A juvenile dermatomyositis: demographics, characteristics and disease outcome in an Egyptian cohort

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Abstract

Objective

To study the demographics, characteristics, management and disease outcome of Egyptian children with juvenile dermatomyositis (JDM).

Methods

Retrospective analysis of the records of 134 JDM patients attending two centres in Cairo, Egypt from January 2010 to December 2019. A total of 128 patients were included in the study, all of which fulfilled either the Bohan and Peter criteria and/or the EULAR/ACR classification criteria of 2017.

Results

The mean age of disease onset was 5.9±2.8 years and the follow-up duration were 6±3.2 years. Female to male ratio was 2.2:1. Constitutional manifestations and cutaneous skin ulcers were common, while gut vasculopathy was rare in our patients. Heliotrope rash was the commonest skin manifestation. Lactate dehydrogenase enzyme was more frequently elevated than creatine kinase. Electromyography was the most frequently used diagnostic procedure, while muscle biopsy and muscle MRI were not commonly done in our patients. Glucocorticoids, methotrexate, hydroxychloroquine, mycophenolate mofetil and IVIG were the most frequently used medications. Sixty (46.9 %) of the patients had clinically inactive disease, at the last follow-up visit. Chronic skin disease, residual muscle weakness, calcinosis and growth failure were among the most common cumulative damage manifestations. The mortality rate was 1.6% over the follow-up period, one death was due to severe infection, and the other due to respiratory failure.

Conclusion

Although our patients shared several similarities with their peers in the Middle East and in Europe, there were some striking differences. These differences can be attributed to the ethnic and environmental disparities.

Key words
dermatomyositis, Egypt, demography, Middle East, children

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Introduction

Juvenile dermatomyositis (JDM) is an autoimmune disease that primarily involves skin and muscle but can also affect other organs. It is the most common idiopathic inflammatory myositis (IIMs) of childhood. The aetiology of the disease is unknown, but it has been proposed that JDM is caused by an autoimmune reaction in genetically susceptible individuals (1-6), possibly in response to infection or other environmental agents (7-14). It has a complex pathogenesis, but underlying vasculopathy and the production of multiple autoantibodies are characteristic features of the disease (14-17). Although JDM occurs in all regions of the world, the incidence and prevalence of the disease as well as the frequency of the various disease features differ due to ethnic variation and may be attributed to a complex interplay between genes and the environment. Over the past few decades several studies have demonstrated this disparity among various ethnicities (18-25). Although cases of JDM are not uncommon in the clinical practice in Egypt, the paucity of data on the disease characteristics among the Egyptian patients had prompted the present study. To our knowledge this is the first study coming from Egypt describing the demographics, clinical characteristics and outcome of JDM in a cohort of Egyptian children.

Patients and methods

Data collection

We retrospectively reviewed data derived from the medical records of 134 JDM Egyptian patients who sought medical advice at two centres in Cairo from January 2010 to December 2019. The two centres enrolled in this study include a large private rheumatology centre and the paediatric rheumatology department, Cairo University Hospitals. Both serve as referral centres as evident by the high percentage of patients referred from different cities and governorates other than Cairo. A total of 128 patients were included in the study, all of them fulfilled either the Bohan and Peter criteria (26) and/or the more recent EULAR/ACR (European League Against Rheumatism/ American College of Rheumatology) classification criteria of 2017 (27, 28). The remaining 6 patients were excluded, 4 patients due to incomplete data on medical records and two patients due to irregular follow-up for one year or more. The following data were collected from patients' medical records: (a) demographic data, including age at disease onset (onset of the first symptom or sign related to JDM), age at diagnosis, and sex; (b) constitutional manifestations, fever and/or weight loss (unintentional weight loss of >5% of body weight over a period of 6–12 months) (29); (c) cumulative clinical manifestations occurring at any time throughout the course of the disease; and (d) PRINTO criteria were used to identify JDM patients with clinically inactive disease (30). The PRINTO criteria include creatine kinase (CK) <150 U/L, childhood myositis assessment scale (CMAS) >48, manual muscle testing score (MMT) >78 and physician global (VAS) <0.2. Patients satisfying any three of these criteria are classified as having clinically inactive disease. Modification of the PRINTO criteria was done in 5 patients presented before 2013 (the date of publication of the PRINTO criteria). Data related to physician global (VAS) in those patients were not available. Instead, any documentation of absence of symptoms and signs of active disease by the treating physician were accepted in those patients. (e) Secondary cumulative damage outcomes included chronic skin changes, residual chronic muscle weakness, growth failure, calcinosis, osteoporosis, interstitial lung disease, lipodystrophy and death. Growth failure was defined by using the criteria of the International Myositis Assessment and Clinical Studies Group (IMACS) and the Egyptian growth curves (31, 32). A Patient was labelled as having growth failure if he had two of the following three features: (i) less than 3 percentile height for age; (ii) growth velocity over 6 months less than 3rd percentile for age; and (iii) growth curve crossing at least 2 centiles (5%, 10%, 25%, 50%, 75%, 95%) on growth chart (31).

