Persistent Elevation of Fibrin D-Dimer Predicts Longterm Outcome in Systemic Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** We previously demonstrated that levels of fibrin d-dimer correlate with disease activity and response to therapies in systemic juvenile idiopathic arthritis (sJIA). We hypothesized that persistence of D-dimer elevation in the patterns previously described, but over a longer followup period, would signal poor outcome.

Methods. We studied 31 children identified from 2 centers. Subjects were assigned a risk category based on their first obtained D-dimer concentration. Risk categories were based on results of our initial study, where normalization of D-dimer in patients no longer taking immunosuppressive therapy predicted good short-term outcome, and persistent D-dimer elevation while taking immunosuppressives predicted bad outcome (radiographic abnormalities, joint replacement surgery, or poor functional class) or a severe systemic manifestation. Outcome was determined at the last followup visit, a minimum of 2 years after measurement of the initial d-dimer level.

Results. The 31 children were a mean 16.4 years old at an average of 8.8 years after their initial diagnosis. Ten children had a severe outcome during this period; all 10 had a study baseline risk category of "high." Of the 14 subjects who had a high risk category at study baseline, none had a mild outcome.

Conclusion. Our study indicated that a paradigm of risk of severe disease based upon persistent elevation of fibrin d-dimer on first measurements (greater than a mean of 29 months in our initial study and at least 24 months in the additional subjects) is promising to predict poor longer-term outcome in sJIA. A larger prospective study is warranted to substantiate the preliminary data and assess the relative comparative value to other biomarkers and clinical endpoints. (First Release Dec 1 2008; J Rheumatol 2009;36:422–6; doi:10.3899/jrheum.070600)

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The systemic form of juvenile idiopathic arthritis (sJIA) poses a formidable challenge to the clinician. It is difficult to predict longterm disease course and outcome based on the initial disease presentation and early course; many patients have a self-limited condition, which can resolve without sequelae. However, a large percentage of these children develop chronic arthritis, and many of these have particularly severe, debilitating, destructive joint disease. Further, severe systemic manifestations such as pericarditis and the "macrophage activation syndrome" may be life-threatening[1].

Attempts have been made at developing useful prognostic biomarkers in JIA. Perhaps the most extensively studied are the proposed prognostic criteria of Schneider, *et al*[2-4], who determined from observation of a large cohort of children with sJIA that those who continued to have thrombocytosis or active systemic features at 6 months after diagnosis had the worst prognosis for developing arthritis-related disability or continuing to have active systemic features at a mean of 7.7 years later. The same authors had earlier established that these criteria predicted articular damage. These practical and easily determined factors have aided pediatric rheumatologists in targeting such children for early aggressive treatment to prevent adverse outcomes. Sandborg, *et al* attempted to improve upon the prognostic value of such criteria by using an innovative combination of classification-tree analysis and multiple logistic regression analysis of potential clinical predictors (determined *a priori* by consensus of several pediatric rheumatologists) of sJIA-related joint damage 2 years after diagnosis. A phenotype combining an active joint count of at least 13 and a platelet count of

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at least 788,000/mm^3 had a relatively high sensitivity (87%), specificity (82%), positive predictive value (87%), and negative predictive value (80%). Although this approach is innovative and well refined by scientific methodology, it would, as the authors point out, potentially lead to overtreatment of 20% of those predicted to progress[5].

Thus, the significant dilemma of diverse potential outcomes of this condition and lack of associated prognostic markers remains. We and others have theorized that biomarkers more closely tied to the pathophysiology of sJIA could potentially predict disease course, response to therapies, and outcomes[6-14]. We reported that D-dimer levels, a potential reflection of the extreme degree of endothelial activation that occurs in sJIA, did relate to clinical disease course and response to immunomodulatory medications. We thus hypothesized that levels of D-dimer would predict longterm outcome in children with sJIA[15].

