

Predictors of Hip Disease in the Systemic Arthritis Subtype of Juvenile Idiopathic Arthritis

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ABSTRACT. Objective. Hip involvement occurs in 20%–40% of all cases of juvenile idiopathic arthritis (JIA). Patients with systemic JIA (sJIA) are affected most frequently. The aim of our study was to investigate the predictors of clinical hip disease and radiographic hip damage in sJIA.

Methods. The medical records (1997–2007) of all children (n = 98) with sJIA were reviewed. Potential clinical and laboratory predictors were examined at presentation and at 3 and 6 months. To account for censored observations, we used survival analysis.

Results. During the study period, 59 children met our inclusion criteria. The mean age at diagnosis was 7.8 years. Thirty patients (51%) developed clinical hip disease, with 12 (20%) developing radiographic evidence of hip damage. The median time to develop clinical hip disease was 24 months. Using Kaplan-Meier estimates, 25% of patients develop radiographically evident hip damage within 43 months. At presentation, patients in whom clinical hip disease later developed had polyarthritis (hazard ratio 2.51, p = 0.01), elevated IgG (HR 1.12, p = 0.01) and IgM (HR 2.71, p = 0.02), and higher CHAQ scores (HR 1.65, p = 0.02). At 3 months after disease onset, patients in whom radiographic hip damage later developed had fever (HR 4.78, p = 0.02), polyarthritis (HR 4.63, p = 0.02), and higher CHAQ scores (HR 3.20, p = 0.005). At 6 months, polyarthritis was the strongest predictor of both clinical hip disease and radiographic hip damage.

Conclusion. Half of patients with sJIA develop clinical hip disease a median time of 24 months from diagnosis. Early identification of predictors of hip disease and damage in patients with sJIA may suggest earlier, more aggressive interventions to prevent joint destruction. (J Rheumatol First Release Feb 1 2011; doi:10.3899/jrheum.101146)

Key Indexing Terms:

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

HIP DISEASE

Systemic juvenile idiopathic arthritis (sJIA) is a chronic arthritis accounting for 10% to 20% of patients with juvenile arthritis¹. sJIA is characterized by spiking fevers, typical rash, generalized lymphadenopathy, hepatosplenomegaly, and pericarditis in addition to arthritis. sJIA may follow a benign, self-limited course or may lead to significant morbidity. In at least one-third of patients², it is a progressive destructive arthritis that accounts for the principal complications of this disease. After longterm followup, 29% of all patients with sJIA and 38% of the chronic subtype have been reported to be in functional class III or IV^{3,4}.

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The hip is a weight-bearing joint in which anatomical deformities can cause serious disabilities. It is rarely the primary joint involved in JIA at disease onset, but may become involved early in the disease process⁵. In JIA, most cases of hip involvement occur early in the disease process, usually in the first 7 years after presentation^{5,6}. Hip involvement occurs in 20%–40% of all JIA cases^{5,6,7} and patients with sJIA are affected most frequently. Studies have reported that 20%–73% of patients in this subgroup have hip involvement^{5,8,9}. A particularly high incidence of hip involvement is thought to occur in sJIA with age of onset < 6 years⁷.

The clinical manifestations of hip joint involvement in JIA include pain and decreased range of motion. Radiographic changes can include osteopenia, subchondral bone erosions of the femur and/or acetabulum, and cartilage loss with narrowing of the joint space^{6,10,11}. In most cases, these changes are bilateral. The time from disease onset to the development of radiographic damage is typically 6 years (range 2–11 yrs)^{6,11,12}. In patients with sJIA, osteopenia of the hip has been reported within 1 year of disease onset; subchondral irregularity, joint space narrowing, and erosions by 2 years; and joint and bone destruction with bilateral protrusio acetabuli are sometimes present by 6 years after disease onset¹⁰. In one study, at 5 years after onset, 75% of systemic patients had evidence of joint space narrowing on any radiographs¹³.

Predictors of chronic destructive polyarthritis in sJIA, other than hip involvement, are thought to include both clinical and laboratory factors. Persistent systemic symptoms and a platelet count $\geq 600 \times 10^9/l$ are highly predictive of the later development of joint destruction¹⁴. These prognostic criteria also predict poor functional outcome in children with sJIA¹⁵. A subgroup of patients with sJIA with early radiographic evidence of erosive changes on radiographs (not just localized to the hips) may go on to develop severe joint destruction¹⁰. These patients have more prolonged systemic disease, with persistent fever at 1 year after disease onset in 80%¹⁴. It is known that early involvement of the hip joint is associated with a poor articular outcome^{16,17,18,19}. In a longterm followup study of adults with JIA, 59.6% of patients with the systemic subtype required prosthetic hip replacement⁴.

