

Ten-year experience of juvenile dermatomyositis: a retrospective study

Shih-Kai Chiu^{1,2}, Yao-Hsu Yang², Li-Chieh Wang², Bor-Luen Chiang²

¹Department of Pediatrics, Buddhist Tzu Chi General Hospital, Taipei Branch, and ²Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

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Background and Purpose: Juvenile dermatomyositis (JDMS) is a rare multisystemic disease of unknown etiology that primarily affects muscle and skin. This study aimed to evaluate the initial laboratory data, clinical manifestations, complications, and clinical outcomes of patients with JDMS in Taiwan.

Methods: We reviewed medical charts of patients younger than 18 years with a diagnosis of JDMS at the pediatric department of National Taiwan University Hospital between 1994 and 2004.

Results: A total of 21 patients were included. The female-to-male ratio was 4.25:1. The mean age at onset of symptoms was 6.4 ± 3.7 years (range, 2 to 14.2 years). The mean age at diagnosis was 6.9 ± 3.9 years (range, 2.2 to 15 years). Among the initial cutaneous features, Gottron's rash (62%) and facial rash (including malar rash, 62%) were the most common findings. Gottron's rash was also the most common sign (81%) at any time during the disease course. Among other systemic features at disease onset, myalgia (33%) was the most common symptom, followed by arthralgia (19%) and dysphagia (19%). Interstitial pneumonitis was a complication in 2 patients, one of whom was a mortality case. Gastrointestinal tract vasculitis was highly suspected in one patient complicated with duodenal perforation and retroperitoneal abscess. Calcinosis developed in 6 patients (28.5%), and one of these patients presented with disseminated calcinosis. Five of 21 patients achieved drug-free remission for 28 to 94 months from the time they discontinued therapy to the end of the study. Two patients with diagnosis of amyopathic dermatomyositis were also included in this study.

Conclusions: The long-term outcomes in this study are thought to be good. Because the understanding of the pathogenesis of JDMS is limited, certain complications are still troublesome clinically.

Key words: Child; Child, preschool; Dermatomyositis; Prognosis; Retrospective studies; Treatment outcome

Introduction

Juvenile dermatomyositis (JDMS) accounts for 85% of the idiopathic inflammatory myopathies in children [1]. It is a chronic inflammatory illness that affects primarily muscle and skin, but can also affect other organs, including the heart, lungs and gastrointestinal tract. It is considered an autoimmune disease that is characterized by various degrees of immune complex vasculitis early in the disease process and the development of calcinosis in the later stages [2]. The etiology is still unknown, although genetics, environmental

exposure and infectious agents are considered to be related to disease pathogenesis [3].

The typical manifestations are skin rash (often consisting of heliotrope rash and Gottron's papules) and symmetric proximal muscle weakness, but the clinical manifestations can vary widely. Although no standard treatment has been established, the mainstay of treatment is corticosteroids with or without other immunosuppressive agents or intravenous immunoglobulin (IVIG). Prognosis has significantly improved under modern treatment during the past few decades. However, JDMS remains continuously active in a substantial proportion of patients and the management of its complications, such as calcinosis, still challenges clinical physicians.

This study was based on a retrospective chart review of all patients diagnosed with JDMS, including

Corresponding author: Bor-Luen Chiang, Department of Pediatrics, National Taiwan University Hospital, Fl. 7, No. 7, Chung-Shan S. Road, Taipei 100, Taiwan.
E-mail: gjcmbor@ha.mc.ntu.edu.tw

patients initially diagnosed at our institution and patients referred from other hospitals with the diagnosis of JDMS, between 1994 and 2004. The initial laboratory data, clinical manifestations, complications, and clinical outcomes of patients with JDMS during these 10 years were analyzed.

Methods

We reviewed the medical charts of 25 patients younger than 18 years with a diagnosis of JDMS at the pediatric department of National Taiwan University Hospital between 1994 and 2004. After thorough review of the charts, 4 patients were excluded from the study because they were found to have a different diagnosis after their disease work-up. Therefore, a total of 21 patients were included in this retrospective study of JDMS.

JDMS was diagnosed according to the published criteria of inflammatory myopathies established by Bohan and Peter in 1975 [4], and included: 1) symmetrical proximal muscle weakness; 2) evidence of chronic inflammation in muscle biopsy; 3) elevations of serum levels of muscle-associated enzymes; 4) electromyographic changes of myositis; and 5) characteristic rashes of dermatomyositis. Definite JDMS was defined by any three of the first four criteria plus the fifth criterium. Probable JDMS was defined by any two of the first four criteria plus the fifth criterion. Possible JDMS was defined by any one of the first four criteria plus the fifth criterion.