MATERIALS AND METHODS

Subjects. This was a retrospective cohort study of 31 children with systemic JIA from 2 centers in the northeastern USA, Floating Hospital for Children, Boston, MA (Center A), and Hasbro Children's Hospital, Providence, RI (Center B). Twenty-two of these subjects (all from Center A) were described in the previous report of D-dimer in sJIA, and were followed for a minimum of an additional 2 years. Nine additional subjects (all from Center B) who had at least 2 years of followup from the time of their initial diagnosis were also studied. Subjects were accrued consecutively within each center. All subjects were assigned a risk category based on their status at the time they were first evaluated for D-dimer concentration (study baseline). Risk categories were based on results of our initial study[15], where normalization of D-dimer in patients no longer taking immunosuppressive therapy (including corticosteroids) predicted good short-term outcome, and persistent elevation of D-dimer in patients continuing immunosuppressive therapy (mean followup of 29 months, range 6–66 months) predicted bad outcome or a severe systemic manifestation at that time. "Low risk" was defined as having no detectable D-dimer and taking no immunosuppressive/immunomodulatory medications. "Medium risk" was defined as having undetectable D-dimer, but still requiring immunosuppressive /immunomodulatory medications for control of arthritis or systemic features. "High risk" was defined as having an elevated D-dimer level despite taking immunosuppressive/immunomodulatory medications (defined as oral or intravenous corticosteroids in a regular dosing regimen, methotrexate, intravenous immunoglobulin, sulfasalazine, or azathioprine in the original cohort; in the current study, biologic therapies and cyclosporine A were also included).

Outcome was classified in the following manner. An outcome category was based on (1) progression of arthritis-related radiographic lesions by retrospective, unblinded review of radiographic data; (2) presence of systemic features or their response to therapy at the time of followup; and (3) Steinbrocker functional class at the time of followup. Radiographic findings associated with arthritis were prespecified as erosions, bone cysts adjacent to the joint space, or narrowing of the joint space. For the systemic-features category, "inactive" refers to known fever, rash, or other systemic manifestation (e.g., pericarditis), "NSAID or low-dose prednisone" refers to control of systemic features with regular daily dosing of a nonsteroidal antiinflammatory drug or prednisone in a dosage ≤ 0.2 mg/kg/day (to a maximum of 10 mg daily), and "steroid-dependent" means either current systemic features despite, or flare of these features with tapering below prednisone in a dosage > 0.2 mg/kg/day or > 10 mg daily. Placement of a new prosthetic joint due to arthritic changes was deemed a surrogate for the "severe" radiographic category. Assignment to an outcome category was based on the most severe manifestation in any of the 3 categories; thus, for example, if a child had a "severe" radiographic finding, she or he was assigned to the "severe" outcome category, even if the rating for the other 2 categories was moderate or severe.

Laboratory indicators. Determination of D-dimer levels. D-dimer values were determined as follows: by Method A in Center A (22 subjects) for the duration of the study period; for Center B (9 subjects), Method A was used until mid-2000, when it was switched to Method B.

Method A: Levels of D-dimer were determined using a commercial semiquantitative latex agglutination assay (Fibrinosticon; Organon Teknika, Boxtel, The Netherlands). The assay utilizes latex particles coated with a monoclonal antibody specific for the D-dimer domain. Levels of D-dimer were determined in semiquantitative fashion based on the maximum dilution of patient plasma at which agglutination was noted. These dilutions were then assigned a range of values of fibrinogen equivalents in ng/dl (no agglutination was assigned a level of < 0.5 ng/dl, agglutination of undiluted plasma was assigned a level of 0.5–2.0 ng/dl, agglutination of 1:2 diluted plasma was assigned a level of 2–8 ng/dl, and agglutination of plasma diluted 1:4 or more was assigned a level of > 8.0 ng/dl). For our data analysis, these levels were classified as no elevation, mild, moderate, or severe elevations, and were assigned scores of 0, 1, 2, or 3, respectively.

In late 2000, a modification of the same assay was developed that subdivided the 0.5–2.0 ng/dl category into 0.5–1.0 and 1.0–2.0 ng/dl. Any test that yielded either value was considered to be equivalent to 0.5–2.0 ng/dl under the previous scoring system. This assay also determined a new upper limit of sensitivity to be > 4 ng/dl. Any result determined to be > 4.0 ng/dl was classified as if it were > 8.0 ng/dl under the previous scoring system.

Method B: D-dimer was determined using the MDA D-dimer kit (BioMerieux, Marcy l'Etoile, France), a quantitative homogeneous-phase immunoassay using latex particles to photooptically detect binding of specific monoclonal antibody to D-dimer. These latex particles aggregate in the presence of fibrin derivatives containing the D-dimer domain. The rate of latex microparticle aggregation is proportional to the concentration of D-dimer in the sample. D-dimer concentration was then interpolated from a reference curve.

Radiography. All radiographs were performed at each respective center and interpreted by a pediatric radiologist experienced in reading skeletal radiographs of children with JIA, at the time they were obtained as part of usual medical care, and reviewed retrospectively at the time of completion of this study (summer 2002) by a pediatric rheumatologist in conjunction with a pediatric radiologist at each center. All radiographs were interpreted using standard techniques.

