occur[3,4,21].

Neurological involvement: Peripheral and central neurological manifestations occur very rarely in JDM. Common symptoms are generalized tonic-clonic seizures, ptosis, hypotonia, flaccid hemiplegia, motor aphasia and bulbar palsy or coma[22,23]. Several mechanisms have been evoked to explain this CNS involvement, including vasculopathy, vasculitis, hypo perfusion, hypertensive encephalopathy, or drug-induced toxicity[23].

Ophthalmologic involvement: Though unusual, thrombosis of vessels at the eyelid margin may be seen in JDM cases. Transient retinal exudates and cotton-wools spots may occur, leading to optic atrophy and visual loss[1,4].

Laboratory findings:

Elevated serum levels of muscle-derived enzymes (e.g. creatinine kinase, aldolase, serum glutamic-oxaloacetic transaminase, and lactic acid dehydrogenase) reflect leaking of muscle membranes[2]. Anti-nuclear antibodies are present in more than 60% of the patients. Myositis specific auto antibodies are seen in about 10% of children with JDM, the most common being anti-Mi2 antibody[4]. Serum levels of neopterin, a pteridin derived from activated macropphages, is elevated in about 60% of patients and it correlates with clinically active disease. Von Willibrand factor released from the damaged endothelial cells is increased in active juvenile dermatomyositis. Absolute lymphocyte counts are usually low in active JDM, but the percentage of B lymphocyte counts are increased with an increase in CD4/CD8 ratio. This blood picture is reverted only after treatment[24].

Electromyography shows changes suggestive of myopathy. However, it can be negative in up to 20% of new onset JDM, despite elevated muscle enzymes. This happens usually due to improper electrode placement into normal areas of muscle[4]. MRI using T2 weighted images can localize the active site of disease for diagnostic muscle biopsy and electromyogram, both of which are non-diagnostic in 20% of instances if not directed by MRI[2]. Muscle biopsy often demonstrates evidence of disease activity and chronicity that is not suspected from the levels of the serum enzymes alone.

Diagnostic critaeria

Strict criteria for the definition of dermatomyositis have been set out by Bohan and Peter in 1975[25]. For a definite diagnosis, three or four of the mentioned criteria are required (Table-I). EMG and muscle biopsy may not be essential if there is typical muscle weakness with raised muscle enzymes and rash[6].

Table-I

Criteria used for diagnosis of juvenile dermatomyositis[3]

1.	Symmetric weakness of the proximal musculature.
2.	Characteristics cutaneous changes consisting of heliotrope discolouration of the eyelids with periorbital oedema, and an erythematous, scaly rash over the dorsal aspects of the metacarpo-phalengeal and proximal interphalangeal joints (Gottron's papules).
3.	Elevation of serum level of one or more of the skeletal muscle enzymes: creatinine kinase, aspartate aminotransferase, lactic dehydrogenase and aldolase.
4.	Electromyographic demonstration of the characteristics of myopathy and denervation.
5.	Muscle biopsy documenting histologic evidence of necrosis and inflammation.

Management

The goals of treatment include controlling the underlying disease and preventing/ treating complications. Complications such as calcinosis and contractures are related to disease, while osteoporosis and cataracts are usually secondary to medication toxicity[26]. The initial choice of therapy depends largely on the clinical presentation of the patient, while long-term therapy is influenced by both the response to therapy and our knowledge of the natural history of the disease.

An experienced paediatric rheumatologist is essential in assessing the need for therapeutic interventions[2]. Corticosteroids are the mainstay of therapy for children with JDM[1-4,20,26] (Table-II). Early and adequate treatment with glucocortocoids is probably the single-most important factor in improved prognosis of JDM during last 50 years. Children with only mild cutaneous findings, normal immune and serologic markers of disease activity, and a negative family history of colour blindness may take hydroxychloroquine (up to 5 mg/ Kg/24hr), with a low daily dose (1mg/kg) of oral corticosteroids. These children should be monitored for the development of muscle involvement by careful physical examination, as well as the laboratory testing for elevation of immune markers and muscle enzymes. With minimal muscle damage, oral corticosteroids (prednisolone, 1-2mg/kg/24hr) may suffice.

Table-II

Medical treatment of Juvenile dermatomyositis[3]

- Glucocorticoids
  Initial: oral prednisolone 2mg/kg/d for 1 month; or 1/V methyl prednisolone 30 mg/kg/d for 1-3 day; then: oral prednisolone 1mg/kg/d followed by a gradual taper in dose over approximately 2 years.
- Hydroxychloroquine
  6mg/kg/d in addition to prednisolone for control of skin disease
- Immuno suppressives
  Methotrexate
  0.35-0.65 mg/kg/week
  Cyclosporin
  3-5 mg/kg/day
  Cyclophosphamide
  1mg/kg/day orally or 500-750 mg/m^2/month
  Azathioprine
  1-3 mg/kg/day
- Intravenous immunoglobulin
  2 gm/kg/month

However, in case of incomplete or absent response, intravenous methyl-prednisolone pulses (1VMP) (30 mg/kg/dose, maximum 1 gm) are given to gain a rapid control of the systemic inflammation. In the presence of dysphagia and dysphonia, pulmonary disease or suspected gastrointestinal vasculopathy, IVMP is usually the initial treatment[1]. Despite the excellent response to corticosteroids in JDM, long term use of corticosteroid is not free from risk like growth retardation, cataracts and osteoporosis. Due to these side effects/complications, steroid sparing agents are used frequently.

