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Population-Based Study of Outcomes of Patients with Juvenile Idiopathic Arthritis (JIA) Compared to non-JIA subjects

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Abstract

Objective—Evaluate healthcare utilization and occurrence of comorbidities in a population-based cohort of patients of juvenile idiopathic arthritis (JIA) with an age- and sex-matched comparator group.

Methods—Prevalent cases of JIA in 1994–2013 were identified in Olmsted County, Minnesota along with age- and sex-matched non-JIA comparators. Surgeries, hospitalizations, pregnancies, and comorbidities were identified by medical record review. Poisson methods were used to generate rate ratios (RR) with 95% confidence intervals (CI) to compare outcomes between JIA and non-JIA cohorts separately during childhood (age<18 years) and adulthood (age ≥ 18 years).

Results—Eighty-nine JIA and 89 non-JIA comparators were identified (64% female; mean [SD] age 8.6[5.1] years at JIA incidence/index date and mean follow-up in childhood 6.3[4.4] years for JIA; similar for comparators). Thirty-eight pairs had follow-up into adulthood with mean follow-up of 8.0[5.5] years for JIA. Children with JIA were more likely to have joint surgery (RR:3.93, 95% CI:1.18–24.94), non-joint surgery (RR:1.90, 95% CI:1.05–3.67), and hospitalizations (RR: 2.25, 95% CI:1.04–5.53) than non-JIA comparators. As adults only joint surgeries remained significantly different (RR:8.5, 95% CI:2.27–120.1). Depression during childhood was more common in JIA (RR:2.49, 95% CI:1.01–6.13). There were no differences in educational achievement, employment status or pregnancy outcomes between the 2 groups.

Conclusions—In a population-based cohort, inpatient healthcare utilization is higher for patients with JIA including surgery and hospitalization during childhood but not extending into

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adulthood. Understanding long-term comorbidities and healthcare needs for patients with JIA is necessary to provide comprehensive care.

Keywords

juvenile idiopathic arthritis; healthcare utilization; depression

Juvenile idiopathic arthritis (JIA) causes wide ranging manifestations extending beyond inflammatory arthritis (1). Classification criteria have evolved over time with the most recent being the ILAR criteria with different long-term outcomes associated with different subtypes (2, 3). While defined by symptoms starting before the 16th birthday, JIA is not isolated to symptoms in childhood. In long-term study patients evaluated 30 years after their diagnosis of JIA, over a third had evidence of active disease and an additional 7% were taking ongoing medication to maintain remission (4). Even in the absence of active disease, patients suffer the complications of damage (5).

Understanding disease activity and its associated damage in isolation will not describe the full impact of JIA on a single individual in the long term. Comorbidities above and beyond JIA impact fatigue, pain, functional capability, and quality of life measures (6). This underscores the requirement of long-term follow-up to understand the impact of JIA as a chronic illness.

This study sought to compare inpatient healthcare utilization and comorbidities among patients with JIA and age- and sex-matched non-JIA comparators in a geographically defined population. Outcomes were assessed during childhood and adulthood to capture the long-term impact of the disease.

Methods

Patient Cohort

All prevalent cases of JIA were identified in Olmsted County, Minnesota between January 1, 1994 and December 31, 2013 utilizing the Rochester Epidemiology Project with its associated access to full medical records for all medical care received in the county including all inpatient and outpatient medical care, telephone communications, medication prescriptions, hospitalizations, and surgeries/procedures (7). In 2010, the total population in Olmsted County was 144,248 persons. Over the time of follow-up, there were 1–2 pediatric rheumatologists at a single time in the county.

These individuals were identified first by diagnosis code and then confirmed by medical record review to meet ILAR criteria for JIA (2). Additional information regarding the search is available in an earlier publication (8). The index date for each subject was the date they first fulfilled ILAR criteria for JIA and lived in Olmsted County. If their diagnosis occurred when they were not living in Olmsted County, then the index date was when they first moved to Olmsted County. Non-JIA comparator subjects were age- and sex matched and selected at random from the same population of Olmsted County, Minnesota. Index date for comparators was the same as the index date of the corresponding JIA case. All subjects were followed retrospectively through their complete medical records (inpatient and outpatient)

until death, migration from Olmsted County or December 31, 2014. There was no minimum follow-up time required for inclusion.