Given that hip disease can lead to decreased mobility, poor functional outcome, and possible surgical intervention, knowing the potential predictors of serious hip disease in patients with sJIA may be valuable; early identification of hip disease in children with sJIA may lead to earlier, more aggressive interventions before joint destruction occurs. The aim of this study was to identify the predictors of clinical hip disease and radiographic hip damage in patients with sJIA.

MATERIALS AND METHODS

This was a retrospective cohort study. The study was approved by The Hospital for Sick Children (SickKids) Research Ethics Board.

Study population. The medical records of all children with a diagnosis of sJIA seen at SickKids, from 1997 to 2007, were reviewed. Patients who fulfilled the following inclusion criteria were examined further: (1) satisfied the International League of Associations for Rheumatology classification criteria for sJIA; (2) were first seen within 3 months of the onset of symptoms; and (3) were followed for at least 6 months (so that adequate predictor information could be obtained).

Definition of hip disease and damage. Patients were considered to have clinical hip disease if they had a positive physical examination (i.e., active hip arthritis as determined by decreased range of motion and pain on range of motion). Hip radiographs were done as clinically indicated without a pre-set protocol. Hip damage on plain radiograph was defined as joint space narrowing, subchondral erosions of either the femur and/or acetabulum, sclerosis of the acetabulum, avascular necrosis of the femoral head, or protrusio. All radiographs were read by a single experienced radiologist blinded to the clinical characteristics and course of the study population.

Clinical and laboratory data. All data were recorded at each visit and entered into the SickKids Rheumatology Clinical Database using a standardized data collection form.

Predictors. Potential clinical and laboratory predictors were examined at presentation, and at 3 and 6 months of followup. Previous studies have shown that clinical predictors can be identified within 6 months after disease onset^{14,17}. Clinical data available included the presence of (1) fever; (2) typical rash of sJIA; (3) hepatomegaly or splenomegaly; (4) lymphadenopathy; (5) serositis; (6) medication use at any time during the disease course or early in the disease course (within the first 6 months of diagnosis); (7) arthritis (further divided into polyarthritis or oligoarthritis); (8) Childhood Health Assessment Questionnaire score (CHAQ; a measure of physical function in childhood arthritis); further classified into no-mild disability or mild-moderate disability with CHAQ score > 0.63 ²⁰; and (9) intraarticular corticosteroid injection of the hip. Medication use was divid-

ed into 3 categories: (1) systemic corticosteroids; (2) disease-modifying antirheumatic drugs (DMARD); and (3) biologic agents, including anakinra, infliximab, and etanercept. Available laboratory data comprised: (1) hemoglobin level; (2) leukocyte count; (3) platelet count; (4) erythrocyte sedimentation rate; (5) C-reactive protein; (6) serum albumin concentration; and (7) quantitative immunoglobulin concentrations.

Statistical analysis. Not all subjects have been followed for the same length of time. To account for censored observations, we used survival-type statistics in our analysis. To answer the primary question, the outcome of interest was the length of time until hip disease or damage (as defined above) occurred. Potential predictors comprised all clinical, demographic and laboratory data (as listed above) at baseline and 3 months and 6 months after diagnosis. Exploratory modeling using Cox proportional hazards regression was used to explore the relationship for each predictor individually. Predictors that were found to be individually significant were used in a final multiple regression model using the Cox method.

Statistical analysis was completed using the JMP[®] software, version 7.0.2 (SAS Institute, Cary, NC, USA), and R, version 2.10.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the study population. During the 10-year study period, the records of 98 patients were reviewed. Fifty-nine children (32 girls) met our inclusion criteria. Thirty-nine patients were excluded from the study; 4 did not meet the classification criteria for sJIA, 14 patients were referred to our hospital more than 3 months after disease onset, and 21 patients were excluded because they were not followed for at least 6 months (e.g., single consultation for second opinion, loss to followup or followup in outreach clinic). The mean age at diagnosis was 7.8 years (SD 4.1 yrs) and the mean length of followup was 52.2 months (range 7–126 mo). Table 1 summarizes the clinical findings at diagnosis and at 3 and 6 month followup. Thirty-eight patients (64%) received at least one course of systemic corticosteroid treatment during the study period (all treated within the first 6 months of presentation), while 12 (20%) patients had intraarticular corticosteroid injections of hip joints (only one patient had injections within the first 6 months of presentation). Patients also received the following medication during the study period: methotrexate (55.9%), intravenous immunoglobulin (15.2%), and cyclosporine (6.8%) as well as biologic agents including anakinra (13.6%), etanercept (15.2%), and infliximab (15.2%). It is important to note that the biologic agents were not available for the first 5 years in our review of this study cohort.