Among our enrolled patients, 12 were initially diagnosed at our hospital. Of these 12 patients, 3 were categorized as definite JDMS, 7 were probable JDMS, and the other 2 patients were diagnosed with the amyopathic form of JDMS. Amyopathic JDMS is a subtype of JDMS defined by the presence of the characteristic rash of dermatomyositis but without evidence of muscle involvement.

The other 9 enrolled patients were referred from other hospitals with a diagnosis of JDMS. Six of these patients were categorized with definite JDMS, 2 were probable JDMS, and one patient was at least probable JDMS because reports of muscle biopsy and electromyography could not be traced.

After thorough reviews of charts, we analyzed the clinical parameters including gender, age at onset of symptoms, age at diagnosis, initial symptoms and signs, duration between onset of symptoms and diagnosis, initial laboratory values, pattern of clinical features, electromyography and muscle biopsy results. Disease

course including occurrence of flares, complications during treatment and current disease status were also evaluated.

Results

Among the 21 patients included in this retrospective study, the ratio of females ($n = 17$) to males (4) was 4.25:1. The mean age at onset of symptoms was 6.4 ± 3.7 years (range, 2 to 14.2 years), and the mean age at diagnosis was 6.9 ± 3.9 years (range, 2.2 to 15 years). The average time between the onset of symptoms and the diagnosis of JDMS was 5.8 months and the maximum was 29 months.

During their initial presentation to a physician, one patient (4.7%) complained of right knee arthralgia alone, 9 patients (42.8%) complained of skin rash alone, 2 patients (9.5%) complained of weakness alone and 9 patients (42.8%) complained of both weakness and skin rash (3 of these 9 also complained of arthralgia). The patient with right knee arthralgia alone developed weakness and characteristic skin rash 3 months after initial presentation. Seven of the 9 patients who initially presented with skin rash alone developed weakness 1 to 5 months later, and one of them developed weakness with arthralgia 1 month later. The other 2 patients with skin rash alone never developed weakness during observation for 6 and 11 years, respectively. The 2 patients who initially presented with weakness alone developed characteristic skin rash 3 months to 1 year later. Most of the weakness was described as difficulty in climbing stairs, getting up from a squatting posture and getting in or out of a car.

Among the initial cutaneous features, Gottron's rash and facial rash (including malar rash) were the most common findings (Table 1). Heliotrope rash was the third most common finding. Gottron's rash was also the most common sign at any time during the disease course. Other systemic features are summarized in Table 2. Myalgia was the most common symptom at disease onset, followed by arthralgia and dysphagia. Three patients had upper respiratory infection with fever and then developed progressive muscle weakness. Hepatomegaly was found initially in one patient with amyopathic JDMS.

The initial laboratory findings of 9 patients with muscle weakness at diagnosis and 2 patients with amyopathic JDMS were recorded and analyzed (Table 3). Markedly elevated muscle-associated enzymes were observed in the 9 patients with muscle weakness at

Table 1. Frequency of cutaneous features in 21 patients with juvenile dermatomyositis

Sign	Disease onset (%)	Anytime (%)
Gottron's rash	13 (62)	17 (81)
Heliotrope rash	11 (52)	12 (57)
Facial rash ^a	13 (62)	15 (71)
Malar rash	10 (48)	14 (67)
Extremities rash	8 (38)	9 (43)
Periungual erythema and telangiectasis	2 (0.1)	NA
Pruritis	NA	5 (24)
Scalp dermatitis	NA	2 (0.1)
Calcinosis	NA	6 (29)

Abbreviation: NA = not assessed

^aFacial rash includes malar rash.

diagnosis. Elevation of lactate dehydrogenase and aspartate aminotransferase (AST) was noted in 100% of these patients, while alanine aminotransferase (ALT) was elevated in 87.5% and creatinine kinase (CK) in 88.9%. The initial measurement of erythrocyte sedimentation rate revealed normal or slightly elevated values. Initial antinuclear antibody titers of 1:160 or higher were found in 3 of 7 patients. Electromyography was performed in 7 patients; 6 demonstrated abnormal myopathy and one had normal results. Muscle biopsy was performed in 8 patients and all pathologic reports were compatible with JDMS.

All 21 patients received treatment with systemic corticosteroids with or without other immunosuppressive agents, including azathioprine, cyclosporine A, hydroxychloroquine and methotrexate. IVIG was administered monthly from 3 to 14 times in 10 patients.

