Mod Rheumatol (2007) 17:413–417
DOI 10.1007/s10165-007-0610-y

ORIGINAL ARTICLE

Yoichi Morinishi · Tsutomu Oh-Ishi · Tomoyuki Kabuki
Kosuke Joh

Juvenile dermatomyositis: clinical characteristics and the relatively high risk of interstitial lung disease

Received: January 12, 2007 / Accepted: June 13, 2007

Abstract To clarify the clinical features of juvenile dermatomyositis (JDM) in Japanese cases, we retrospectively evaluated the characteristics of 16 children with JDM that were treated at Saitama Children's Medical Center between 1985 and 2004. The age at disease onset ranged from 3.5 to 14.1 years old (7 boys, mean age 7.9 years; 9 girls, mean age 9.2 years). In 14 patients more than two muscle enzymes were elevated at diagnosis. The antinuclear antibody at diagnosis was positive in all girls but one, while it was positive in only two boys (2/7; $P < 0.01$). Three patients were complicated with interstitial lung disease (ILD) (18.8%) and their serum KL-6 levels were already elevated on admission. Our findings suggest that serum KL-6 levels seemed to be sensitive to the detection of ILD in an early phase, and the relatively high frequency of JDM-associated ILD indicated that a careful evaluation of the lungs was therefore required in any individuals with JDM. Of 16 patients, two boys showed a favorable improvement and prognosis without relapse for over 9 years after the termination of treatment. Overall, in girls, there is a tendency to be a delay in the diagnosis/treatment for JDM, and this disease also demonstrated a severe course.

Key words Interstitial lung disease · Juvenile dermatomyositis · Steroid

Introduction

Juvenile dermatomyositis (JDM) is a rare idiopathic inflammatory myopathy with cutaneous manifestations, occurring in 0.3 to 0.4 per 100000 children each year.[1,2] In general, JDM is relatively homogeneous and it tends to demonstrate a good prognosis; it is also a separate disease entity from adult DM. In this study we investigated the medical records of JDM cases in our hospital and attempted to clarify the clinical features of JDM.

Patients and methods

The subjects in this study included 16 children, 7 boys and 9 girls, who were treated and followed up at Saitama Children's Medical Center between 1985 and 2004. Of the 16 patients, 10 met the diagnostic criteria of JDM proposed by Bohan and Peter,[3] and all 16 met the guidelines for the diagnosis of DM established by the Japanese Ministry of Health and Welfare.[4]

We conducted a retrospective analysis of the following variables: sex distribution, age at disease onset, clinical symptoms, laboratory findings such as serum muscle-derived enzymes, electromyogram (EMG), muscle biopsy and magnetic resonance imaging (MRI), drug therapy, complications, and prognosis. Magnetic resonance imaging was taken at the site where muscle weakness or grasping pain was revealed. A chest X-ray was routinely examined to identify any interstitial lung disease (ILD) in all patients, and computed tomography (CT) of the chest was subsequently added for several cases suspected to have ILD. A statistical analysis was performed using Student's *t*-test.

Results

The age at disease onset ranged from 3.5 to 14.1 years (mean age, 8.9 years; seven boys, mean age 7.9 years; nine girls, mean age 9.2 years) and the male-to-female ratio was 1:1.3 (Table 1). There was no particular age for disease onset. The mean duration of time between disease onset and diagnosis was 7.4 months (range: 2–29 months). The duration of follow-up ranged from 4 months to 19.8 years

Y. Morinishi · T. Oh-Ishi · T. Kabuki · K. Joh
Division of Infectious Disease, Immunology and Allergy, Saitama Children's Medical Center, Saitama, Japan

Y. Morinishi (✉)
Department of Pediatrics, National Defense Medical College, 3-2 Namiki, Tokorozawa 359-8513, Japan
Tel. +81-4-2995-1211; Fax +81-4-2996-5204
e-mail: grd1711@ndmc.ac.jp