Demographic data including date of birth, sex, and race/ethnicity were obtained. Patient reported employment status, highest education status achieved, and tobacco use was also recorded for those individuals who had follow-up beyond the age of 18 years. Healthcare utilization, specifically joint surgeries, other surgeries (excluding joint surgeries), and hospitalizations (hospitalizations that occurred specifically for surgery were not included) that occurred after index date were recorded. Comorbidities including malignancy, diabetes mellitus type 1, celiac disease, and autoimmune hepatitis were identified based on clinician diagnosis irrespective of index date. Information regarding clinician diagnosed depression was also obtained in addition to hospitalizations specifically for depression. Pregnancy information was abstracted including information regarding live births, spontaneous abortions, and elective abortions.

This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Statistical Analysis

Characteristics of patients with JIA and non-JIA comparators were described using numbers with corresponding percentages for categorical variables and mean with standard deviation (SD) for continuous variables. Differences between patients with JIA and non-JIA comparators were tested using chi-square tests for categorical variables and rank sum tests for continuous variables. Analysis was performed separately for outcomes in childhood, as defined prior to age 18 years, and in adulthood for pairs of patients with JIA and non-JIA comparators in which both individuals had follow-up past the age of 18. If only a single individual of the pair had follow-up into adulthood then they were excluded from the adult analysis.

Hazard ratios (HR) with 95% confidence intervals (CI) were obtained from Cox models adjusted for age, sex, and calendar year of index date to evaluate depression. Rate ratios (RR) with 95% CI were calculated using Poisson methods to compare rates of outcomes that could more than once in the same patient, such as joint surgeries, non-joint surgeries, hospitalizations, hospitalizations for depression, and pregnancies. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics

Eighty-nine patients were identified with JIA as well as 89 corresponding non-JIA comparators. The mean age (SD) at index date was 8.6 (5.1) years for those with JIA and 8.9 (5.0) years for those without JIA (Table 1). Among the JIA, 82 (92%) were included at incidence and the remaining 7 prevalent cases had median disease duration at index date of 1.3 (range: 0.2–4.0) years, and all were seen by a pediatric rheumatologist at least once. JIA subtypes included 53 (60%) oligoarthritis of which 43 were persistent, 8 were extended, and

2 did not have follow-up past 6 months to further classify. Four (4%) had rheumatoid factor positive polyarthritis and 11 (12%) had rheumatoid factor negative polyarthritis. Three (3%) patients had psoriatic arthritis. An additional 3 (3%) had enthesitis related arthritis. Two (2%) had systemic arthritis. Twelve (13%) were undifferentiated. A single patient had their diagnosis outside of the institution and there was insufficient data to categorize. In each group, there were 57 (64%) females. The follow-up time in the pediatric setting (<18 years old) was similar for both groups, mean 6.3 (4.4) years in patients with JIA compared to 6.5 (4.3) in patients without JIA with few patients (12 JIA and 7 non-JIA) migrating from Olmsted County prior to age 18 years. There were no differences in race/ethnicity between both groups ($p=0.30$) with the majority of patients reporting Caucasian (75 [84%] in patients with JIA and 77 [87%] without JIA). In those with JIA, additional self-reported race/ethnicity included 4 (4%) black, 3 (3%) Asian, 2 (2%) Hispanic, 1 (1%) other, and 4 (4%) unknown.

Thirty-eight pairs (43%) had follow-up over the course of this study into adulthood (< 18 years old) (Table 2). Length of follow-up during adulthood was similar in patients with JIA mean (SD) of 8.0 (5.5) years and 8.9 (5.7) years for those without JIA. No deaths occurred over the course of follow-up.

There were no differences in the rates of tobacco use ($p=0.65$). Seven (18%) in both groups were current smokers. There was no difference in educational status achieved ($p=0.48$). In those with JIA, 25 (66%) had some educational experience beyond high school while 22 (58%) of those without JIA did.

Further, there were no differences in employment status. Twenty-seven (71%) of persons with JIA reported they were employed as compared to 31 (82%) of those without JIA ($p=0.28$). Ten (26%) individuals with JIA reported that they were students as compared to 4 (11%) without JIA ($p=0.076$). In those with JIA, 3 (8%) were unemployed as compared 2 (5%) in those without ($p=0.64$). No patients with JIA reported that they were disabled in terms of their employment status.