Ethics

All procedures performed in the study were in accordance with the ethical

standards of the institutional and/or national research committee and in accordance with the 1964 Helsinki declaration and its later amendments.

Statistical analysis

All data were analysed and entered using Statistical Program for Social Science (SPSS) v. 25. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative variables were expressed as frequencies (number of cases) and relative frequencies (percentages).

Results

Demographics and clinical characteristics

Eighty-eight patients (68.8%) were females, while 40 patients were males (31.2%) with female to male ratio of 2.2:1. The age of disease onset, time lag from disease onset to diagnosis and duration of follow-up are shown in Table I. Fifty-two (40.6%) of our patients run a monocyclic course, while 76 (59.4%) patients run a polycyclic or chronic course. Constitutional manifestations at disease onset were found in 70 (54.7%) patients. History of preceding infection was reported in 30 (23.4%) patients, mostly upper respiratory tract infection in 28 cases, gastrointestinal in one case and skin abscess in another case with a median time to onset of JDM symptoms of 3 weeks (range 1 week to 2 months). All our patients had one or more of the characteristic skin manifestations of the disease. Heliotrope's sign was the most common skin manifestation in 100 (78.1%) of our patients, followed by Gottron's sign or papules in 92 (71.9%), diffuse malar erythema in 90 (70.3%), periungual erythema in 64 (50.0%) and Holster's sign in only 8 (6.3%) of the patients. On the other hand, 114 (89.1%) patients had clinically evident symmetrical progressive muscle weakness of the upper and/ or lower limbs more proximal than distal. Sixteen (12.5%) patients had dysphagia, while 12 (9.4%) patients had pseudobulbar muscle weakness. Other manifestations such as arthritis were found in 61 (47.7%) patients, Raynaud's in 6 (4.7%), pneumonitis in 18 (14.1%), cutaneous ulcers in 40 (31.3%) and gastrointestinal vasculopathy in one (0.8%) patient (Table I).

Table I. Demographic data and clinical manifestations of 128 Egyptian children with JDM compared to other populations.

Variable	Egypt	Arab (24)	European (33)
No. of patients	128	92	248
Female (no., %)	88 (68.8%)	58 (63.0%)	169 (68.1%)
Age at disease onset (mean, years)	5.9 (± 2.8)	6.0 (±3.0)	6.9 (±3.7.0)
Time to diagnosis (mean, years)	0.8 (± 1.9)	1.5 (±5.6)	0.6 (±1.1)
Follow-up duration (mean, years)	6.0 (± 3.2)	5.0 (±4.4)	7.7
Monocyclic: polycyclic/chronic %	40.6: 59.4%	37: 63%	39.3: 60.7%
Clinical features %			
Constitutional	54.7	40	28.6
Skin involvement			
Heliotrope's	78.1	70	58.1
Gottron's	71.9	78	65.7
Periungual erythema	50	NA	NA
Diffuse malar erythema	70.3	NA	NA
Holster sign	6.3	NA	NA
Muscle involvement			
Weakness	89.1	94	86.3
Dysphagia	12.5	15	20.2
Pseudobulbar	9.4	NA	NA
Others			
Arthritis	47.7	49	34.7
Raynaud's	4.7	4	5.3
Pneumonitis	14.1	11	NA
Cutaneous ulcers	31.1	8	6.3
GIT vasculopathy	0.8	13	0.2