Table 1. Sixteen cases of juvenile dermatomyositis

Patient	Age at onset (years)	Duration (onset–diagnosis, months)	Initial symptoms	Initial therapy	Additional therapy	Max. CK (IU/l)	Complication	Relapse/outcome
Boys								
1	8	2	Easy fatigue, muscle weakness	PSL (2 mg/kg)		100		2/Referral
2	5	15	Rash	PSL (2 mg/kg)		162		0/Off therapy
3	6	2	Fever, rash	PSL (2 mg/kg)		9480	Pleurisy, hypoproteinemia	0/Off therapy
4	12	5	Fever, rash	PSL (1 mg/kg)		7580		0/Remission
5	4	4	Muscle weakness	Pulse	Pulse	1558	Calcinosis	1/Remission
6	14	2	Muscle weakness	PSL (1 mg/kg), MTX		16760		0/Remission
7	6	7	Rash, easy fatigue	Pulse	CyA	194	ILD, glaucoma[a]	0/Dead
Mean ± SD	7.9 ± 3.8*	5.3 ± 4.7*						
Girls								
8	3	29	Rash	PSL (2 mg/kg)	Pulse	370	Calcinosis	6/Remission
9	13	18	Arthritis, rash	PSL (1 mg/kg)	MTX, IVIG, CyA	73	Melena, meningoencephalitis	0/Remission
10	9	9	Muscle weakness	PSL (2 mg/kg)	CyA, Pulse, IVIG, MTX	122	Calcinosis	2/Remission
11	7	3	Rash	PSL (1 mg/kg) Aspirin,	MTX	97		0/Remission
12	11	10	Rash	PSL (1 mg/kg)	MTX, CyA	257	Chronic thyroiditis, ILD	1/Remission
13	9	4	Rash	Ibuprofen	PSL	1862	ILD	0/Remission
14	6	4	Rash	PSL (1 mg/kg)	CyA, MTX	284	Fracture[a]	0/Remission
15	13	2	Myalgia	PSL (2 mg/kg)	MTX, Pulse, CyA, AZA, MMF	7530	CyA-induced encephalopathy[a]	0/Remission
16	12	6	Rash	PSL (2 mg/kg)	MTX, MMF	520		0/Remission
Mean ± SD	9.2 ± 3.4*	9.4 ± 8.8*						

PSL, prednisolone; Pulse, methylprednisolone pulse; MTX, methotrexate; CyA, cyclosporine; IVIG, intravenous immunoglobulin; AZA, azathioprine; MMF, mycophenolate mofetil; ILD, interstitial lung disease; CK, creatine kinase

[a] Drug-induced complication

* No statistically significant difference between boys' group and girls' group

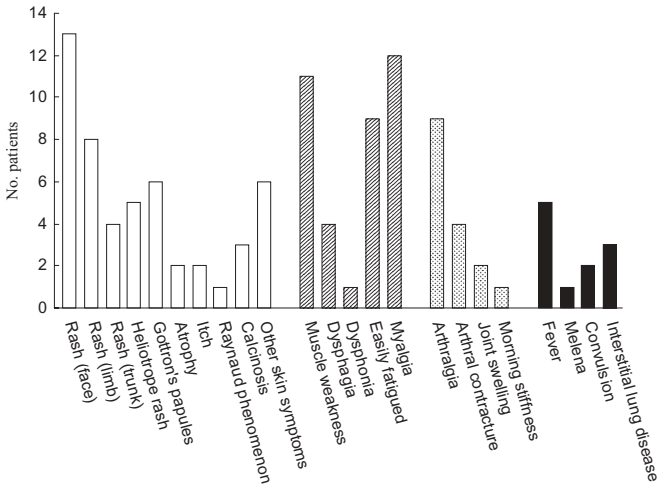

Fig. 1. Characteristics in the disease course of juvenile dermatomyositis. Skin (*white bars*), muscle (*gray lined bars*), joint (*gray dotted bars*), others (*black bars*). Rash indicates erythematous or violaceous eruptions

Table 2. Abnormalities of laboratory findings at diagnosis

Laboratory studies (normal value)	*n*, abnormal/tested	(%)
AST (8–30 IU/l)	13/16	(81.3)
ALT (4–30 IU/l)	8/16	(50.0)
LDH (140–300 IU/l)	15/16	(93.8)
CK (10–125 IU/l)	11/16	(68.8)
Aldolase (1.5–5.7 IU/l)	12/16	(75.0)
Myoglobin (<60 ng/ml)	8/10	(80.0)
CRP (<0.06 mg/dl)	0/16	(0.0)
ESR (1–11 mm/h)	7/13	(53.8)
KL-6 (<500 U/ml)	3/7	(42.9)
IgG (800–1800 mg/dl)	4/16	(25.0)
ANA	10/16	(62.5)
EMG	5/9	(55.6)
Muscle biopsy	12/15	(80.0)
MRI	9/11	(81.8)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; EMG, electromyogram; MRI, magnetic resonance imaging

(mean: 8.3 years). Regarding the duration between disease onset and diagnosis, although it was longer in the girls' group, there was no statistically significant difference (Table 1).

