Evaluation of the Presentation of Systemic Onset Juvenile Rheumatoid Arthritis: Data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR)

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ABSTRACT. ***Objective.*** To characterize the initial clinical and laboratory features of patients with systemic onset juvenile rheumatoid arthritis (soJRA) through a Web-based registry.

Methods. Patients diagnosed with soJRA in the last 15 years at 3 medical centers in Pennsylvania were identified. Data were collected retrospectively using a Web-based interface in compliance with patient privacy standards. Inferential statistics were used to compare features of patients with and without macrophage activation syndrome.

Results. We identified 136 patients; 88% of patients presented with arthritis (8% mono-, 45% oligo-, 47% polyarticular). The most common joints involved were the knee (68% of patients with arthritis), wrist (68%), and ankle (57%). The International League of Associations for Rheumatology criteria for systemic juvenile idiopathic arthritis (SJIA) identified only 30% of patients at presentation.

Conclusion. We successfully characterized the presenting features of a relatively rare disease, soJRA, through the use of a Web-based registry. Current classification criteria for SJIA may not be particularly sensitive for diagnosis at presentation. (First Release Dec 15 2007; J Rheumatol 2008;35:343–8)

Key Indexing Terms:
SYSTEMIC ONSET JUVENILE RHEUMATOID ARTHRITIS — WEB-BASED REGISTRY
SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS — CLASSIFICATION

Systemic-onset juvenile rheumatoid arthritis (soJRA) is defined by 6 weeks of arthritis accompanied by daily or twice-daily intermittent fever for at least 2 weeks in a child less than 16 years of age, in the absence of an identifiable underlying etiology[1]. This definition is currently being supplanted by the newer International League of Associations for Rheumatology (ILAR) criteria, which more strictly define the quotidian nature of the fever and require the presence of at least 1 of the other 4 characteristic systemic signs: rash, generalized lymphadenopathy, organomegaly, or serositis[2]. Since the ILAR criteria did not come into common use in the United States until quite recently, retrospective studies such as this one still make use of the soJRA criteria.

soJRA is usually accompanied by laboratory evidence of inflammation, including elevated erythrocyte sedimentation rates (ESR), neutrophilia, and thrombocytosis. The nonspecific nature of these signs and symptoms make the diagnosis difficult. The diagnosis is one of exclusion, requiring that the plethora of other entities that share these signs and symptoms be ruled out before the diagnosis of soJRA is given and treatment initiated[3].

The presentation of soJRA is protean. Some patients do not develop arthritis until weeks to months after systemic symptoms begin. Others present with atypical fever patterns, or lack any systemic features besides the fever. The presentation of soJRA may be complicated by the presence of clinical macrophage activation syndrome (MAS). MAS may result in

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a lower ESR, and relative neutropenia and thrombocytopenia compared to patients with soJRA presenting without clinically evident MAS[4]. Thus, the diagnosis of soJRA, particularly at onset, can be challenging.

soJRA composes only 10%–20% of all diagnoses of JRA, and therefore collecting large numbers of patients to allow for an accurate description of the presentation of soJRA is difficult. To address this, we created an Internet-based data collection system for patients diagnosed with soJRA in the state of Pennsylvania over the last 15 years. Using the data collected through this system, our primary aim was to characterize the clinical and laboratory features at presentation of soJRA to improve the accuracy of diagnosis.

MATERIALS AND METHODS

Participating institutions identified patients with a diagnosis of soJRA seen at their clinic from 1990 to 2005 from their individual patient databases. Three of 4 academic centers with pediatric rheumatologists in the state of Pennsylvania participated in the study. Diagnoses were confirmed and data collected by a retrospective chart review of these identified patients. Patients were included based on the diagnosis of soJRA made by an attending pediatric rheumatologist as recorded in the patient chart. Data from the first encounter with the rheumatologist were collected (regardless of whether soJRA criteria were met at that time). Patient data were collected in accord with and with the approvals of the institutional review boards of all 3 institutions. Data were entered into the database using a Web-based interface, with validation of data for completeness and consistency performed at the time of entry. Incompletely filled out forms or inconsistent data were not allowed; the option to list data as not available was present. The Web application was written using PHP 5.0 and the database software was mySQL 3.23. Beta testing of the written software was performed at one site (The Children's Hospital of Philadelphia) prior to formal data collection. Statistical analysis was performed using Stata 9.0 (Stata Corp., College Station, TX, USA). Laboratory values were compared using the Wilcoxon rank-sum and Fisher's exact tests where appropriate.