A number of second-line agents are used in the treatment of JDM, including methotrexate, cyclophosphamide, cyclosporine, azothiarpine and hydroxy-chloroquine. However, methotrexate (MTX) appears to be the most accepted one. MTX was the first proposed drug as a second-line agent for refractory JDM along with steroids[27]. It is now more widely prescribed as a steroid sparing agent. Treatment combining high-dose corticosteroids and MTX started within 4 weeks after the initiation of treatment in the absence of improvement, may decrease the incidence of long-term complications such as calcinosis[28]. Al-Mayouf et al in their 12 patient pilot study, treated 6 patients with oral MTX in combination with intermittent IVMP within 6 weeks after diagnosis. Other 6 patients were treated with IVMP intermittently along with oral steroid. MTX and IVMP group of patients improved clinically and the oral corticosteroid dose could be decreased in five patients. None of these patients developed calcinosis. This small study concluded that early use of MTX in combination with IVMP may be useful in JDM[29]. Another study found that using MTX as a first line treatment experienced much less exposure to corticosteroid because of an aggressive taper and a lower cumulative dose. The patients experienced fewer side effects with a greater height velocity and smaller weight gain[30]. All these study results suggest that early use of MTX seems to be a safe and effective therapeutic modality.

However, all the JDM patients do not respond to the combination of MTX and corticosteroids. In some patients, the extent of disease may be so severe, that additional agents are needed. In other cases, there is an early response but an inability to taper therapy. In both the clinical settings use of intra-venous immunoglobulin (IVIG) is practiced by several

rheumatologists[1,26]. Many studies have been done using IVIG showing good response[31,32]. In these studies IVIG was used for different indications, including relapse, incomplete response, or for steroid sparing purposes. The dose, the number of courses, and the time interval varied greatly among the different studies. However a well accepted practice is addition of IVIG to the corticosteroid/ MTX regimen (2 g/kg/ dose up-to a maximum of 70g) initially every 2 weeks for five infusions and then every 4 weeks up-to a year. After that lengthening the interval between infusions should be done to 6 weeks, 8 weeks, and then to 12 weeks[1,26]. Patients who can tolerate infusions spaced 12 weeks apart are usually able to discontinue the therapy completely without flare of symptoms. Several case reports and reviews are there showing successful cyclosporine therapy in JDM[33-35]. Some investigators suggested that this drug should be considered as first line therapy.

Very severe initial diseases with severe vasculo-pathy (involving skin, lung, gastrointestinal or nervous system) probably needs more aggressive immuno-suppression with cyclophosphamide(CYP)[1,26]. Riley et al reviewed the efficacy and tolerability of intravenous pulse CYP for high-risk patients. Most of the patients in their series had substantial improvement[36]. However, almost all patients received concurrent second-line treatment (MTX, cyclosporin).

Biologic agents: Evidence suggests that TNF-α plays a role in the pathophysiology of dermatomyositis both in children and in adults[37]. While small series have suggested a beneficial role of anti-TNF-α agents in the treatment of dermatomositis, ultimately, their role is still unclear[26]. Rituximab, a monoclonal CD20+B cell-depleting antibody, a promising new biologic, which is investigated in a broad range of conditions involving B-cells. Few studies done using rituximab in JDM suggested a favourable out-come[38,39].

Other aspects of treatment : A multidisciplinary team consisting of nurses, physiotherapists, occupational therapists, dieticians and social workers is necessary for the optimal management of many of these patients.

All children with JDM should use a sunscreen that provides maximum protection against ultraviolet A and B, even in winter[2]. Vitamin D with calcium supplementation is needed for correction of osteopenia and decreasing the frequency of bone fracture. Physiotherapy should be initiated at the time of diagnosis. While the skeletal muscles are actively inflammed, attention should be given on preventing loss of range of motion[3]. During the healing phase, physical therapy should be increased to normalize function as far as possible and to minimize development of contractures secondary to muscle weakness or atrophy.

Complications from active disease and its treatment represent a significant degree of morbidity for these patients. Approximately 20 to 40 percent of children develop calcinosis during the course of the disease[3]. Many treatments have been tried, including diltiazem, aluminium-hydroxide, probenecid, bisphosphonates, infliximab and local corticosteroid injections among others[3,17,26]. No treatment has been proven to be very effective. As calcinosis in many patients tend to regress over time (often years), any uncontrolled study may not strongly suggest any benefits[26]. Surgical excision of calcifications that mechanically interferes with function may be indicated[3].

Course and Prognosis

The course of JDM in children usually has several phases. The early prodromal phase is followed by a period of progressive muscle weakness and rash that then stabilizes for 1 to 2 years before recovery. The entire disease duration can be as brief as 8 months with complete recovery, or it can last 2 or more years with a continuing requirement for treatment. Acute exacerbations and remission without any stabilization of the initial course of the disease may occur in about 20 percent of children[3]. Late progression of JDM is reported with a recurrence of active disease after a prolonged remission[3]. Fortunately, the overall outcome of JDM has improved quite dramatically over the past decades[26]. This may be correlated with more aggressive treatment with corticosteroids and immunosuppressive medications.

Unlike many adults, children with JDM are usually able to repair their vasculature and muscle damage. Long-term survival in JDM is more than 90 percent, but in the pre-steroid era, this disease was associated with very high mortality. Overall, with appropriate test to monitor the disease activity and to guide the use of more aggressive therapy, the prognosis of JDM has markedly improved.

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