Monocyclic: one disease episode that responds to standard treatment without relapse; Polycyclic/chronic: characterised with multiple remissions and relapses or runs a chronic persistent course with complications. NA: not available; Holster's sign: poikiloderma (characteristic telangiectasias and skin atrophy) of the upper outer thigh; GIT: gastrointestinal tract.

Table II. Diagnostic procedures in 128 Egyptian JDM patients at diagnosis.

Variable	
Muscle enzyme	
no. of patients with elevated enzymes (%)	118/128 (92.2%)
Value: mean± SD IU/L (range)	
CK	1135± 2642 (15-17090)
LDH	519± 291 (104- 1590)
AST	53± 62 (7-341)
ALT	73± 84 (9-449)
ANA	83/128 (64.8%)
Muscle biopsy: no. (%)	8/128 (6.3%)
EMG: no. (%)	82/128 (64.1%)
Muscle MRI: no. (%)	9/128 (7.0%)

SD: standard deviation; CK: creatine kinase (normal range up to 170 IU/l); LDH: lactate dehydrogenase (normal up to 280 IU/l); AST: aspartate aminotransferase (normal up to 38 IU/l); ALT: alanine aminotransferase (normal up to 38 IU/l); IU/l: international unit per liter; EMG: electromyography; MRI: magnetic resonance imaging.

Diagnostic procedures

Elevated muscle enzymes at some stage of the course of the disease were found in 118 (92.2%) of our patients. The most frequently elevated enzyme was lactate dehydrogenase (LDH) in 104 (81.3%), followed by aspartate aminotransferase (AST) in 74 (57.8%), creatine kinase (CK) in 60 (46.9%), and alanine aminotransferase (ALT) in 46 (35.9%) of the patients. Aldolase was tested in only seven patients and was elevated in five of them. However, elevated levels of CK compared to upper limit of normal values were higher than the elevation of LDH compared to its normal values (Table II). Antinuclear antibody was positive in 83 (64.8%) of our patients. Muscle biopsy was performed in only 8 (6.3%) of the patients and showed the

Table III. Frequency of drugs used and cumulative damage in our series compared to Arab and European populations.

	Egyptian	Arab (24)	European (33)
Drug: % of patients			
Oral prednisone	100	100	97.6
IV methyl prednisolone pulse	68.8	60	50
Methotrexate	84	86	50.8
Hydroxychloroquine	70.3	17	26
Mycophenolate mofetil	56.3	NA	NA
IVIG	48.4	33	17.1
Pulse methyl prednisone	54	60	50
Cyclophosphamide	6.3	7.6	6.6
Cyclosporine	2.3	10	35
Biologics (rituximab)	0.8	10.8	2.2
Frequency of damage: % of patients			
Chronic skin disease	40.6	17.4	55.5
Residual muscle weakness	25.0	13	29.7
Growth failure	29.7	28.2	6.4
Calcinosis	32.8	29.3	21.3
Osteoporosis	10.9	12	6
Pulmonary	3.1	4.4	3.8
Lipodystrophy	1.7	3.3	8.6
Death	1.6	2.2	NA

IV: intravenous; NA: not available; IVIG: intravenous immunoglobulins.

characteristic features of the disease, including perifascicular atrophy, muscle fibre degeneration and regeneration and perivascular inflammation in all the biopsied patients. Electromyographic examination (EMG) was done for 82 (64.1%) of the patients, whereby the results showed myopathic potentials with the characteristic fibrillation, recruitment pattern and insertional activity consistent with myositis. Muscle MRI was performed as part of the diagnostic work-up in 9 (7.0 %) patients (Table II).