RESULTS

Demographics of patients with soJRA. One hundred thirty-six patients from 3 academic pediatric rheumatology clinics in the state of Pennsylvania (64 from The Children's Hospital of Philadelphia, 35 from Pennsylvania State Hershey Medical Center, 37 from Children's Hospital of Pittsburgh) were entered into the registry. As expected from the previous literature we did not find any significant sex bias among patients with soJRA[5]; 54% of patients were female. The age at presentation had a broad peak between 0 and 5 years of age, with 2 years being the most common (Figure 1). Eighty-two percent of the patients in the cohort were Caucasian, with African Americans (14%) representing the second most common group, reflecting the ethnic makeup of the state of Pennsylvania, based on the 2000 U.S. Census[6]. Fifty patients (37%) lived more than 50 miles from their medical center, and most (83%) patients had some form of private insurance.

Clinical characteristics at presentation. The symptoms at the time of initial presentation are documented in Figure 2A. Fever (98%), arthritis (88%), and rash (81%) were the most common symptoms, followed by 31% of patients presenting

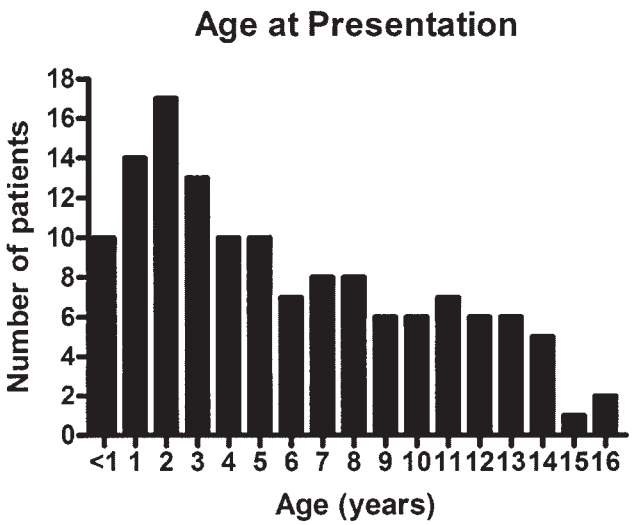

Figure 1. Age at presentation of patients with soJRA. A broad peak between age 0 and 5 years defines the most common age of presentation for soJRA.

with lymphadenopathy. Few patients presented with organomegaly, and only 10% had pericarditis at the time of diagnosis. These findings are consistent with a report from a cohort of patients from the United Kingdom, France, and Spain[7]. In Pennsylvania, the pattern of arthritis in affected patients was split equally between oligoarticular (< 5 joints involved) and polyarticular (> 4 joints involved). A small minority of patients with arthritis presented with a single joint involved (Figure 2B). The most common joints involved in those patients with arthritis at presentation were the knee, wrist, and ankle (Figure 2C). The small joints of the hand and elbow were the next most common joints involved, followed by the shoulder, hip, and small joints of the foot. Arthritis of the cervical spine was found in 13% of patients at presentation, and sacroiliitis was present in only one patient of the 136 in the cohort. Although 98% of patients had fever at presentation, the pattern of fever showed considerable variability: 12% of the children had daily morning fevers, 37% had daily evening fevers, 15% had twice daily fevers, 27% had intermittent fevers (defined as periods of febrility and afebrility with regular periodicity), and 5% had continuous fevers (defined as an unremitting fever during the time of presentation).