Table 2. Frequency of systemic features and complications in 21 patients with juvenile dermatomyositis

Sign/symptom or complication	Disease onset (%)	Any time (%)
Preceding URI with fever	3 (14)	NA
Arthralgia	4 (19)	5 (24)
Myalgia	7 (33)	NA
Dysphagia	4 (19)	5 (24)
Hoarseness	NA	1 (5)
Hepatomegaly	1 (5)	NA
Duodenal perforation	NA	1 (5)
Mood disorder	NA	1 (5)
Interstitial pneumonitis	NA	2 (10)
Herpes zoster	NA	2 (10)
Neutropenic fever	NA	1 (5)
Renal failure	NA	1 (5)

Abbreviations: URI = upper respiratory tract infection; NA = not assessed

Table 3. Initial laboratory findings in 11 patients with juvenile dermatomyositis (JDMS)

Variable	Nine patients with muscle weakness at diagnosis Mean ± SD (patient numbers)	Amyopathic JDMS	
		Case 1	Case 2
ESR (mm/h)	22 ± 12 (4)	11	7
Range	9-34		
LDH (U/L)	1389 ± 1320 (9)	475	440
Range	523-4050		
AST (U/L)	244 ± 268 (8)	25	20
Range	38-830		
ALT (U/L)	176 ± 182 (8)	12	10
Range	12-578		
Creatinine kinase (U/L)	4197 ± 5677 (9)	40	184
Range	109-16640		

Abbreviations: SD = standard deviation; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase

Medications and dosage were adjusted according to the clinical condition of patients. Three of 21 patients experienced disease flare-up with exacerbated symptoms of skin rashes and muscle weakness during tapering of their immunosuppressive agents. Treatment was discontinued in 7 of 21 patients who received therapy for 24 to 85 months, but disease recurred in 3 of them one month to 7 years after therapy was discontinued. One patient developed recurrent muscle weakness without characteristic skin rash 7 years after therapy was discontinued. Another one of these 3 patients with recurrence of disease achieved drug-free remission for 47 months after a second course of treatment. At the end of this study, 12 patients received medical therapy, including 2 patients with recurrence of disease who received a second course of treatment for 63 and 114 months, respectively, and another 10 patients who received treatment for a mean of 55.7 ± 42.9 months (range, one to 134 months), after the diagnosis of JDMS was established. In summary, at the end of this study, 5 patients achieved drug-free remission for periods ranging from 28 to 94 months after therapy was stopped, 12 patients still received medical treatment, 3 patients were lost to follow-up and one patient whose disease was complicated by interstitial pneumonitis died 15 months after diagnosis and treatment.

Several patients experienced complications during the course of their disease (Table 2). One patient suffered from recurrent abdominal pain 2 months after disease onset, that was complicated by duodenal perforation with retroperitoneal abscess [5]. JDMS-related intestinal

vasculitis was strongly suspected in this patient. Interstitial pneumonitis occurred in 2 patients, one of whom died [6]. The other one was cured after supportive care, broad-spectrum antibiotic treatment and methylprednisolone pulse therapy. Herpes zoster was noted in 2 patients; in both cases it resolved with no sequelae after treatment with oral acyclovir. Neutropenic fever occurred in one patient and it was thought to be related to the adverse effects of azathioprine. One patient was diagnosed with corticosteroid-induced psychosis, and one patient developed chronic renal failure after taking herbal medicine for 2 years.

Calcinosis developed in 6 patients (28.5%) [Table 1], one of whom experienced disseminated calcinosis universalis after receiving frequent methylprednisolone pulse therapy (12 times total) at another medical center [7]. One patient with amyopathic JDMS also developed calcinosis.

Medical history reviews revealed no family history of dermatomyositis and no evidence of malignancy in any patient during the follow-up period.

Discussion

JDMS is a chronic inflammatory illness of children defined as proximal muscle weakness combined with characteristic cutaneous rash. The diagnostic criteria originally proposed by Bohan and Peter in 1975 remain standard criteria for diagnosis of JDM. However, many clinicians consider that it is not necessary to fulfill the criteria of Bohan and Peter for the diagnosis of JDMS in a majority of patients. Because invasive tests such as muscle biopsy and electromyography may cause suffering in children and are not 100% sensitive, many pediatric rheumatologists consider that these invasive tests should be reserved for selected patients with an indeterminate diagnosis [8,9]. Absence of muscle biopsy and electromyography was the main reason for probable cases being more frequent than definite cases in our study.

Although JDMS is the most common form of the idiopathic inflammatory myopathies in children, it remains a rare disease. Previous studies report an incidence of 2 to 3 cases per 1,000,000 people per year [3]. The gender ratios reported in most studies in the western world reveal that girls are affected more frequently than boys, with the ratio of girls to boys ranging from 1.7:1 to 5:1 [8]. In contrast, data from Japan, Saudi Arabia and India show a female-to-male ratio of 1:1.3-1.7 [10-12]. The ratio in our study was

4.25:1, similar to that seen in studies in the western world, and the mean age at disease onset was 6.4 years, similar to the mean of 6.9 years reported in the United States [13].