Initial symptoms (Table 1)

Skin rash, the most common symptoms at disease onset, appeared in 11 patients (six on the face, four on extremities, and one on both). One patient presented with both cutaneous and muscular manifestations at the disease onset.

Clinical symptoms

Regarding the clinical course (Fig. 1), the skin manifestations appeared on the face, and the characteristic facial rash or heliotropic erythema was found in all the patients. Raynaud's phenomenon was seen in one patient. None of the patients had photosensitivity. Calcinosis was seen in 3 of 16 patients (18.8%) over the course of illness. Of the 3 patients, 1 (patient 8) required a surgical resection of ectopic calcifications that developed in the subcutaneous tissue of the fascia of the thigh. In another patient, calcifications on both knees (patient 5) became progressive, protruding from the skin and discharging calcium milk in spite of treatment with oral diltiazem 1 mg/kg per day. However, calcinosis gradually improved and resolved finally.

Laboratory findings

The serum muscle enzymes or protein examined before initial therapy were aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), creatine kinase (CK), aldolase, and myoglobin. In 14 of 16 patients (87.5%), at least two serum muscle enzymes and/or protein were elevated (Table 2). Creatine kinase levels in the disease course did not seem to reflect the severity of muscle damage among the patients (Table 1). Lactic dehydrogenase was elevated in almost all patients whether the CK level was normal or not. Antinuclear antibody (ANA) was positive in 10 patients (8 of 9 girls, 2 of 7 boys), thus indicating the positive rate to be significantly higher for girls than for boys ($P < 0.01$). Of those patients, three showed a homogeneous pattern, two a speckled pattern, two a homogeneous-speckled pattern, one a nucleolar pattern, and two unknown. Three girls with hypergammaglobulinemia (range 1790–3266 mg/dl) demonstrated high titers of ANA. One girl (patient 12) was complicated with Hashimoto's thyroiditis and was positive for antithyroid antibody, while simultaneously demonstrating an elevation of von Willebrand factor activity and neopterin concentrations in the serum. Additionally, she had amyopathic DM, because she had normal findings of EMG, muscle biopsy, and MRI scan, and severe cutaneous manifestations developed in spite of the fact that she was successfully treated for fairly mild muscle weakness.

Therapy and prognosis

The treatment administered to each patient in this study varied according to disease severity (Table 1). Sixteen patients (93.8%) were started on systemic corticosteroids as the initial therapy: six patients received low-dose steroid therapy (prednisolone 1 mg/kg per day) including combined oral methotrexate, seven received high-dose steroid therapy (2 mg/kg per day), and the other two patients were administered pulse therapy followed by low-dose oral prednisolone. Of these, 3 girls (patients 9, 10, and 15) with severe or refractory disease were given several additional medications. Overall, there seemed to be no significant difference in the relapse rates between the boys' group and girls' group.

The diagnosis of ILD was made in one boy and two girls (patients 7, 12, and 13) with the detection of an abnormally

elevated serum KL-6-level (normal reference value <500 U/ml) and the chest CT findings. One boy (patient 7) complained of muscle weakness and malar rash, which began 7 months before his hospitalization. His serum KL-6 levels were extremely elevated (2950 U/ml). On admission methylprednisolone pulse therapy was started concurrently with a diagnosis of ILD-associated JDM. Unfortunately, his respiratory dysfunction rapidly progressed with subcutaneous and mediastinal emphysema, thus resulting in death despite cyclosporine A administration as an additional therapy. Interestingly, the serum KL-6 levels of the three patients with ILD on admission were markedly elevated in comparison with those of four examined patients without ILD (mean ± SD 1508 ± 1263 vs 172 ± 32 IU/ml), although none of them demonstrated any respiratory symptoms.

There were no patients complicated by malignant tumors. Of the 16 patients, 2 showed a favorable prognosis without relapse during treatment and for over 9 years after the termination of treatment.