Using the ILAR criteria for SJIA[2], only 42/136 (30%) patients fulfilled criteria for diagnosis at their initial presentation to a pediatric rheumatologist. The reasons for failure to meet criteria, as well as the number of patients in each category of failure, are listed in Table 1. Importantly, all 48 patients in the category meeting criteria for both arthritis and at least 1 out of the 4 minor criteria had fever documented. However, since the fever was not of a quotidian pattern or was not greater than 39°C, they did not meet ILAR criteria. The most common pattern of fever in this group of patients with arthritis and at least 1 of 4 additional criteria was an intermittent pattern (26/48, 54%). We did not consider the exclusion criteria as the necessary data were not available to us; how-

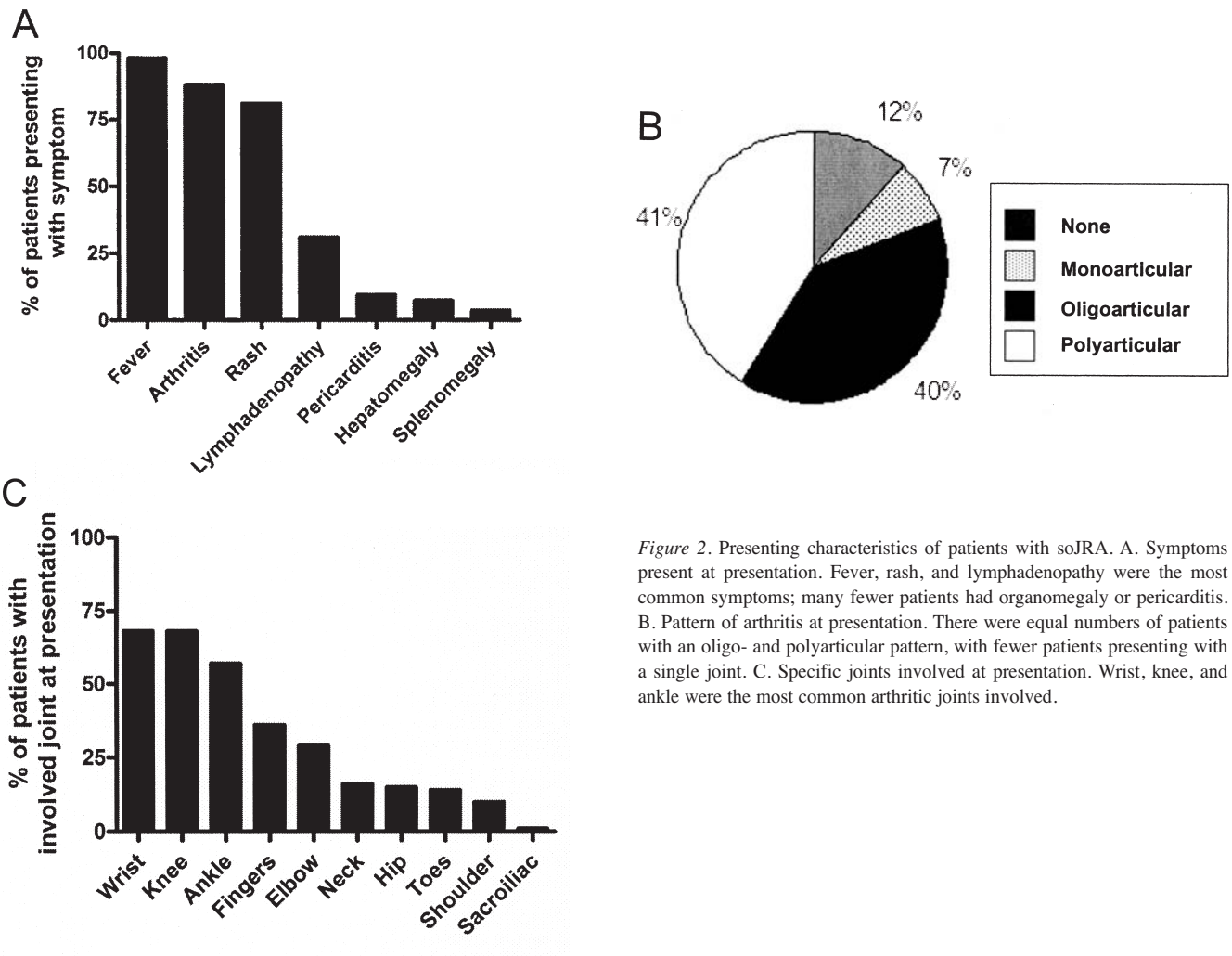

Figure 2. Presenting characteristics of patients with soJRA. A. Symptoms present at presentation. Fever, rash, and lymphadenopathy were the most common symptoms; many fewer patients had organomegaly or pericarditis. B. Pattern of arthritis at presentation. There were equal numbers of patients with an oligo- and polyarticular pattern, with fewer patients presenting with a single joint. C. Specific joints involved at presentation. Wrist, knee, and ankle were the most common arthritic joints involved.