RESULTS

Patient demographic data are given in Table 1. In brief, there were roughly equal numbers of girls and boys, whose mean age was 16.4 years at followup, which occurred after a mean of 8.8 years of disease activity. At followup, 26/31 (84%) evaluable subjects were still receiving arthritis treatment (Table 1).

Clinical outcome. The results when subjects' initial D-dimer risk category was compared to subsequent disease course are given in Table 2A. Of 10 patients with severe outcomes, 6 had severe radiographic change (major erosions, major joint space narrowing, cystic changes, fusion), 5 had joint replacement surgery, 5 were corticosteroid-dependent for active systemic features, and 5 were Steinbrocker functional class III or IV.

Thus, the relationship of "high-risk" category to severe outcome was found to have a sensitivity of 10/10 (100%), positive predictive value of 10/14 (71%), and negative pre-

Table 1. Patient demographic data.

Total no. of subjects	31
Boys/girls	14/17
Age at followup, yrs, mean (range)	16.4 (6–25)
Disease duration at followup, yrs, mean (range)	8.8 (2.5–22)
Disease features at initial measurement, n (%)	
Active systemic features	29 (94)
Active arthritis	30 (97)
Disease features at followup, n (%)	
Active systemic features	7 (23)
Active arthritis	17 (55)
Medications at followup (no. patients)	
NSAID (total users)	26
NSAID only	9
Any immunomodulatory medication	17
Prednisone	8
Methotrexate	9
Cyclosporine	2
TNF inhibitors	3
None	5

NSAID: nonsteroidal antiinflammatory drug.

dictive value of 17/17 (100%). No subject in the high-risk category had a mild outcome, and no one in the mild-outcome group had been in the high-risk group.

It is possible that our results could have been confounded by differing results in the 2 different centers due to differing referral patterns, treatment paradigms, or patient demographic factors. Thus, we also separated results by center as shown in Table 2B ("original" patients from Center A, and subsequent patients from Center B). Subjects from the original sample showed a trend toward having been classified as "medium-risk" at the time of the first D-dimer determination (10/20 at Center A vs 1/9 at Center B; $p = 0.096$ by Fisher's exact test). For all subjects from both centers, medium-risk patients mostly had good outcomes (8/11), although the remaining 3 (all at Center A) had moderate outcomes.

Also, as the disease course and progression could affect the results, and because perhaps the highest potential utility of this candidate biomarker is to predict early in the disease course who will progress to more severe disease, we also divided results by time since diagnosis at the time the initial D-dimer level was obtained. These results, based on whether the initial D-dimer level was measured less than or more than 1 year since diagnosis, are presented in Table 2C.

We made the following observations based on our data. (1) The group that was more remote in time from onset at first determination contained proportionally more "high-risk" patients, 9/10 of whom had a severe outcome on followup. The remaining patient had a moderate outcome (there was no patient with a good outcome in this subgroup). (2) No "low-risk" patients had a severe outcome, regardless of duration since onset at first determination (only 1/5 had a moderate outcome). (3) "Medium-risk" patients were more common in the group with measurement at earlier duration since onset; 6/9 of this subgroup had a mild outcome, but 3 had a moderate outcome.

Table 2A. Subjects' initial D-dimer risk category compared to subsequent disease course. Of those 10 patients with severe outcomes, 6 had severe radiographic change.

	Outcome			
Risk Category	Mild	Moderate	Severe	Total
Low	5	0	0	5
Medium	8	4	0	12
High	0	4	10	14
Total	13	8	10	31

Table 2B. "Original" patients from Center A, subsequent patients from Center B.

	Center A: Outcome			
Risk Category	Mild	Moderate	Severe	Total
Low	2	0	0	2
Medium	7	3	0	10
High	0	3	5	8
Total	9	6	5	20
	Center B: Outcome			
Low	2	0	0	2
Medium	1	0	0	1
High	0	0	6	6
Total	3	0	6	9

Table 2C. Results based on whether initial D-dimer level was measured less than or more than 1 year since diagnosis.