Joint Surgeries

Only a minority of patients had a joint surgery as a child. Six (7%) of those with JIA had at least 1 joint surgery. None of these surgeries were joint arthroplasties. In contrast among those without JIA, 2 had a single joint surgery. It was more likely for children with JIA to have joint surgeries as compared to those without JIA, RR 3.93 (95% CI 1.18, 24.94) (Table 3). The rate of childhood joint surgery for patients with JIA was 1.6 per 100 person-years.

Extending into adulthood, patients with JIA continued to require more joint surgeries compared to those without JIA, RR 8.50 (95% CI 2.27, 120.1) (Table 4). Six (7%) patients with JIA had at least 1 joint surgery after the age of 18. In contrast, only one patient without JIA had a single joint surgery. The rate of joint surgery as an adult with JIA was 3.6 per 100 person-years. Again none of these surgeries were joint arthroplasties. In both children and adults, the types of joint surgeries were quite variable but the most common included synovectomies, knee meniscus procedures, and arthrodesis procedures.

Non-Joint Surgeries

In both groups 14 (16%), had at least 1 non-joint surgery. However, it was more likely for those with JIA to have multiple surgeries. The rate of non-joint surgeries for those with JIA was 5.0 per 100 person-years as compared to 2.6 without JIA, RR 1.90 (95% CI 1.05, 3.67) (Table 3). Tonsillectomy was the most common surgery in both groups.

In contrast, for patients followed into adulthood, there was no difference in the rates of non-joint surgeries, RR 1.92 (95% CI 0.89, 4.57) (Table 4) as adults. Eleven patients (29%) with JIA had at least 1 surgery as compared to 7 (18%) patients without JIA.

Non-surgical Hospitalizations

Twelve (13%) patients with JIA had at least 1 hospitalization while in those without JIA, 5 (6%) were hospitalized. There was increased risk of hospitalizations in children with JIA, RR 2.25 (95% CI 1.04, 5.53) with hospitalization rate of 3.2 per 100 person-years in those with JIA (Table 3).

There was no difference in rates of hospitalization as adults, RR 1.79 (95% CI 0.69, 5.25) (Table 4). Six (16%) patients with JIA had at least 1 hospitalization as an adult as compared to 4 (11%) without JIA.

Infection accounted for a total of 6 hospitalizations: pyelonephritis (2), herpes zoster, enterovirus meningitis, cutaneous abscess, and viral oral ulcers. Two hospitalizations occurred specifically for management of JIA.

Comorbidity

Depression prior to JIA diagnosis/index date occurred in 7 (8%) of children with JIA and 4 (4%) of those without JIA ($p=0.35$, no significant difference). When excluding those with depression prior to index date, the risk of depression for children with JIA was higher as compared to those without JIA (HR 2.49; 95% CI 1.01, 6.13). The cumulative incidence of depression at 10 years for those with JIA was 24.9% ($\pm 6.7\%$) compared to 13.4% ($\pm 5.5\%$) without JIA ($p=0.045$).

Five children with JIA required hospitalization for depression, 3 were hospitalized once and 2 were hospitalized twice. In children without JIA, 3 required hospitalization for depression 2 were hospitalized once and 1 was hospitalized three times. There was no difference in the occurrence of hospitalization for depression (RR 1.41; 95% CI 0.47, 4.70).

In adulthood, no difference was noted in development of depression in patients with JIA versus those without (HR 0.48 [0.10, 2.26]) after excluding those with a diagnosis of depression in childhood. The cumulative incidence of depression at 10 years was 18.7% ± 5.9 compared to 19.1% ± 9.5 ($p=0.56$), in those with JIA and without, respectively.

There were no differences in the rates of hospitalization for depression as adults (RR 0.26; 95% CI 0.02, 1.11). Only 1 patient with JIA required a single hospitalization for depression as an adult; two subjects without JIA had a single hospitalization each, and 2 had 2 hospitalizations.

No patients developed a malignancy over the course of follow-up. There were no episodes of diabetes mellitus type 1 or celiac disease. A single patient had concomitant autoimmune hepatitis and JIA.