Discussion

In the present study ILD was found in three patients (18.8%). Although none of them showed any respiratory symptoms at the diagnosis of JDM, serum KL-6 levels for all of them were demonstrably elevated. KL-6 is produced by type II pneumocytes and respiratory bronchiolar epithelial cells, and it is considered to be a useful marker for interstitial lung disease.[5–7] Kobayashi et al. also reported that the measurement of serum KL-6 levels might be useful for evaluating JDM-associated ILD.[8] In the present study the serum KL-6 level was sensitive to the detection of ILD. The frequency of ILD in JDM has been reported to be low in comparison with that in adult DM.[9–11] However, the report by Kobayashi et al.[6] indicated that the frequency of ILD seems to be high in our study (Table 3). These results might be associated with the severity of the disease, and recent advances in such diagnostic modalities as CT scans and serum KL-6, or Japanese ethnogenesis, e.g., human leukocyte antigen molecules and genes.[12]

Creatine kinase and aldolase are effective for evaluating the treatment of the disease in adult DM and the abnormalities of what are more incidental to JDM than adult DM.[4,9,13,14] Of 4 patients (3 boys and 1 girl) with maximum CK levels >7000 IU/l and extremely high levels of aldolase and myoglobin, 3 boys had a favorable clinical course, thus suggesting that the earlier diagnosis (<6 months) and therapy initiation contributed to their good outcome. In their clinical course, CK levels almost paralleled aldolase. In another patient (patient 1), however, all serum muscle enzymes were normal despite the presence of clear muscle signs. Kikuchi et al. reported that the elevation of serum muscle enzyme may not always be remarkable in JDM, though the incidence of abnormalities in those enzymes is high.[10]

The positivity for the antinuclear antibody in our cases was more frequent than that described in previous reports, with an incidence 15%–23%, thus indicating a similarity in adult DM.[9,13] In our study the antinuclear antibody was not considered to be a helpful marker of the disease severity or activity.

The positive rates for EMG and muscle biopsy in JDM with muscular signs have been reported to be 60%–100% and 90%–100%, respectively,[9,11] and they have thus been established as a valuable tool for the diagnosis of JDM.[15,16] In recent MRI studies, fat-suppressed MRI made it easy to identify the muscular, cutaneous, subcutaneous, and fascial changes in the early disease course.[17] We conducted MRI at the site where muscle symptoms of the patients were mainly observed, thus resulting in a high positive rate for these examinations.

Overall, high-dose steroid therapy in treating JDM is more effective than low-dose therapy, while Tabarki et al. suggested that irrespective of steroid dosage, the earlier therapy was started, the better the recovery was.[18] It was also reported that pulse therapy effectively prevented a relapse and thus allowed for a gradual decrease in the administered steroid dose.[19] On the other hand, the optimal treatment of DM-associated ILD remains to be established. As observed in patient 7, the early administration of other immunosuppressive agents, especially cyclosporine A, is often required for steroid-resistant ILD.[6,8] In adult DM patients with progressive ILD, a single or concomitant use of intravenous cyclophosphamide has also been reported to be effective.[20,21] It may be important that the aggressive therapy should be commenced before the irreversible changes of the lung have developed.

Interstitial lung disease is a more frequent complication in patients with JDM than previously reported. Therefore, regardless of the clinical symptoms such as cough and dyspnea, investigation to detect ILD should be pursued using serum levels of KL-6, chest CT scan, and other pulmonary function tests early in the disease course.

Table 3. Incidence of juvenile dermatomyositis-associated interstitial lung disease

First author[Ref.]	Year	No. of JDM	No. of ILD (dead)	Incidence of ILD
Kikuchi[10]	1985	68	1 (0)	1.5%
Hiketa[9]	1992	29	0	0.0%
Kobayashi[11]	1997	102	4	3.9%
Higuchi[22]	1997	22	1 (1)	4.6%
Ito[19]	1998	11	0	0.0%
Kobayashi[6]	2003	10	5 (1)	50.0%
Present study		16	3 (1)	18.8%

JDM, juvenile dermatomyositis; ILD, interstitial lung disease

References

1. Pachman LM, Hayford JR, Chung A, Daugherty CA, Pallansch MA, Fink CW, et al. Juvenile dermatomyositis at diagnosis: Clinical characteristics of 79 children. J Rheumatol 1998;25:1198–234.
2. Huber AM, Lang B, LeBlanc CM, Birdi N, Bolaria RK, Malleson P, et al. Medium- and long-term functional outcomes in a multicenter cohort of children with juvenile dermatomyositis. Arthritis Rheum 2000;43:541–9.

3. Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975;292:344–7.
4. Tanimoto K, Kano S, Nakano K, Nishitani H, Sato T. Revised diagnostic criteria of dermatomyositis/polymyositis (in Japanese). Annual Report: The Ministry of Health and Welfare of Japan, Results of a study in 1992. 1993; p. 25–8.
5. Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, Yamakido M, Akiyama M. New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6. Ches*t* 1989;96:68–73.
6. Kobayashi I, Yamada M, Takahashi Y, Kawamura N, Okano M, Sakiyama Y, et al. Interstitial lung disease associated with juvenile dermatomyositis: clinical features and efficacy of cyclosporin A. Rheumatology 2003;42:371–4.
7. Al-Salmi QA, Walter JN, Colasurdo GN, Sockrider MM, Smith EO, Takahashi H, et al. Serum KL-6 and surfactant proteins A and D in pediatric interstitial lung disease. Chest 2005;127:403–7.
8. Kobayashi I, Ono S, Kawamura N, Okano M, Miyazawa K, Shibuya H, et al. KL-6 is a potential marker for interstitial lung disease associated with juvenile dermatomyositis. J Pediatr 2001;138: 274–6.
9. Hiketa T, Matsumoto Y, Ohashi M, Sasaki R. Juvenile dermatomyositis: A statistical study of 114 patients with dermatomyositis. J Dermatol 1992;19:470–6.
10. Kikuchi R, Arai Y, Kaneko K, Hidano A. Survey of 68 cases of childhood dermatomyositis, especially on its prognosis. J Pediatr Dermatol 1985;4:507–11.
11. Kobayashi S, Higuchi K, Tamaki H, Wada Y, Wada N, Kubo M, et al. Characteristics of juvenile dermatomyositis in Japan. Acta Paediatr Jpn 1997;39:257–62.
12. Tomono N, Mori M, Nakajima S, Miyamae T, Ito S, Mitsuda T, et al. HLA-DRB1*15021 is the predominant allele in Japanese patients with juvenile dermatomyositis. J Rheumatol 2004;31: 1847–50.
13. Callen JP. Dermatomyositis. Lancet 2000;355:53–7.
14. Norins AL. Juvenile dermatomyositis. Med Clin North Am 1989;73:1193–239.
15. Ramanan AV, Feldman BM. Clinical features and outcomes of juvenile dermatomyositis and other childhood onset myositis syndromes. Rheum Dis Clin North Am 2002;28:833–57.
16. Winkelmann RK. Dermatomyositis in childhood. Clin Rheum Dis 1982;8:353–68.
17. Kimball AB, Summers RM, Turner M, Dugan EM, Hicks J, Miller FW, et al. Magnetic resonance imaging detection of occult skin and subcutaneous abnormalities in juvenile dermatomyositis. Implications for diagnosis and therapy. Arthritis Rheum 2000;43: 1866–73.
18. Tabarki B, Ponsot G, Prieur AM, Tardieu M. Childhood dermatomyositis: clinical course of 36 patients treated with low doses of corticosteroids. Eur J Paediatr Neurol 1998;2:235–11.
19. Ito S, Imagawa T, Miyamae T, Katakura S, Mori M, Tomono J, et al. Clinical analysis of 11 cases of juvenile dermatomyositis and polymyositis (in Japanese). Ryumachi 1998;38:785–92.
20. Schnabel A, Reuter M, Biederer J, Richter C, Gross WL. Interstitial lung disease in polymyositis and dermatomyositis: clinical course and response to treatment. Semin Arthritis Rheum 2003; 32:273–84.
21. Kameda H, Nagasawa H, Ogawa H, Sekiguchi N, Takei H, Tokuhira M, et al. Combination therapy with corticosteroids, cyclosporin A, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. J Rheumatol 2005;32:1719–26.
22. Higuchi K, Wada N, Fukunaga K, Kobayashi S, Okabe N, Kubo M, et al. Childhood dermatomyositis: an analysis of clinical and laboratory features and the clinical course in 22 cases (in Japanese). Jpn J Pediatr 1997;50:465–70.