Table 1. ILAR criteria met by patients not satisfying full criteria.

ILAR Criteria for SJIA were Met	No. of Patients Failing Criteria (% of total of 94)
None	4 (4)
No. 1 only	4 (4)
No. 2 only	16 (17)
No. 3 only	5 (5)
No. 1 and 2	14 (15)
No. 1 and 3	3 (3)
No. 2 and 3	48 (51)

No. 1: quotidian fever with maximum temperature > 39°C. No. 2: arthritis. No. 3: at least 1 of the following: evanescent erythematous rash, generalized lymph node enlargement, hepatomegaly and/or splenomegaly, or serositis. All 3 items must be satisfied for the ILAR diagnosis of SJIA. ILAR: International League of Associations for Rheumatology; SJIA: systemic juvenile idiopathic arthritis.

ever, this would only have further decreased sensitivity. By comparison, using the 1986 American College of Rheumatology soJRA criteria, 81/136 (60%) patients met full criteria at initial evaluation.

Laboratory abnormalities at presentation. The vast majority of patients had laboratory evidence of systemic inflammation at the time of presentation (Table 2). Ninety-five percent of patients evaluated had an elevated Westergren ESR (mean 78 mm/h), and 96% (54/56) of patients evaluated had C-reactive protein (CRP) greater than normal. The median white blood cell (WBC) count was 17.6×10^3 cells/μl, and platelet counts were elevated with a median of 539×10^3 cells/μl. Most patients also had a mild anemia, with a median hemoglobin of 10.1 g/dl. About one-quarter of patients presented with elevated liver transaminases: ALT > 2× normal in 16% of those evaluated (18/114), AST > 2× normal in 25% of those evaluated (29/117). Elevated serum ferritin levels (> 500 ng/ml) were present in 70% of patients evaluated (46/66), 83% (23/29) had elevated D-dimers, and 73% (19/26) of patients had an aldolase above normal at the time of presentation.

Because not all patients were evaluated for these markers, we examined the subsets of patients tested for each laboratory value for differences in presentation from patients not tested. No differences were found between patients tested for D-dimers or aldolase and those patients who did not have these

Table 2. Laboratory values at presentation.

Laboratory Test (cutoff value)	Median (IQR)	Percentage of Patients Above Cutoff
ESR (20 mm/h)	76 (47)	95 (128/135)
CRP (> 1 × normal)	NA	96 (54/56)
WBC (10^3 cells/μl)	17.6 (12.8)	NA
Hgb (g/dl)	10.1 (2.4)	NA
PLT (10^3 cells/μl)	539 (282)	NA
ALT (70 U/l)	24 (37)	25 (18/114)
AST (65 U/l)	37 (36)	15 (29/117)
D-dimer (> 1 × normal)	NA	83 (24/29)
Ferritin (500 ng/ml)	1539 (4228)	70 (46/66)
Aldolase (9.9 U/l)	11.1 (8.4)	73 (19/26)
Triglyceride (200 mg/dl)	103 (98)	18 (3/17)

IQR: interquartile range; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cells; NA: not available.

tests including age, sex, fever, rash, arthritis, organomegaly, ESR, CBC, ALT, AST, stay in an intensive care unit, or performance of a bone marrow biopsy. Patients who had a ferritin test were more likely to have been admitted to an intensive care unit (8/66 vs 0/70; p = 0.002, Fisher's exact test), or to have had a bone marrow biopsy (22/66 vs 6/70; p = 0.0004, Wilcoxon rank-sum test). Although this suggests that patients with ferritin levels may have had more severe disease, 49% of the cohort (66/136) had a ferritin performed. Further, all other measures tested were the same between the group of patients with ferritin tests and those without. This leads us to believe that although there may be a slight bias in patients with ferritin tests, these results are likely generalizable to soJRA at large.

