Filling the Gap: Toward a Disease Activity Tool for Systemic Juvenile Idiopathic Arthritis

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J Rheumatol 2018;45;3-5
http://www.jrheum.org/content/45/1/3

Editorial

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Systemic juvenile idiopathic arthritis (sJIA) accounts for 5%–15% of all children with chronic arthritis seen in Europe and North America, but is much more common in Asia, with reported frequency in India and Japan as high as 25% and 50%, respectively[1]. It is rather distinct from the other forms of JIA, owing to the association of arthritis with peculiar extraarticular symptoms, which include high-spiking fever, erythematous macular rash, diffuse lymphadenopathy, hepatosplenomegaly, and serositis, especially pleuritis and pericarditis[2,3]. Arthritis may be absent at onset and develop during the disease course, weeks, months, or rarely, years after the occurrence of systemic manifestations. Characteristic laboratory features include anemia (usually hypochromic and microcytic), leukocytosis, thrombocytosis, elevated immunoglobulins, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and hypoalbuminemia. Children with sJIA are uniquely susceptible to develop a potentially fatal hyperinflammatory complication known as macrophage activation syndrome[4].

Regular measurement of the level of disease activity in children with sJIA through the application of well-established tools is important in monitoring the disease course over time and in assessing the effectiveness of therapeutic interventions. However, clinical instruments specifically validated for use in sJIA are lacking. In recent randomized controlled trials of sJIA, the American College of Rheumatology Pediatric 30 criteria have been adapted for measuring therapeutic response by adding, besides the 6 core set variables, the demonstration of the resolution of fever (≥ 38°C) during the week preceding the evaluation[5,6] or of the absence of fever (≥ 38.5°C) in the previous 2 weeks, and the reduction of systemic corticosteroid dosage by at least 10% from baseline in patients taking these medications[7]. Published criteria for clinically inactive disease[8,9] and minimal disease activity[10] are suitable for use in sJIA. However, they are intended to define a particular disease activity state and do not allow quantitative estimation. In the last decade, the Juvenile Arthritis Disease Activity Score (JADAS) has gained increasing popularity for the measurement of the level of disease activity in children with JIA[11,12,13]. However, although the JADAS has been used in studies of sJIA[14], it has been validated only in children with oligoarthritis and polyarthritis, including sJIA without extraarticular features, but not in children with sJIA and active systemic manifestations[15].

Because systemic symptoms have a major influence on a child's well-being and play a key role in driving therapeutic decisions, any instrument used to assess the level of disease activity in sJIA must incorporate their assessment. Although these manifestations are partially recorded by the physician's and parent's/child's global assessment scales, there is currently no tool that enables their specific measurement. In the past, quantitative systemic feature scores have been devised[16,17] (Table 1), but none have been widely embraced.

In this issue of *The Journal*, Limenis, *et al*[18] report the results of the final phase of a 3-step process aimed to develop a tool to measure disease activity in sJIA. In the first step, 292 items relevant to disease activity were generated through interviews with 14 children with sJIA and their parents. The second stage consisted of a Delphi survey of international experts, which led to identification of the 29 most important indicators of disease activity in sJIA. The final step described in the present article was organized into the following 3 parts: (1) scrutiny of the metrologic performances of the 29 items in 57 patients recruited in 3 Canadian centers; (2) resurvey of experts with review of the data obtained in the validation study; and (3) proposal of a core set of disease activity measures.

A very detailed methodology was used to score disease activity in the study patients, which included an 18-item patient questionnaire, a 12-item parent questionnaire, the Childhood Health Assessment Questionnaire of physical disability, and a series of physician evaluations, consisting of the global assessment of disease activity (PGA) measured on a 10-cm visual analog scale (VAS), 10 clinical

See sJIA disease activity measures, *page 115*

Table 1. Composition and scoring of systemic feature scores published in the literature.