Treatment and disease outcome

Oral prednisone was used initially in all patients (100%). Methotrexate was the most frequent disease modifying and steroid sparing drug used in 84% of our patients. On the other hand, biologics were the least frequently used drugs; rituximab was used in only one (0.8%) of our patients. Hydroxychloroquine, mycophenolate mofetil, intravenous methylprednisolone, intravenous immunoglobulin (IVIG), pulse intravenous cyclophosphamide and cyclosporine were used in 70.3%, 56.3%, 54%, 48.4%, 6.25%, and 2.3% respectively. The frequency of use of the different drugs in management of JDM in our patients compared to the Arab and European population is shown in Table III. Sixty patients (46.9%) had clinically inactive disease, at the last follow-up visit. Fifty-two patients (40.6%) had chronic skin disease at one or more of the involved areas, while residual muscle weakness was found in 32 (25.0%) of the patients. The mortality rate in our series was 2/128 (1.6%) over the follow-up period, one death was due to severe infection, and the other due to respiratory failure. The frequency of the different manifestations of cumulative damage in our patients compared to other populations is shown in Table III.

Discussion

JDM is the most common idiopathic inflammatory myopathy in childhood, accounting for approximately 85% of cases (34, 35). It is characterised by capillary injury that results in perifascicular muscle fibre atrophy (36). The disease is probably an "antibody-dependent, complement-mediated disease" with unknown aetiology. Like other autoimmune rheumatic diseases, its pathogenesis represents a complex interplay between genetic and environmental factors and therefore, disparity among different races and ethnic populations are expected. Hence, it is important to highlight the differences and similarities between our cohort and other cohorts, particularly those from the Middle East and Europe. All patients in this cohort fulfilled the Bohan and Peter criteria (26) and/or the more recent EULAR/ACR (European League Against Rheumatism / American College of Rheumatology) classification criteria of 2017 (27, 28). Although 34 (26.6%) of the patients presented before the date of publication of the EULAR/ACR criteria and did not meet the Bohan and Peter criteria, the available data on medical records suggested their classification as having JDM according to the more recent EULAR/ACR classification criteria. The reasons for satisfying the EULAR/ACR but not the Bohan and Peter criteria in all the 34 patients was the absence of muscle biopsy or EMG confirmation, and unlike most previously published myositis diagnostic and classification criteria, the EULAR/ACR IIM classification criteria are based on clinical information collected from patients with myositis. The new criteria involve muscle biopsies, but an alternative set of criteria was optimised for use when muscle biopsy data are unavailable. The original Bohan and Peter criteria were replaced to a large extent because invasive procedures such as EMG and muscle biopsy are no longer used as frequently in many centres, especially in patients with the characteristic skin rash and proximal muscle weakness. In an international survey, all paediatric rheumatologists routinely used the clinical features of JDM to make the diagnosis of JDM.[37] In this survey, elevated serum muscle enzymes, muscle biopsy, and EMG were used as diagnostic aids in 87, 61, and 55% of cases, respectively (37). In a study comparing the 2017 EULAR/ACR criteria with Bohan and Peter criteria, Bohan and Peter classified 73% and EULAR/ACR 82% of patients when biopsy was excluded, and both sets of criteria classified over 90% of patients with dermatomyositis (38).

With reference to the demographic data analysis of our patients age of disease onset and female predominance were similar when compared to their peers from the Arab and European cohorts. The time lag between appearance of the first disease symptom or sign to disease

diagnosis was shorter in our patients compared to the study on the Arabs but slightly longer than the European cohort (Table I). Constitutional manifestations in the form of fever and unintentional weight loss are more frequent in our patients (58.6%) than in Arabs (40%) and Europeans (28.6%) (24, 33). Interestingly, Heliotrope's sign was the most common skin manifestation in our cohort (78.1%), followed by Gottron's rash (71.9%), diffuse malar rash (70.3%), periungual erythema (50%) and Holster's sign in (6.3%). On the other hand, Gottron's rash was more frequent than heliotrope's sign in both the Arab and European cohorts (24, 33). In addition, in a case series study from a single tertiary Canadian centre of 105 patients with JDM, Gottron's rash was present in 91% and heliotrope rash in 83% of JDM patients (35).