Hemophagocytosis at time of presentation. Clinically evident MAS at the time of presentation can cloud the diagnostic picture due to alterations in laboratory values. For example, while a high ESR, neutrophilia, and thrombocytosis are features of soJRA, MAS may be characterized by a low ESR and normal, or low, WBC and platelet counts. The pathologic correlate to clinical MAS is the presence of hemophagocytosis on bone marrow examination. We investigated whether children with hemophagocytosis in their bone marrow aspirates at presentation were different from those without hemophagocytosis. Bone marrow aspirates/biopsies were performed on 28 patients at time of presentation (21%). Twelve (42%) of these biopsies were read as positive for hemophagocytosis. This represents about 8% of the entire cohort. Consistent with the presence of clinical MAS, patients with hemophagocytosis in their bone marrow aspirates had lower ESR than patients without hemophagocytosis (median 60 and 100 mm/h, respectively; p = 0.03, Wilcoxon rank-sum test). Further, patients with hemophagocytosis had a lower WBC than patients without (median 17.8 and 25.5 × 10^3 cells/μl, respectively; p = 0.05, Wilcoxon rank-sum test). Interestingly, patients with and without hemophagocytosis in their marrow both had elevated ferritin and D-dimers, with no differences between the groups (p = 1.0 and p = 0.53, respectively, Fisher's exact test; Table 3). Patients with hemophagocytosis in their bone marrow were more likely to be in remission as defined by absence of arthritis or systemic symptoms at their last visit (43% vs 92%; p = 0.02, Fisher's exact test). Most of the remissions in the group with hemophagocytosis were still taking medications (8/11).

DISCUSSION

Diagnosing soJRA can be difficult due to the lack of specific biomarkers, the variable presentation, and the overlap of its symptoms with many other illnesses. These difficulties can result in a delay of diagnosis while the disease process develops until the clinician can recognize the symptom complex of soJRA. Utilizing the data from our registry of 136 patients, we have described the typical features of soJRA at the time of initial presentation. To our knowledge, this is the second largest cohort of soJRA patients in the literature[5]. Although the peak age is between 0 and 5 years, children continue to present at a steady rate until mid-adolescence. In particular, the diagnosis should still be considered in children earlier than one year of age, although earlier presentation may raise suspicion for other entities such as familial hemophagocytic lymphohistiocytosis[8]. Although the classic description of the quotidian fever is a high spiking fever each evening[3], surprisingly few patients had this pattern upon presentation (37%). Indeed, 32% of children presented with fevers that did not have a regularly repeating pattern. Because the quotidian pattern of fever is part of the ILAR criteria, 43 patients (31%) who would otherwise have been correctly labeled as SJIA at presentation did not meet ILAR criteria. Although fever was almost uniformly present at disease onset (Figure 2A), its pattern was highly variable. Since our study was not designed to test a set of classification criteria, we do not intend to propose a new standard. Rather, these data serve to reinforce that the

Table 3. Comparison of patients with and without hemophagocytosis on bone marrow biopsy.

Hemophagocytosis	Median ESR, mm/h	Median WBC, 10^3 cells/μl	D-dimer > 1× normal (%)	Ferritin > 500 ng/ml (%)	Median Ferritin, ng/ml	No. of Patients in Remission at Last Visit (%)
Absent, n = 16	100*	25.5**	7/9 (78)	11/13 (85)	3279	7 (44)***
Present, n = 12	60*	17.8**	2/4 (50)	7/9 (78)	2627	11 (92)***

* p = 0.03, Wilcoxon rank-sum test. ** p = 0.05, Wilcoxon rank-sum test. *** p = 0.02, Fisher's exact test. ESR: erythrocyte sedimentation rate; WBC: white blood cells.

ILAR criteria were developed as a research tool; thus, reliance on them for diagnostic purposes is not only a misuse of their original purpose, but also a pitfall for possible missed or delayed diagnosis.