	> 1 Year from Onset: Outcome			
Risk Category	Mild	Moderate	Severe	Total
Low	1	0	0	1
Medium	2	1	0	3
High	0	1	9	1
Total	3	2	9	14
	≤ 1 Year from Onset: Outcome			
Low	3	1	0	4
Medium	6	3	0	9
High	0	2	2	4
Total	9	6	2	17

DISCUSSION

Our report suggests that children with sJIA who have persistent elevation of D-dimer over several initial measurements, especially despite aggressive therapies, have high likelihood of a more severe longer-term outcome. As proposed for prognostic criteria by Schneider, *et al*[2-4], this simple blood test may aid the clinician in targeting specific patients earlier in their disease for more intensive therapy. Earlier, intensive therapy in rheumatoid arthritis has been well demonstrated to correlate with better outcomes in radiographic progression and physical functioning. Such defini-

tive data have been scarce in JIA, and especially sJIA, yet are assumed to be effective by many pediatric rheumatologists[1,16,17]. Indeed, pediatric rheumatology has promoted the development of remission criteria in order to facilitate the use of that endpoint as a goal in future clinical trials[18].

Based on previous data we believe that endothelial activation is a key component in the pathogenesis of sJIA. For example, we previously noted that the soluble forms of the adhesion molecules ICAM-1 (found primarily in endothelium) and E-selectin (specific to endothelium) are elevated in children with active sJIA as compared to healthy age-matched controls and those with other JIA subtypes. Elevation of D-dimer was correlated with elevation of sICAM-1[9]. We also found levels of the same adhesion molecules to be elevated in synovial fluids of children with all sJIA subtypes; levels were highest in those with the highest synovial fluid leukocyte counts, who tended to have sJIA[19]. We have also noted that all children tested with sJIA had antiendothelial cell antibodies (AECA), and in titers higher than those seen in other JIA subtypes; all controls were negative for AECA[20]. In other conditions that involve extreme endothelial activation, such as Takayasu arteritis, such AECA have been found to be pathogenic by inducing endothelial cell apoptosis[21-23]. We had previously found that levels of fibrin D-dimer correlated with short-term outcome and response to immunomodulatory therapies in patients with sJIA. Further, Factor VIIa, which is activated by tissue factor, initiates the fibrinolytic pathway that produces fibrin D-dimers, and this factor is elevated in patients with sJIA[8]. Because proinflammatory cytokines including tumor necrosis factor-α, interleukin 1 (IL-1), and IL-6 are known to be highly elevated in sJIA[24-26] and to induce tissue factor expression[11], we theorized that the high levels of D-dimer seen in active sJIA are a result of cytokine induction of endothelial activation, including tissue factor expression. This phenomenon has been documented in adult rheumatoid arthritis[27] and in *in vitro* endothelium-based models[28,29]. In support of this concept, in a prospective study of an experimental IL-1 inhibitor, rilanocept, subjects with sJIA had a dramatic reduction in D-dimer concentration that correlated well with decreased disease activity[30].

Relative weaknesses of this study include the following. (1) The data from this retrospective review could have been biased by multiple factors. Treating pediatric rheumatologists were not blinded to D-dimer results, which could have led to changes in treatment on the basis of those results. (2) Radiographic data were based on radiologist's subjective clinical opinion at the time the radiographs were obtained in the course of normal clinical practice; thus, no standardized scoring methods were used, such as the Poznanski score, or adult RA scales that have since been validated in children, such as the Larsen or Sharp scores[31,32]. However, the radiographs were interpreted by a pediatric radiologist experienced in the review of studies from pediatric arthritis patients and re-reviewed with at least one of the pediatric rheumatologist authors present. Findings also were consistent with typical radiographic abnormalities seen in systemic JIA[33]. It is possible that "moderate-risk" patients may really have been at the borderline of "mild" or "severe" and that another observer would have put them into one of those categories. However, all 8 of the moderate-risk subjects also met objective clinical criteria that placed them into this category. (3) Identical D-dimer assays were initially used at each center; however, during the last 2 years of the study period, each center changed its assay (thus producing different assays at each center, both of which differed from the original). Although results derived from different assays generally perform similarly in general clinical use and correlate well, with similar amounts of fibrinogen equivalents as determined by other sensitive assay techniques such as the enzyme immunoassay (BioMerieux assay package insert), it is possible that the changes render the results insufficiently comparable for research purposes.

Nonetheless, theoretically, as D-dimer is more closely tied to the pathogenesis of sJIA, it is possible that it more accurately reflects disease activity and prognosis than clinical features. However, it is likely that the highest potential utility of such a test would be in predicting future course early in the disease. Because the design of our pilot study did not allow comparisons against other well established clinical tests, prognostic criteria and disease features, was not blinded, and was retrospective, further study will be necessary to determine the role of the D-dimer test in clinical practice and clinical trials.

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