Clinical hip disease. Two patients had clinical hip disease at presentation. Thirty (51%) of the 59 patients developed clinical hip disease at some point in the course of followup. The median time to develop clinical hip disease was 24 months (95% CI 9 months – undefined). “Undefined” is reported where the confidence limit cannot be estimated as it is not included within the survival time range of the study. Twenty-five percent of patients developed clinical hip disease within 3 months of presentation (95% CI 2–9 mo). Sex or age at diagnosis was not associated with the time to develop hip disease or damage.

Table 1. Clinical and laboratory features at presentation and at 3 and 6 months followup.

Characteristic	Presentation	3 Months	6 Months [†]
Patients' clinical features, n (%)			
Fever	59 (100)	7/56 (12.5)	7/58 (12.1)
Rash	49 (83)	25/56 (44.6)	24/58 (41.4)
Hepatosplenomegaly	22 (37)	4/56 (7.1)	5/58 (8.6)
Lymphadenopathy	30 (51)	7/56 (12.5)	6/58 (10.3)
Serositis	4/28 (14)	3/28 (10)	—
Oligoarthritis*	23 (39)	14/53 (26)	16/58 (28)
Polyarthritis*	25 (42)	13/53 (24)	14/58 (24)
Laboratory results, mean ± SD			
Hemoglobin, g/l	102.2 ± 13.8	113.6 ± 17.2	115.7 ± 16.3
Leukocyte count, × 10 ⁹ /l	17.8 ± 11.9	15.6 ± 9.3	18.7 ± 26.9
Platelets, × 10 ⁹ /l	484.1 ± 183.8	424.3 ± 156.3	428.3 ± 174.6
ESR, mm/h	82.3 ± 36.5	32.6 ± 29.9	28.9 ± 26.9
CRP, mg/l	93.6 ± 85.5	25.3 ± 50.9	44.5 ± 66.2
Albumin, g/l	36.0 ± 4.5	38.6 ± 4.4	40.7 ± 4.8
IgG, g/l	13.9 ± 4.5	12.4 ± 6.5	13.0 ± 3.5
IgM, g/l	1.5 ± 0.5	1.9 ± 2.0	1.5 ± 0.5
CHAQ score, mean ± SD			
Mild-moderate score (> 0.63) (%)	34/46 (73.9)	12/45 (26.6)	5/38 (13)

* The remaining 19% of patients developed documented arthritis within 6 months of disease onset. † One patient had missing clinical data despite being seen at 6 months with regular followup laboratory investigations. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CHAQ: Childhood Health Assessment Questionnaire.

Using Cox proportional hazards regression, patients who ultimately developed clinical hip disease had polyarthritis [hazard ratio (HR) 2.51, $p = 0.01$; Figure 1] and elevated IgG (HR 1.12, $p = 0.01$) and IgM (HR 2.71, $p = 0.02$) levels at presentation. Corticosteroid use was not associated with the development of clinical hip disease (HR 1.24, $p = 0.28$) nor was early DMARD use (within the first 6 months of diagnosis; HR 1.24, $p = 0.31$). However, DMARD use at any time during the disease course, use of biologic agents,

and having had intraarticular corticosteroid injections of the hip were found to be predictive of later development of clinical hip disease (HR 2.59, $p = 0.02$; HR 1.85, $p = 0.002$; and HR 1.88, $p = 0.002$, respectively). The CHAQ score at presentation was also predictive of development of hip disease (HR 1.65, $p = 0.02$). A multivariable regression model using the Cox method was used to examine the relationship of multiple predictors. Both the presence of polyarthritis (HR 3.18) and elevated IgG level (HR 14.9) at presentation were independent significant predictors (model $p = 0.0016$).