Woo, *et al*[16]		Vojinovic, *et al* [17]	
Feature	Score	Feature	Score
Fever*	1	Fever†	1
Rash	1	Rash	1
Cervical lymphadenopathy	1	Lymphadenopathy	1
Axillary lymphadenopathy	1	Hepatomegaly or splenomegaly	1
Inguinal lymphadenopathy	1	Serositis**	1
Hepatomegaly	1	ESR ≥ 20 mm/h	1
Splenomegaly	1	CRP ≥ 10 mg/l	1
Serositis**	1	WBC count ≥ 12 × 10^9/l	1
		Hemoglobin ≤ 11 g/dl	1
		Platelet count ≥ 400 × 10^9/l	1
Score range	0–8	Score range	0–10

*At the assessment visit or in the 24 hours preceding the assessment visit. ** Pericarditis, pleuritis, or peritonitis. † As documented in a diary. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell.

and laboratory items, and questions regarding changes to medications.

The PGA was used as a criterion standard for the study, and for some analyses patients were dichotomized into those with mildly active or inactive disease and with moderately to severely active disease, based on whether the VAS for the PGA was < 1.5 or ≥ 1.5, respectively. This cutoff was chosen arbitrarily because it was meant to be "clinically sensible" and allowed dividing the patients into 2 roughly equal groups.

For continuous variables (e.g., active joint count), the strength of association with the criterion standard was first determined by calculating Pearson correlation coefficient. Then, receiver-operating characteristic curves (ROC) were created for each item to calculate the optimal cutoff value and the overall diagnostic value. For dichotomous variables (e.g., presence or absence of rash), sensitivity and specificity were computed in relation with the dichotomized criterion standard. The results of this analysis were used to calculate the likelihood ratios for a positive test.

The results of the validation study were subsequently submitted to the same group of international experts surveyed in the earlier step of the process. Based on the review of these data and their own judgment, the experts were asked to select the 10 items that they felt were most relevant to disease activity. The PGA was excluded from the survey because it was used as a criterion standard. The response rate of 154/187 (82%) was remarkable.

The final core set of items for measuring disease activity in sJIA was set up by selecting the outcome variables that were assigned the highest number of expert votes and had a minimum Pearson correlation of 0.5 with the criterion standard. The core set includes 6 clinical measures (PGA, child's and parent's global assessments, active joint count, rash, and fever) and 3 laboratory tests (ESR, CRP, and hemoglobin). For continuous variables, the cutoff points calculated with the ROC method in validation analyses that correspond to moderately or severely active disease are provided.

The outcome variables included in the core set proposed by Limenis, *et al* appear appropriate because they are part of the classic indicators of disease activity in sJIA and were agreed upon by a large number of international expert pediatric rheumatologists. There is, however, a problem with the cutoff points for moderate/high disease activity, which seem too mild for a highly inflammatory illness such as sJIA. Examples are the values for CRP (> 5.5 mg/l), hemoglobin (< 119 g/l), and parent's and child's global assessments (> 0.9 cm and > 0.4 cm, respectively).

This shortcoming is partly due to the study design and the characteristics of the study population. Patients were recruited in routine followup visits rather than at initial presentation or during times of disease flare, and as a result had a low prevalence of systemic manifestations. Indeed, only 3 of them had fever, only 7 had rash, and chest pain, lymphadenopathy, splenomegaly, and hepatomegaly were each detected in only 1 patient (although all different patients). The paucity of extraarticular symptoms explains the poor sensitivity of these variables for higher disease activity. Another limitation of the Limenis, *et al* analysis is the use of a 2-week time frame to assess fever and rash, which appears too lengthy to evaluate these features in conjunction with disease activity at a particular clinic visit. In our opinion, a 1-week time frame would be more appropriate. As discussed, the cutoff chosen to dichotomize the PGA is arbitrary and subjective and not supported by literature evidence. A further problem with the proposed core set is that it only enables distinction of patients with inactive disease or mild disease activity from those with moderate or high disease activity, but is not suitable to quantify the absolute level of disease activity.

Despite these limitations, the authors are to be commended for accomplishing a valuable research effort and

for providing a core set of disease activity measures that may constitute the basis for the future development of response criteria specific for sJIA. A further important initiative in this area of research, which is currently in progress, is the international collaborative effort aimed to devise a JADAS version for sJIA. In the study plan, a modification of the original instrument has been envisioned to enable the quantification of extraarticular symptoms, with an approach similar to that of the systemic feature scores reported in Table 1. A key objective of the project is the establishment of the cutoffs in the new score that correspond to the states of inactive disease and low, moderate, and high disease activity in sJIA.

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J Rheumatol 2017;44:3–5; doi:10.3899/jrheum.170703