

# Predicting time to remission of juvenile dermatomyositis: the role of clinical features

*"Persistent skin disease and abnormal nailfold capillaries may be a marker for more severe and refractory vasculopathy with these children representing a more severe 'phenotype' of juvenile dermatomyositis."*

Juvenile dermatomyositis (JDM) is a chronic inflammatory disease of childhood characterized by proximal muscle weakness and pathognomonic skin rashes [1,2]. An essential component of the histopathology of this disease is vascular damage affecting the capillaries, venules and small arterioles. While JDM is a rare condition with an incidence of approximately 3.2 cases in each million children per year, children with this disease require on-going follow up, often for many years [3,4]. The outcome for children with JDM has dramatically improved over the last 50 years, with the prompt initiation of high-dose corticosteroids undoubtedly being one of most important therapeutic interventions in reducing morbidity and mortality [5,6]. Despite this, we found that approximately 60% of children followed at our center demonstrated evidence of active disease and/or were continued on medication for 3 years after diagnosis [7]. The remainder appeared to have a 'simpler' course of disease, being able to halt treatment and remain in remission within 3 years of diagnosis. The presentation of JDM can also be quite variable; some patients present with life-threatening weakness and ulcerating disease, while others present with a relatively mild rash and weakness.

Juvenile dermatomyositis is clearly a heterogeneous disease and is likely to be represented by more than one clinical phenotype. Moving forward, the real challenge is to increase our understanding of these phenotypes, or subsets of patients. We hope that in time, a clinical or biological marker (or a combination of both) might help to predict which patients may best respond to a given medication with the hope of being able to individualize treatment, thereby decreasing medication-related toxicity and optimally treating disease activity. We recently reported a study that looked at whether clinical and/or laboratory features could predict the time to remission and disease course at the diagnosis of JDM, or soon thereafter [7].

The objectives of our study were to determine the time to remission in an inception cohort of children with JDM, to determine the proportion of patients who had a chronic or nonchronic disease course and to find predictors of time to remission and/or disease course. We found that the median time to remission was 4.67 years (where we defined remission as 'off treatment without evidence of muscle or skin disease for 6 months'). We also found that the majority of children had a chronic course of disease and the earliest predictors of time to remission were the persistence of Gottron's papules at 3 months, and the presence of abnormal nailfold capillaries (NFCs) in addition to persistent Gottron's papules at 6 months. Features of muscle disease (weakness and muscle-enzyme levels) did not predict chronicity of course.

Christen-Zaech *et al.* also recently conducted a study examining predictors of disease course and concluded that a chronic course (in their study this was called 'nonunicyclic' and had a slightly different definition to ours) was a reflection of continuing skin involvement and persistently abnormal NFCs, since they found that muscle disease appears to be rapidly reversed regardless of course [8].

The relationship between skin disease, abnormal NFCs and disease course has long been an area of interest in the context of JDM. Early observations found that NFC abnormalities were associated with more severe and chronic disease [9]. Pathological studies of skin in JDM have demonstrated endothelial damage in dermal capillaries and venules leading to obstruction and occlusion of the vessel – the latter was felt to be the underlying mechanism of the hallmark features of NFC changes (dilated loops, tortuosity and capillary dropout) [10]. Persistent skin disease and abnormal NFCs may be a marker for more severe and refractory vasculopathy with these children representing a more severe phenotype of JDM.



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The findings in our study and previous studies draw attention to two important questions: first, should children with persistent skin disease and persistently abnormal NFCs be treated differently? and second, are there other factors (e.g., biological, imaging or biopsy findings) that could help to predict the course of JDM at diagnosis and therefore allow us to individualize treatment earlier?

The optimal treatment for JDM is presently unknown; however, a recent survey of North American rheumatologists indicated that corticosteroids and methotrexate (MTX) in combination appears to be the standard of care when initiating treatment for typical cases of JDM [11]. As part of that survey, we also asked whether the rheumatologists would modify treatment if skin disease persisted (but they still had normal strength and muscle enzymes) in a patient treated initially with corticosteroids and MTX; we found that the majority would add either hydroxychloroquine and/or intravenous immunoglobulin. It is our practice to add intravenous immunoglobulin as a steroid-sparing agent to therapy in a patient with persistent skin disease after initial treatment with corticosteroids and MTX, even in the face of clinically quiescent muscle disease.

However, based on the present understanding of predictors of disease course in JDM, we feel that we cannot yet know which child will do well with a more limited immunosuppressive treatment approach versus a more aggressive treatment approach.

The importance of optimizing treatment for JDM patients as early in the disease course as possible might be demonstrated by our work and the work of Christen-Zaech *et al.* (in which they found that normalization of NFCs and improvement of skin disease activity were associated with

a shorter duration of untreated disease and a unicentric course) [8]. The choice of treatment at diagnosis will become even more relevant as new agents for the treatment of JDM become available. For example, are there patients in whom B-cell depletion should be used as initial therapy? For patients at risk of a chronic course, we hope that early introduction of a therapy that controls disease more effectively will alter the ensuing disease course and reduce the risk of disease-related complications, but this has not been conclusively demonstrated.

Recent work has continued in the search for predictors of disease course in JDM and has included the discovery of a novel autoantibody, the anti-p155/140 kDa doublet protein. This autoantibody appears to be clinically significant in JDM and may define a subset of patients with more extensive skin disease and ulceration [12,13]. Muscle biopsy features may also provide important information regarding disease course. Severe intramuscular arteriopathy, the presence of nonregenerative muscle fibers and severe focal loss of capillary beds each increased the odds of having a chronic disease course in a retrospective study of 72 children [14].

Each study that attempts to find predictors of disease course adds valuable information to our understanding of this complex disease. The next step, we believe, is to design a multicenter collaborative study in which clinical and laboratory data are systematically collected, and candidate predictors are tested prospectively.

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#### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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