At 3 month followup, a significant relationship was found between the time to develop hip disease and an elevated IgG level (HR 1.14, $p = 0.04$) and CHAQ score (HR 2.24, $p = 0.005$). In a multiple regression Cox model, leukocyte count (HR 1.19), IgG level (HR 1.09), and CHAQ score (HR 5.15) independently predicted hip disease ($p = 0.001$). Patients with mild-moderate disability (CHAQ > 0.63) at 3 months were more likely to develop clinical hip disease (HR 1.82, $p = 0.005$).

At 6 month followup, the only predictor for the development of hip disease was extant polyarthritis (HR 2.65, $p = 0.02$).

Radiographic hip damage. Twenty-three of the 30 patients with clinical hip disease (77%) had hip radiographs. The remaining 7 patients had resolution of clinical hip findings in followup. Twelve (20%) patients developed radiographic evidence of hip damage, with 4 patients having damage on their first radiograph. The descriptive radiographic findings from those patients with hip damage are summarized in Table 2. Three patients eventually required total hip replacement surgery for severe hip pain and endstage hip disease.

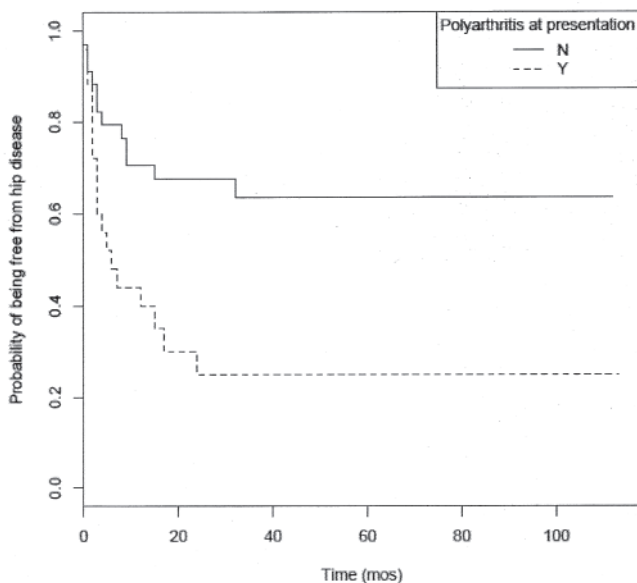


Figure 1. Kaplan-Meier curve shows the probability of being free of hip disease in patients with systemic JIA who present with polyarthritis. Each step represents one or more patients.

Table 2. Descriptive radiographic findings of the 12 patients who developed radiographic evidence of hip damage.

Radiographic Finding	No. Patients (%)
Bilateral involvement	9 (75.0)
Joint space narrowing	11 (91.7)
Erosions	9 (75.0)
Sclerosis of acetabulum	9 (75.0)
Avascular necrosis	3 (25.0)
Protrusio	1 (8.3)

Figure 2 illustrates the progression of damage ultimately leading to arthroplasty.

Twenty-five percent of patients developed hip damage within 43 months (95% CI 36 months – undefined). Once again, “undefined” is reported where the confidence limit cannot be estimated as it is not included within the survival time range of the study. Corticosteroid use was not significantly associated with the development of hip damage (HR 1.74, $p = 0.11$) nor was early DMARD use (within the first 6 months of diagnosis; HR 1.75, $p = 0.09$). However, DMARD use at any time during the disease course, use of biologic agents, and having had intraarticular corticosteroid injections of the hip were found to be predictive of later development of radiographic hip damage (HR 2.59, $p = 0.02$; HR 2.51, $p = 0.002$; and HR 3.86, $p = 0.001$, respectively). At 3 months after disease onset, patients in whom hip damage later developed had fever (HR 4.78, $p = 0.02$), polyarthritis (HR 4.63, $p = 0.02$), and higher CHAQ scores (HR 3.20, $p = 0.005$). The only significant predictor at 6 months was polyarthritis (HR 3.98, $p = 0.02$; Figure 3). When the maximum number of active joints within the first 6 months of presentation was examined, patients with ≥ 10 active joints had a significantly higher risk of developing radiographic hip damage (HR 3.49, $p = 0.03$). Early-onset clinical hip disease (within 6 months of presentation) was found to be a predictor of later development of radiographic hip damage (HR 3.51, $p = 0.03$).

DISCUSSION

Patients with sJIA have hip involvement more frequently than patients with the other JIA subtypes. In our study, the median time to develop clinical hip disease was 24 months. Twenty percent of our patients went on to develop radiographic evidence of hip damage, most often involving both hips. This is in keeping with a recent study in which 20% of patients with sJIA had radiographic hip involvement⁸. In our study the mean time to develop clinical hip disease as well as radiographic hip damage was similar to that found in other studies^{10,12}.