Arthritis is also quite common at presentation (88%, Figure 2A), and the pattern of arthritis at the onset of soJRA occurs in a distinctive pattern. Wrist, knee, and ankles are by far the joints most commonly affected at presentation. This is in contrast to pauciarticular JRA, where the wrist is affected in 1% of patients with monoarticular disease, and only represents 4% of all arthritic joints in this condition[9]. The sacroiliac joint is the least involved in soJRA; indeed, the combination of back pain and systemic symptoms should raise the suspicion of malignancy as opposed to soJRA[10]. Although the wrist, knee, and ankle seem to be common to most patients, the number of involved joints is variable. Equal numbers of children presented with an oligoarticular pattern as with a polyarticular pattern. This is in distinction to data from a UK cohort where twice as many patients presented with an oligoarticular pattern[7]. This difference may be reflective of other differences in disease expression between European and North American patients with soJRA, such as the general lack of amyloidosis in North American patients[11]. Presentation with a single involved joint was much less common (7%), and 12% of patients did not have any arthritis at presentation. Thus, although the lack of arthritis at initial presentation does not rule out the possibility of soJRA, the majority of children will have more than one joint involved at the onset of their illness.

Laboratory markers are other useful diagnostic tools, although somewhat nonspecific for helping to make the diagnosis of soJRA. Patients with soJRA present with markers of systemic inflammation in their laboratory values, evidenced by high ESR and CRP[7], and neutrophilia, anemia, and thrombocytosis are found in the complete blood count. We identified other shared laboratory abnormalities in these patients, as well. In particular, patients with soJRA present with increased ferritin levels. This may be a response to the augmented interleukin 1ß (IL-1ß) signaling that is increasingly being recognized in patients with soJRA, since IL-1ß increases ferritin mRNA translation[12,13]. We also confirmed that patients with soJRA present with elevated D-dimers, even at disease onset[14]. Interestingly, elevated aldolase, most likely reflecting liver involvement, was found in 73% of patients tested. Although elevated aldolase has been reported in a series of 16 patients with adult-onset Still's disease[15], to our knowledge, this has not been previously reported in soJRA. Thus, while elevated inflammatory markers remain a nonspecific finding of soJRA, the combination of high serum ferritin, elevated D-dimers, and elevated aldolase may provide additional context to allow the clinician to make the diagnosis.

MAS, a form of secondary hemophagocytic lymphohistiocytosis, is a serious complication of the systemic inflammation of soJRA. Its presence can confuse the diagnosis of soJRA since patients with clinical MAS may have a normal ESR, and lower than expected or declining cell counts on the CBC[16]. Indeed, the patients in our study who had hemophagocytosis on bone marrow examination, consistent with clinically evident MAS, did have lower WBC and ESR than those with a normal marrow.

We recently reported that the majority of patients with soJRA who underwent bone marrow examination showed evidence of hemophagocytosis, despite the absence of other clinical signs of MAS[17]. Indeed, many marrows initially read as normal were found to have more subtle hemophagocytosis upon closer review. We suggested that soJRA simply represents "occult" MAS, and as the disease becomes more severe, the patient presents as "clinical" MAS. Accordingly, in the data set presented here, we found no difference in ferritin levels or D-dimers in patients with hemophagocytosis on bone marrow examination compared to patients without. Since elevated ferritin and D-dimers have traditionally been associated with MAS, these laboratory values may suggest "occult" MAS in these patients. It is possible that with closer inspection, or with the use of immunohistochemical markers such as CD163[17-19], these negative bone marrows might show evidence of hemophagocytosis that was not appreciated on the initial evaluation. The general finding of elevated ferritin and D-dimers among all patients with soJRA, even in those that did not have bone marrow aspirates performed, also extends the concept of occult MAS to all patients with soJRA. Curiously, patients with hemophagocytosis in their bone marrow at presentation had an increased likelihood of being in remission at their last visit. It is possible that patients presenting with MAS may represent a particular subtype of soJRA that has a different clinical course than those patients that have normal marrows. Alternatively, physician concern for MAS may lead to more aggressive therapy, resulting in higher remission rates.

Although our study has the strength of large numbers, there are a few limitations that should be recognized. Not all patients with soJRA from the last 15 years from all 3 centers may have been identified. Further, clinical and laboratory data were collected retrospectively and typically from patients' charts, raising the possibility of omission of data. Nonetheless, our study demonstrates the feasibility of using a Web-based data collection system for relatively easily accumulating data on rare diseases from multiple sites/institutions.

As long as the fundamental etiology of soJRA remains a mystery, specific biomarkers or genetic testing will remain elusive. Thus, diagnosis on the basis of clinical grounds will continue to be the standard. Early diagnosis will remain difficult; however, the description provided by our study may aid the clinician in deciding the relative likelihood of the diagnosis of soJRA.

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