Concise Report

Assessment of an infectious disease history preceding juvenile dermatomyositis symptom onset

C. Manlhiot¹, L. Liang¹, D. Tran², A. Bitnun², P. N. Tyrrell¹ and B. M. Feldman³,⁴

Introduction

Juvenile dermatomyositis (JDM) is the most common paediatric inflammatory myopathy, but overall remains a rare disorder with an estimated yearly incidence of 3.2 cases per million children under the age of 17 yrs [1, 2]. Although widely studied, the causes still remain largely a mystery [3]. While a genetic predisposition almost certainly exists [4–6], numerous case reports of JDM symptoms occurring concurrently with an infection have led many to believe that infections may trigger JDM onset [7–15]. Previous cohort studies have found a moderately high incidence of infectious symptoms associated with the onset of JDM [16, 17]. However, the heterogeneity of symptoms and the overlap between symptoms typically associated with JDM and infectious symptoms [3] have precluded the identification of specific infectious agents that might trigger or cause the disease. To-date no single pathogen has been identified as a probable cause in serological analyses [18–25].

In addition to genetic predisposition and perhaps infection, inconsistent reports of a summer peak in JDM onset [26, 27] have suggested a possible environmental influence, potentially from ultraviolet radiation [28–30].

We sought to determine, in a large cohort of JDM patients, the frequency of infections temporally associated with JDM onset, the seasonal variation associated with symptom onset, and whether the presence of an infection is related to patient characteristics at diagnosis or disease outcomes.

Objectives. A number of studies have looked at the role of infectious diseases in triggering juvenile dermatomyositis (JDM). Previous studies have found a moderately high frequency of infectious symptoms prior to disease onset; however, no specific pathogens could be identified. We sought to correlate preceding infectious symptoms with onset and outcomes of JDM.

Methods. We studied an inception cohort of all JDM cases diagnosed at The Hospital for Sick Children (SickKids) between 1988 and 2006. Data pertaining to symptoms at onset, diagnosis and disease outcomes were abstracted. Two independent paediatric infectious disease specialists reviewed all records of patients with symptoms or tests suggestive of infection.

Results. A total of 110 patients were reviewed; of these, 78 had sufficient information about disease onset for inclusion. Potential indications of an infectious process prior to JDM onset were found in 55/78 (71%) patients and were further evaluated for evidence of infection temporally associated with symptom onset. Features suggestive of infection prior to JDM symptom onset were found in 40/55 [probable (30/40) or possible (10/40)]. Most children with probable infections had respiratory illnesses [24/30 (80%)]. Fewer patients than expected had disease onset during summer months. The presence of an infection at onset was not found to be associated with differences in characteristics at diagnosis or disease outcomes.

Conclusions. A substantial number of JDM patients have a clinical history consistent with an infection prior to onset. Newly diagnosed patients should undergo a full infectious disease assessment as part of their initial work-up; specific attention should be given to respiratory infections.

Key words: Juvenile dermatomyositis, Idiopathic inflammatory myopathies, Infection, Autoimmunity, Seasons.

Patients and methods

We studied an inception cohort comprising all patients diagnosed with JDM from January 1988 to January 2006 at The Hospital for Sick Children (SickKids), Toronto. Patients transferred to SickKids after diagnosis were excluded because of limited data regarding disease onset. The study was approved by the institutional research ethics board; requirement for individual consent was waived for this retrospective cohort study.

Patients referred to SickKids for assessment of possible JDM undergo a standard evaluation protocol with consultations by a number of physician specialists (rheumatology, neurology, ophthalmology, dermatology) providing a very detailed clinical history for each patient. All new patients are asked about symptom onset and history of infectious disease as part of their initial consultation. In addition, by protocol, new patients are screened for serological evidence of infectious agents known to be associated with myositis (influenza, enterovirus, toxoplasma, Trichinella). Data regarding symptom onset were abstracted; particular attention was given to month of skin and muscle symptom onset, antibiotic use and presence of infectious symptoms at and prior to onset. Additionally, demographic information, detailed clinical characteristics at diagnosis and disease outcomes were recorded. Delay in diagnosis was defined as time between the first symptoms and official diagnosis.