We were able, within the first 6 months of disease onset, to identify both clinical and laboratory factors that were predictive for later development of clinical hip disease and radiographic hip damage. Early presentation with polyarthritis and more marked disability predicted the development of clinical hip disease. Elevated immunoglobulin levels were found to be predictive early in the disease course. Cassidy, *et al* measured immunoglobulin concentrations in 200 patients with systemic JIA²¹. They reported a direct correlation between IgA levels and the extent of articular disease in these children²¹. We found that ongoing fever at 3 months as well as polyarthritis and more marked disability predicted development of radiographic evidence of hip damage. At 6 months, polyarthritis was the strongest predictor of both clinical hip disease and radiographic hip damage, with patients with higher joint counts being most at risk. Polyarthritis has been shown to be a predictor of joint damage in patients with systemic JIA¹⁷.

The severity of systemic symptoms at disease onset has not been considered predictive of chronic arthritis or outcome¹⁸. However, persistent systemic symptoms at 3 and 6 months were shown to be predictive of later development of joint destruction¹⁴. In keeping with this, we found fever at 3 months to be predictive of later development of radiographic hip damage.

Corticosteroid use was found not to be predictive for the development of clinical hip disease or radiographic hip



Figure 2. Serial radiographs of a 16-year-old patient with systemic JIA who first developed evidence of bilateral clinical hip disease 2 months after presentation. She initially presented at 8 years of age with polyarthritis. Radiographic evidence of hip damage appeared 3 years later with joint space narrowing and acetabular sclerosis (A). Progressive joint space narrowing with marked femoral head erosions with avascular necrosis and acetabular sclerosis was seen 6 years after presentation (B). She required a total hip replacement 1 year later for ongoing significant pain (C).

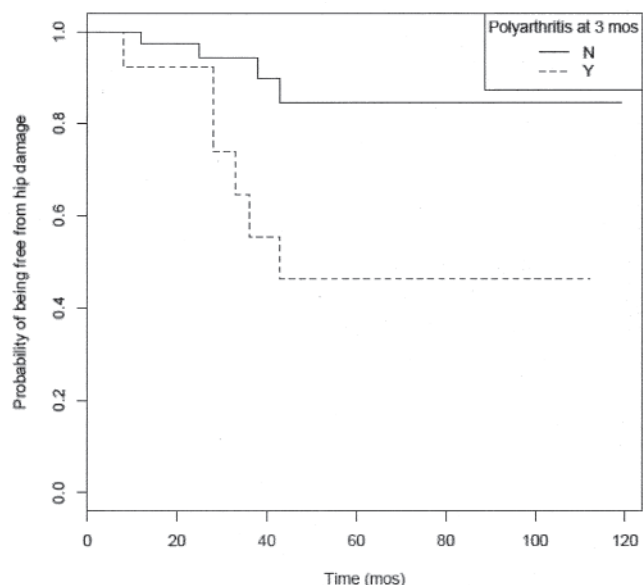


Figure 3. Kaplan-Meier curve shows the probability of being free of hip damage in patients with systemic JIA who, at 3 months after presentation, have polyarthritis. Each step represents one or more patients who develop radiographic evidence of hip damage. $P = 0.01$.

damage. Similarly, early treatment with DMARD (within 6 months of presentation) was not predictive. However, patients treated with DMARD, biologic agents, or intra-articular corticosteroid injections were more likely to develop hip disease/damage. This may be explained by confounding by indication. Patients with hip involvement, or other markers of eventual hip involvement (e.g. polyarthritis), may be more likely to be treated with these therapies.

One limitation of this study is the relatively small sample size of our population. This may have impaired our power to detect clinical or laboratory predictors with a small effect. Also, we used plain radiographs to define hip damage; although remaining the “gold standard” for joint anatomy and integrity evaluation, plain radiographs are less sensitive at detecting hip joint abnormalities in early disease in comparison to ultrasound and magnetic resonance imaging^{12,22}. We may have underestimated the amount of early anatomic damage in our sample.

Patients with systemic JIA more frequently have hip involvement than patients with other JIA subtypes. Early identification of an increased risk of hip disease in patients with systemic JIA might suggest earlier, more aggressive interventions to prevent joint destruction.

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