Clinical manifestations of JDMS may vary widely, but typically JDMS presents with easy fatigue, general malaise, muscle weakness, and, in some patients, fever and then cutaneous rash develop or become obvious in the first few weeks after the onset of muscle symptoms [14]. Interestingly, in our study, 7 patients (33.3%) experienced cutaneous rash preceding the symptoms of muscle weakness, compared to 2 patients (9.5%) with muscle weakness preceding cutaneous rash. However, the exact order of occurrence of weakness and cutaneous features was difficult to define in the group that initially presented with both weakness and cutaneous features.

Among the cutaneous features in our study, Gottron's rash was the most common finding at onset and at any time during the disease course. In a large study of 120 patients conducted by Ramanan and Feldman [8], Gottron's rash (91%), heliotrope rash (83%), nailfold capillary change (80%) and malar/facial rash (42%) were the 4 most common initial cutaneous features. Other systemic features such as myalgia (33%), arthralgia (19%) and dysphagia (19%) were common at disease onset in our study, similar to the findings of Ramanan and Feldman [8].

No standard treatment for JDMS has been established worldwide; treatment has been based on the experience of individual physicians. To date, it is widely accepted that corticosteroids play the most important role in the treatment of JDMS. Our treatment protocol was essentially corticosteroids combined with other immunosuppressive agents including azathioprine, cyclosporine A, hydroxychloroquine and methotrexate, or with IVIG. Although IVIG has been proven to have some benefit in the acute stage of JDMS, its long-term efficacy observed in our previous study was not satisfactory [15]. In this study, a high relapse rate (3 of 7 patients, 42.9%) after discontinuing medical therapy was noted, although 5 of 7 patients (71.4%) who discontinued therapy finally achieved drug-free remission within a period of 28 to 94 months of long-term follow-up. Relapse was even seen to occur after drug-free remission for 7 years.

Approximately 20% to 40% of children with JDMS develop calcinosis during the course of disease [2,8]; in our study, it developed in 28.5% of patients. Calcinosis can occur within 6 months of onset of the disease but

usually develops later, and it can cause long-term disability in some patients. The mechanism of calcinosis development remains uncertain and there is still no standard treatment of calcinosis. It is not clear whether frequent methylprednisolone pulse therapy is critical for the development of disseminated calcinosis.

Dysphagia and gastrointestinal tract vasculitis are the major complications of gastrointestinal tract involvement in JDMS. The complaints of dysphagia in our patients were all transient and resolved soon after appropriate control of disease activity. However, gastrointestinal tract vasculitis may result in intestinal perforation and bleeding. This was highly suspected in one patient in our study who had complications of duodenal perforation and retroperitoneal abscess. Although this patient recovered from the episode after operation, recurrent abdominal pain still persisted, even under aggressive treatment with corticosteroids and immunosuppressive agents.

We reported 2 patients with amyopathic JDMS, neither of whom had any clinical evidence of weakness during long-term follow-up of 6 and 11 years, respectively. However, these 2 patients did not completely meet the criteria defined by Euwer and Sontheimer in 1993 [16]. They had characteristic cutaneous features with Gottron's rash and malar rash combined with extremities rash or heliotrope rash. One had no elevated muscle enzyme, but her electromyography report revealed myopathy. Mildly elevated CK levels, but normal AST and ALT values were found in the other patient. Muscle biopsy was not performed in either of these 2 patients. Both of them were still receiving treatment at the end of this study. Skin rash still waxed and waned in one patient although aggressive therapy including oral prednisolone, azathioprine, hydroxychloroquine and IVIG were given. Skin rash in the other one resolved after therapy with oral prednisolone and hydroxychloroquine but this patient developed calcinosis and chronic renal failure. The cause of chronic renal failure was considered to be related to herbal medicine. The development of calcinosis in patients with amyopathic JDMS was also observed in a previous report [8].

There is still considerable controversy about amyopathic JDMS, and it is still unclear whether or not it is a distinct entity. Most patients with unremarkable muscle weakness have mildly elevated muscle enzymes or develop obvious weakness later in the disease course [17-19], but few patients have been reported to have true amyopathic JDMS after long-term follow-up [19,20].

Although the mortality rate (now <5%) has decreased markedly and the prognosis has improved in the past 40 years, especially after the use of corticosteroids [21], the understanding of the pathogenesis of JDMS is still limited today. The long-term outcomes in this 10-year retrospective study are thought to be good. However, in our experience, certain complications such as gastrointestinal tract vasculitis, calcinosis, and refractory interstitial pneumonitis still challenge clinical physicians. In addition, long-term relapse is still possible. Finally, it should be noted that functional outcomes were not evaluated in our study and need to be further investigated by the use of validated tools.

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