Two infectious disease specialists independently reviewed all cases that had a medical history suggesting (either through symptoms, clinical notes, laboratory results or antibiotic drug prescription) a potential infection in the 3 months prior to the first JDM symptoms. Assessors had to answer the following two questions: is the clinical history consistent with an infection in the 3 months preceding the onset of JDM symptoms? If yes, can a specific pathogen be identified? Each assessor separately reviewed the cases; when disagreement occurred, the clinical data were discussed until consensus could be reached. Cases were defined as possible infection when clinical history and symptoms were suggestive of an infection but infectious symptoms were overlapping with ‘traditional’ JDM symptoms. Cases were defined as

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Infectious diseases preceding JDM onset

### Table 1. Results from infectious diseases (ID) assessment

<table>
<thead>
<tr>
<th>Pre-assessment</th>
<th>Cohort (n = 78)</th>
<th>&lt;6 month delay (n = 54)</th>
<th>&gt;6 month delay (n = 24)</th>
<th>P</th>
<th>Sent for ID evaluation (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infectious indication at onset (%)</td>
<td>23 (29)</td>
<td>11 (20)</td>
<td>12 (50)</td>
<td>0.02</td>
<td>-</td>
</tr>
<tr>
<td>Potential infectious indication at onset (%)</td>
<td>55 (71)</td>
<td>43 (80)</td>
<td>12 (50)</td>
<td>0.008</td>
<td>-</td>
</tr>
<tr>
<td>Any infectious symptoms (%)</td>
<td>43 (55)</td>
<td>34 (63)</td>
<td>9 (38)</td>
<td>0.03</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory symptoms (%)</td>
<td>30 (38)</td>
<td>26 (48)</td>
<td>4 (17)</td>
<td>0.008</td>
<td>-</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>22 (28)</td>
<td>18 (33)</td>
<td>4 (17)</td>
<td>0.13</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal symptoms (%)</td>
<td>19 (24)</td>
<td>15 (28)</td>
<td>4 (17)</td>
<td>0.29</td>
<td>-</td>
</tr>
<tr>
<td>Antibiotics prescription (%)</td>
<td>25 (32)</td>
<td>18 (33)</td>
<td>8 (33)</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Is medical history consistent with infection in the 3 months preceding JDM onset?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable infectiona (%)</td>
<td>30 (38)</td>
<td>25 (58)</td>
<td>5 (42)</td>
<td>0.21</td>
<td>30 (55)</td>
</tr>
<tr>
<td>Possible infectionb (%)</td>
<td>10 (13)</td>
<td>8 (19)</td>
<td>2 (16)</td>
<td>0.31</td>
<td>10 (18)</td>
</tr>
<tr>
<td>No infection (%)</td>
<td>38 (49)</td>
<td>10 (23)</td>
<td>5 (42)</td>
<td>0.88</td>
<td>15 (27)</td>
</tr>
</tbody>
</table>

*p-values refer to the comparisons between groups characterized by delay in diagnosis of less or more than 6 months.

aInfectious symptoms, clinical notes, antibiotic prescription, positive virology or microbiology laboratory results in the 3 months preceding JDM onset.
bHistory is consistent with an infection in the 3 months preceding JDM symptoms onset. cHistory is possibly consistent with an infection in the 3 months preceding JDM symptoms onset, but infectious symptoms are overlapping with ‘traditional’ JDM symptoms.