Clinically, manifest muscle weakness was in our series midway between the Arabs and Europeans (89.1% compared to 94% and 86.3%, respectively), while dysphagia (12.5%) was less frequent in the Egyptian patients compared to Arabs (15%) and Europeans (20.2%) (24, 33). Gut vasculopathy was rarely encountered in our and the European cohorts (<1%); and both were less frequent than in the Arab cohort (13%). One of the striking features in our cohort is the frequency of skin ulcers; it is present in almost 31% of patients as opposed to 8% and 6.3% in the Arab and European cohorts (24, 33). Skin ulcers in our cohort are usually small ulcers, seen early in the course of the disease, more among younger patients and not associated with particular clinical features or with a more severe course. They usually responded to intravenous methylprednisolone and when extensive or severe pulse cyclophosphamide was used. The discrepancy between these studies could be attributed to differences in environmental and genetic backgrounds of the population of each cohort.

Elevated muscle enzymes were found in 118 (92.2%) of our patients. Similar to the Arab cohort, the most frequently elevated enzyme was lactate dehydrogenase (LDH) in 104 (81.3%) patients. This was followed by aspartate aminotransferase (AST) in 74 (57.8%), creatine kinase (CK) in 60 (46.9%), and alanine aminotransferase in 46 (35.9%) of the patients. This is in contrast with other studies from Europe and South-Africa, in which creatine kinase was the most commonly elevated enzyme (25, 33). Creatine kinase, however, may be elevated to an extremely high level compared to lactate dehydrogenase (Table II). The significance of elevation of different muscle enzymes and the value of its comparison with other studies is unknown. There are methodological differences in assays between studies, in addition the timing of measuring the enzymes relative to disease course varies between patients in the same study and between different studies. We did not observe any significant difference in the clinical manifestations, disease course or response to therapy between children who have different muscle enzymes elevation and normal CK levels compared to those with high CK. Antinuclear antibodies were positive in 83/128 (64.8%). Commercially available myositis-specific testing (MSAs) is becoming more common, and MSA testing has become routine at some sites, however, testing for MSAs is not routinely performed and not readily available in Egypt.

EMG was the most commonly performed diagnostic procedure; it was performed on 82/128 (64.1%) of the Egyptian patients. It is worth noting that performing other diagnostic procedures, such as muscle biopsy and muscle MRI, were less frequently used in our series compared to other cohorts. Eight (6.3%) of our patients underwent muscle biopsy as opposed to 48% in both the Arab and South African populations (24, 25). Muscle MRI, specifically T2-weighted and fat-suppressed images, can detect muscle inflammation and is increasingly used in the diagnosis of childhood inflammatory myopathy to avoid invasive procedures, such as muscle biopsy and EMG. Muscle MRI, as part of the diagnostic work-up, was performed in only 9 (7%) of the patients as compared to 75/92 (86%) of Arabs. In one study from the United Kingdom and Ireland, 78 of 102 patients (76%) and 36% underwent MRI and muscle biopsy, respectively, while EMG was performed in only 8% of the patients in this cohort (34). This disparity between our study and other peer studies can be explained by the resource constrained economy in Egypt compared to rich-resource countries such as gulf countries and United Kingdom. Diagnostic modalities, such as EMG, may provide cheaper and more cost-effective alternative for demonstrating evidence of muscle inflammation.