Pregnancy

Among 28 women with JIA, 9 (32%) women had at least 1 pregnancy. Among 28 women without JIA, 13 (46%) had at least 1 pregnancy. The rate of pregnancies was 8.2 per 100 person-years in those with JIA compared to 12.0 per 100 person-years without JIA. There were no significant differences in the rate of pregnancies (RR 0.68; 95% CI 0.38, 1.20). There was no difference in the number of live births ($p=0.34$). There was no identified difference in number of spontaneous abortions (1 in women with JIA, 3 in women without JIA, $p=0.68$) or elective abortions (1 in women with JIA, 4 in women without JIA, $p=0.28$).

Adult Follow-up

Twenty-seven out of 38 (71%) patients with JIA who had follow-up time into adulthood had one visit with a rheumatologist after the age of 18. Sixteen (42%) of these patients had been seen within preceding year of their last follow-up by a rheumatologist.

Discussion

This study demonstrated higher inpatient healthcare utilization in children with JIA compared to those without JIA including joint surgery, non-joint surgery, and hospitalizations. This increased use did not extend into adulthood in terms of non-joint surgery or hospitalizations. However, the occurrence of joint surgeries continued to be higher in adults who had been diagnosed with JIA as compared to those who had not. While the risk of depression was higher for children with JIA as compared to those without, there was no difference of new onset of depression as adults. Similar rates of employment and educational achievement were achieved between both groups. There was no significant difference in number of pregnancies, but there was a tendency for patients with JIA to have fewer pregnancies than those without JIA. There were no occurrences of malignancy in this cohort.

Earlier studies have reported similar rates of educational achievement in persons with and without JIA (9–12), and a few studies have even demonstrated even better educational achievement of those with JIA with variable comparator groups (13, 14). A single study demonstrated lower postsecondary education rates for women with JIA as compared to those without (55% versus 71%) but not for men (15). Utilizing a cross sectional design, JIA subtype was not associated with educational achievement (16).

Despite similar to higher educational achievement, employment rates, particularly in older studies, have been lower in those with JIA (9, 11, 13, 14). However, other studies have shown similar employment rates for those with JIA when compared to other comparator groups similar to our study (5, 12, 15). These studies are from widely varying geographical areas and comparison groups, which may contribute to the variability of results. Studies showing no difference in employment rates tend to be from more recent years.

In an earlier study from this same population base, there were no differences in live births or miscarriages, as also noted in this update (9). Another study utilizing a survey reported higher risk of miscarriage for those with JIA (17). Our study may have missing information about pregnancy loss if this information was not recorded in the medical record, but has the advantage of recording of pregnancy loss captured in patient clinic visits. The small numbers of pregnancies in the current study may have obscured the ability to detect a difference between the two groups.

There are widely varying reports of the occurrence of depression in JIA with ranges of 2–19%. This wide range is likely related to different definitions, ascertainment, and study populations (18, 19). In a cohort with longstanding disease, 5% of adults had depression at the time of follow-up but 21% had prior diagnosis (20). This mirrors our study with findings of higher rates of depression in children with JIA as compared to those without but no difference when adults.

Overall rates of arthroplasty for patients with JIA have been noted to be reducing by almost 50% over the time period of 1991–2005 as well as the age at arthroplasty was increased by almost 6 years (21). In our study, no individuals underwent an arthroplasty. While higher rates of joint replacement have been reported in other cohorts, any comparison is difficult because that cohort represented a referral population with severe disease requiring ongoing treatment as adults (22).

A study utilizing Medicaid data reported a higher rate of malignancy in those with JIA (SIR 4.4, 95% CI 1.8–9.0) (23). The absolute number of occurrences is fortunately low, and malignancies in other cohorts are low or absent, similar to our study (18, 24).

Understanding comorbidities is critical to help encompass the impact of health and quality of life in patients with JIA (6). These comorbidities are likely a source of dissatisfaction registered by individuals with JIA on the current scales/questionnaires measuring quality of life (25).

This was a retrospective study and thus identical information was not available for all patients. Information regarding educational achievement, vocational status, and smoking habits were available for all patients who had follow-up beyond the age of 18 years. Furthermore, not all patients had follow-up into adulthood either because they moved out of the county or at the time of the study were still children. If patients received medical care outside of the county, it is possible that it would not be captured by this study, but such care is referenced in the medical record on patient visits or when copies of outside medical records are sent for review. Due to the size of cohort and overall low rate of events such as pregnancy, there are limits in the ability to detect differences between the groups.