### Results

A total of 110 patients (77 females) were diagnosed with JDM during the study period. Adequate details concerning symptom onset were not available for 32 patients, leaving a final cohort of 78 patients. Patients were diagnosed at a mean age of 7.8 yrs, with no significant difference between males and females (7.9 vs 7.6 yrs, respectively, \( P = 0.69 \)). Median delay in diagnosis was 3 months from skin symptom onset (range 2 weeks–3 yrs)—with 8 patients (10%) being diagnosed without skin symptoms—and 10 weeks from muscle symptom onset (range 2 weeks–2.5 yrs); 13 (17%) patients were diagnosed without musculoskeletal symptoms. All patients who presented with incomplete symptoms eventually showed the full range of clinical manifestations with the exception of one patient subsequently diagnosed with juvenile polymyositis. Skin symptoms appeared first in 32 patients (42%), while musculoskeletal symptoms appeared first in 22 patients (28%); the remaining 30% had disease onset with concurrent skin and muscle symptoms.

Of the 78 patients for whom data was available, 55 (71%) had some symptoms or signs that may have been consistent with infection and were referred for consensus evaluation of infection. The remaining 23 patients had no such indication. Agreement after individual assessment was seen in the majority of cases (40/55, 73%); 15 cases had to be discussed in order to obtain consensus.

Thirty of 78 patients (38%) were found to have a history of clinical symptoms, not typically associated with JDM, that were suggestive of a probable infection (Table 1). Although possibly associated with infection prior to onset, a definite answer could not be reached in 10 (13%) cases because limited information was available and the infectious symptoms overlapped with ‘traditional’ JDM symptoms. The remaining cases had no evidence of infection. Specific pathogens could be identified in only seven cases; however, clinically, respiratory infections were common (24/30).

Patients with a delay in diagnosis of <6 months were more likely to report infectious symptoms (63 vs 38%, \( P = 0.03 \)), mainly respiratory symptoms (80 vs 50%, \( P = 0.008 \)), but were not more likely, upon case review by infectious diseases specialists to be found to have had a probable (58 vs 42%, \( P = 0.21 \)) or possible infection (19 vs 16%, \( P = 0.31 \)) in the 3 months prior to JDM onset. This might suggest an important recall bias, or important missing information when symptoms occur long before hospital presentation.

The seasonal distribution of symptom onset for the entire cohort, for patients with probable or possible infections and for patients without a history of infection is detailed in Table 2. Intervals were divided according to distribution of infectious disease activity in Southern Ontario where most of patients came from (43° latitude) [31–33]. Children whose JDM onset was associated with a possible/probable infection were significantly less likely to experience their first JDM symptoms between August and October. This pattern was not seen for the entire cohort or for patients in whom no signs of infection were found. An aggregation of cases in the summer was not observed in our cohort as seen in other studies from lower latitudes [26, 27].

Patients whose symptom onset was associated with infection had a slightly different presentation than the rest of the cohort, being more likely to have nail-fold abnormalities (97 vs 81%, \( P = 0.05 \)), persistent fever (37 vs 13%, \( P = 0.03 \)) and dysphonia (33 vs 13%, \( P = 0.05 \)) at diagnosis. Additionally, a trend against disease onset with skin symptoms first (37 vs 55%, \( P = 0.13 \)), shorter delay in diagnosis from skin symptom onset (4.5 vs 6.7 yrs \( P = 0.09 \)) and younger age at diagnosis (7.7 ± 4.2 yrs vs 9.2 ± 4.5 yrs old, \( P = 0.18 \)) was observed—albeit not statistically significant. No differences in disease severity at diagnosis (7.3 ± 2.3 vs 7.3 ± 2.7, \( P = 0.93 \)) or long-term outcomes were found. Myositis-specific or myositis-associated antibodies are no longer routinely examined in our patients as the frequency in our cohort is very low [34]. Patients with probable infection at onset and no infection at onset had a similar frequency of receiving i.v. immunoglobulin (45 vs 39%, \( P = 0.63 \)) and a similar average number of visits per year (4.5 ± 2.2 vs 4.8 ± 3.4, \( P = 0.62 \)), time from diagnosis to disease improvement defined as a 50% reduction from baseline in disease activity, prednisone dose and
functional physical limitations (hazard ratio 0.70, $P = 0.64$), time from diagnosis to treatment discontinuation (hazard ratio 0.71, $P = 0.41$) and frequency of disease re-occurrence (20 vs 16%, $P = 0.18$).