In the absence of evidence-based guidelines for management of JDM, the management of the disease differs among the different centres. Recently, a consensus-based recommendation for the management of the disease has been suggested (39). Glucocorticoids remain the mainstay of management. As expected, all patients in this cohort received oral or intravenous glucocorticoids. In most patients (68.8%), we usually start with intravenous methyl prednisolone pulse for 3 days (20 mg/kg/BW). We commonly add second line drugs, the most used drug was parental methotrexate (84%), usually in a dose between 0.3–0.5 mg/kg/BW, we shift to oral methotrexate only in children who cannot tolerate the parenteral route. Addition of methotrexate to the initial therapy shortens the duration of glucocorticoid therapy considerably, reduces the total cumulative glucocorticoid dose, and improves efficacy compared with glucocorticoid therapy alone (40, 41). Mycophenolate mofetil was used in 56.3% of the patients; it may be added to methotrexate in refractory cases or as an alternative in children who cannot tolerate methotrexate. Other second line drugs included hydroxychloroquine (70.3%), usually combined with other immunosuppressives mainly in patients with extensive skin rash, and cyclophosphamide (6.3%), mainly for patients with severe skin ulceration. Cyclosporine was used in only 2.3% of the patients; the drug is not commonly used in the management of JDM in our centres. Intravenous immunoglobulin (IVIG) was used in nearly half (48.4%) of our patients, while biologics (rituximab) were used in one (0.8%) refractory patient. As compared to other studies on JDM, we used more hydroxychloroquine, mycophenolate mofetil, and IVIG; but less cyclosporine and biologics (Table III).

Juvenile dermatomyositis is a chronic disease, and many patients may never achieve a clinically inactive disease state. According to PRINTO criteria, 46.9% of our patients had clinically inactive disease at the last review. Similarly, Sun *et al*. analysed the treatment outcome among JDM patients over a ten-year period in a Taiwanese hospital and found that only 33% among the cohort of 39 patients were symptom free at last review (42). In addition, 40% of 25 patients with JDM in the South African cohort were symptom free after a median follow up period of 50 months (25). The frequency of cumulative disease damage compared to other cohorts is shown in Table III. Residual muscle weakness and skin disease were less frequent than the Europeans but more frequent than the Arabs. Calcinosis occurred in approximately one third of our patients, more than the peer cohorts. Growth failure in the current and Arab's cohorts was more frequent than in the European cohort. In Egypt, this can be attributed to the more prolonged use of high dose corticosteroids in the management of the disease, mainly due to economic considerations.

The reported mortality rate has declined from greater than 30% in the 1960s (43), to less than 2–3% in the 2000s with the routine use of glucocorticoid therapy and the early combination with immunosuppressive therapy (44, 45). The mortality rate in our series was 2/128 (1.6%) over the follow-up period, one death due to severe infection, and one due to respiratory failure. Higher mortality rates 8-9.5% were found in two small studies from South Africa (25, 46).

There are some limitations of this study; the first is related to the nature of the retrospective studies, which provide inferior level of evidence compared to the prospective studies. Secondly, the inclusion of 34 (26.6%) patients who did not meet the Bohan and Peter criteria; based on the retrospective fulfilment of the more recent EULAR/ACR classification criteria. Thirdly, the assessment of damage has been made by evaluating the frequency of various forms of damage, the use of a more standardised tool such as Myositis Damage Index (MDI), would have been more appropriate to assess the cumulative damage and to facilitate the comparability with other series, however, the lack of some data on the files of our patients has made this task difficult considering that files were recruited from two different centres. However, the current study had several strengths: this study represents a step forward towards unveiling the magnitude of the problem of JDM in Egypt, making it to the best of our knowledge the first study of its kind in our country. In addition to the demographics and clinical features of JDM, special attention was given to the diagnostic procedure and disease outcome. Moreover, this study is also a step forward towards increased awareness with the problem of growth failure among rheumatologists in our region and that strategy modification towards less steroid and more use of immunosuppressives and biologics is mandatory.

Overall, in view of the absence of uniform management in different centres, further prospective studies on a wider scale and from different centres in Egypt are required and could be useful in providing better quality data, especially on disease outcome.

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