The results of this study using a population-based cohort describes important health related outcomes in patients with JIA and allowed for comparison of healthcare utilization and comorbidities. Individuals with JIA have higher rates of joint surgeries both as children and adults, nonarticular surgeries as children, and hospitalizations as children compared to individuals without JIA. This study emphasizes that providing comprehensive care for

individuals with JIA as they advance into adulthood requires a global assessment beyond evaluation of joint damage.

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Table 1

Demographics of a population based cohort of patients with juvenile inflammatory arthritis (JIA) and non-JIA comparator subjects during childhood

	JIA (N=89)	non-JIA (N=89)	p value
Age at index date in years, mean ($\pm$SD)	8.6 ($\pm$ 5.1)	8.9 ($\pm$ 5.0)	0.56
Female sex	57 (64%)	57 (64%)	1.00
Length of follow-up to age 18 in years, mean ($\pm$SD)	6.3 ($\pm$ 4.4)	6.5 ($\pm$ 4.3)	0.66
Race/Ethnicity			0.30
Caucasian	75 (84%)	77 (87%)	
Hispanic	2 (2%)	2 (2%)	
Black	4 (4%)	0 (0%)	
Asian	3 (3%)	6 (7%)	
Other	1 (1%)	0 (0%)	
Unknown	4 (4%)	4 (4%)	

Values in table are n (%) unless otherwise specified.

Table 2

Comparison of juvenile inflammatory arthritis (JIA) and non-JIA during adulthood

	JIA (N=38)	non-JIA (N=38)	p value
Age at index date in years, mean ($\pm$SD)	11.2 ($\pm$ 4.4)	11.4 ($\pm$ 4.5)	0.80
Female sex	28 (74%)	28 (74%)	1.00
Length of follow-up after age 18, years, mean ($\pm$SD)	8.0 ($\pm$ 5.5)	8.9 ($\pm$ 5.7)	0.52
Time from index date to age 18, years, mean ($\pm$SD)	6.8 ($\pm$ 4.4)	6.6 ($\pm$ 4.5)	0.80
Race/Ethnicity			0.22
Caucasian	36 (95%)	33 (87%)	
Hispanic	1 (3%)	2 (5%)	
Asian	0 (0%)	3 (8%)	
Unknown	1 (3%)	0 (0%)	
Tobacco at time of follow-up			0.64
Never smoker	26 (68%)	23 (61%)	
Former smoker	5 (13%)	8 (21%)	
Current smoker	7 (18%)	7 (18%)	
Highest education level if greater than 18 years old			0.32
Some high school but did not graduate	2 (5%)	0 (0%)	
High school graduate or GED	11 (29%)	16 (42%)	
Some college or 2 year degree	16 (42%)	11 (29%)	
4 year college graduate	5 (13%)	8 (21%)	
Post graduate studies	4 (11%)	3 (8%)	
Employed	27 (71%)	31 (82%)	0.28
Unemployed	3 (8%)	2 (5%)	0.64
Work Disabled	0 (0%)	2 (5%)	0.15
Student	10 (26%)	4 (11%)	0.08

Values in table are n (%) unless otherwise specified.

Table 3

Hospitalizations and surgeries in patients with juvenile inflammatory arthritis (JIA) and comparator subjects during childhood

	Rate per 100 py in JIA	Rate per 100 py in non-JIA	Rate ratio (95% CI)
Joint surgeries	1.6	0.3	3.93 (1.18, 24.94)
Non-joint surgeries	5.0	2.6	1.90 (1.05, 3.67)
Hospitalizations	3.2	1.4	2.25 (1.04, 5.53)
Hospitalizations for depression	1.3	0.9	1.41 (0.47, 4.70)

py=person-years

Table 4

Hospitalizations and surgeries in patients with juvenile inflammatory arthritis (JIA) and comparator subjects in adulthood

	Rate per 100 py in JIA	Rate per 100 py in non-JIA	Rate ratio (95% CI)
Joint surgeries	3.6	0.3	8.50 (2.27, 120.1)
Non-joint surgeries	5.2	2.6	1.92 (0.89, 4.57)
Hospitalizations	3.3	1.8	1.79 (0.69, 5.25)
Hospitalizations for depression	0.3	1.8	0.26 (0.02, 1.11)
Pregnancies	8.2	12.0	0.68 (0.38, 1.20)

py=person-years