Discussion

This study provides additional confirmatory evidence that a substantial number of JDM patients have a medical history consistent with infection in the 3 months prior to symptom onset. An infection in the 3 months prior to JDM onset was probable in over one-third of cases and possible in an additional 17%. Respiratory presentations accounted for 80% of probable infections. Finally, a history of infection prior to disease onset was found to have little impact on a patient’s medical condition at diagnosis and did not seem to influence clinical outcomes.

The main obstacles to the identification of an infectious disease at the onset of JDM are 2-fold. First, JDM symptoms often progress over time and lengthy delays from symptom onset to diagnosis often preclude comprehensive testing for infection and may lead to recall bias. Second, many symptoms often considered to be related to infections (e.g., fever, gastrointestinal problems, lethargy, myalgias or rash) are also JDM symptoms. On the other hand, some of these clinical features, such as fever and gastrointestinal problems, are rarely seen after diagnosis; perhaps in some cases, early fever and gastrointestinal upset is associated with unrecognized infection [3]. A proposed infectious diseases clinical work-up, specific to JDM, has been included (see Supplementary Appendix 1, available as Supplementary Data at Rheumatology Online).

Studies based on patient self-report showed a moderately high prevalence of infectious symptoms in the 3 months prior to disease onset [16]. The latest study by Pachman and colleagues [17] found 42% of patients reporting fever, 57% with respiratory symptoms and 30% with gastrointestinal complaints in the 3 months preceding JDM symptoms in a cohort of 286 newly diagnosed patients. The overall proportion of patients reporting infectious symptoms, regardless of delay in diagnosis, are slightly lower in our study. When only our patients with a delay in diagnosis of ≤6 months are considered, the numbers become similar. Moreover, the clinical presentation of a substantial number of these patients led infectious disease specialists to conclude that the presence of an infectious process prior to onset was possible based on clinical symptoms overlapping with JDM symptoms suggesting the possibility that some ‘traditional’ JDM symptoms such as fever and dysphonia might sometimes be related to infection instead of JDM.

The process by which molecular mimicry between *Streptococcus pyogenes* type M5 protein and human skeletal myosin, which may be a target of the immune response in JDM, could create autoimmunity and lead to JDM has been described in previous studies [35, 36].

In recent years, many authors have also hypothesized a possible role for other environmental factors, especially ultraviolet radiation, after inconsistent reports of seasonal distribution of onset of symptoms in Southern European JDM populations [26, 27]. However, in our cohort, those with a probable infection actually had a reduced frequency in the sunniest months. A seasonal effect, other than the one potentially linked to infectious disease activity, was not seen in our cohort, which is consistent with recent reports from UK [37].

Results from this study must be viewed in light of some limitations. The retrospective nature of the study limits the amount of information available; we saw many children in consultation for whom there was insufficient recorded data to evaluate. An important recall bias cannot be ruled out; some cases of infection may have been missed. These limitations most likely would have led to an underestimation of the frequency of an infectious disease at the onset of JDM in our cohort. As infections are common in this age group, it is likely that some cases of infections that are temporally associated with the onset of JDM symptoms occurred by chance alone.

The moderately high frequency of possible/probable infection prior to disease onset suggests that an infectious process is, in some cases, associated with JDM onset. The high frequency of identified respiratory infections gives clues about the type of pathogens most likely associated with JDM; given the high frequency of respiratory infections found in this cohort and experimental evidence of molecular mimicry from previous work, agents causing respiratory infections may be an important trigger.

The presence of a probable/possible infection prior to JDM onset was not found to affect characteristics at presentation and disease outcomes; perhaps we have underestimated the frequency of infection and it is a more universal trigger. We suggest that an infectious disease consultation and thorough laboratory testing for infection be included as an integral part of assessment for new JDM patients with special attention directed towards respiratory infections.

**Rheumatology key messages**

- A substantial number of children with JDM have a history compatible with infection prior to symptom onset.
- Respiratory infections may trigger JDM.

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**Supplementary data**

Supplementary data are available at Rheumatology Online.

**References**

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