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Juvenile Idiopathic Arthritis and Future Risk for Cardiovascular Disease: A Multicenter Study

Jason H. Anderson, MD[1], **Katelyn R. Anderson, MD**[2], **Hanne A. Aulie, MD**[3], **Cynthia S. Crowson, MS**[4,5], **Thomas G. Mason, MD**[5,6], **Stacy P. Ardoin, MD**[7], **Ann M. Reed, MD**[6], and **Berit Flatø, MD, PhD**[3,8]

[1]Department of Pediatric and Adolescent Medicine/Division of Pediatric Cardiology, Mayo Clinic, Rochester MN

[2]Department of Dermatology/Division of Pediatric Dermatology, Mayo Clinic, Rochester MN

[3]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

[4]Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester MN

[5]Department of Internal Medicine/Division of Rheumatology, Mayo Clinic, Rochester MN

[6]Department of Pediatric and Adolescent Medicine/Division of Pediatric Rheumatology, Mayo Clinic, Rochester MN

[7]Department of Internal Medicine/Division of Rheumatology & Immunology, Ohio State University, Columbus OH

[8]Medical Faculty, Institute for Clinical Medicine, University of Oslo, Oslo, Norway

Abstract

Objective—Evaluate the frequency of cardiovascular disease (CVD) and CVD risk factor development in adult patients previously diagnosed with juvenile idiopathic arthritis (JIA).

Methods—A cohort study was conducted utilizing patients at two academic institutions (Cohorts 1 and 2). Each institution evaluated the common endpoint of CVD outcomes and CVD risk factor development in adults age ≥30 years and at 29 year follow-up from disease onset in cohorts 1 and 2, respectively, with comparison to control groups of similar age and sex.

Results—Cohort 1 included 41 patients with JIA and follow-up ≥30 years of age with comparison to 41 controls. Three patients (7%) had CVD, compared to 1 control (2%; p = 0.31). Cohort 2 included 170 patients with JIA and median of 29 year follow-up from disease onset with comparison to 91 controls. Two patients (2%) had CVD, compared to 0 controls (p = 0.29). The presence of CVD risk factors were found to be increased in the JIA group compared to controls in three categories: family history of CVD (cohort 1), hypertension (cohort 2), and ever smokers (cohorts 2).

Conclusions—There is no increase in CVD events in patients with JIA 29 years following disease onset when compared to the general population. As these cohorts age, it will be

ADDRESS FOR CORRESPONDENCE (reprints and correspondence) Jason H. Anderson, MD, Mayo Clinic, Rochester, MN 55905, 507-538-0154 (phone), 507-284-0160 (fax), ; Email: Anderson.Jason@mayo.edu

informative to evaluate if this baseline risk remains present or a trend toward increasing CVD emerges. Continued longitudinal follow-up of these cohorts and larger population-based studies are needed to establish a definitive relationship between JIA and CVD.

Keywords

Arthritis; Juvenile; Cardiovascular Disease

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory arthritis among children and adolescents under the age of 16, with an estimated incidence of 1-12/100,000 and prevalence of 12-132/100,000 based on the source population[1]. Forty to fifty percent of patients affected with JIA will continue to demonstrate active disease in adulthood[2-6].

In adults with rheumatoid arthritis (RA), there is a 48% increased risk of incident cardiovascular disease (CVD), including myocardial infarction, cerebrovascular accidents, and congestive heart failure, in comparison to the general population[7]. This increased predisposition for CVD appears to be independent of established risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking[8], although an increase in the development of cardiovascular risk factors has also been demonstrated in the RA population [9, 10]. These results have led to formal recommendations for yearly cardiovascular risk assessment in patients with RA[11].

The role of inflammation and pathogenic overlap of JIA with adult inflammatory arthritis raises concern for an increased predisposition for CVD in adult patients with a prior diagnosis of JIA[12]. However, a study on the risk of developing cardiovascular events in adult patients previously diagnosed with JIA has yet to be reported. The objective of this study was to evaluate the frequency of CVD and CVD risk factors in adults with a prior diagnosis of JIA compared to controls.

METHODS

A retrospective, population-based cohort study was conducted utilizing patients at two academic institutions (Cohorts 1 and 2). Each institution employed a unique methodology to evaluate for the common endpoints of CVD outcomes and CVD risk factor development. Results from each cohort were compared to control groups of similar age and sex. CVD events diagnosed at the time of autopsy were excluded as these could not be adequately compared to a control group.

Cohort 1

Cohort 1 utilized a previously identified population-based cohort of 65 Rochester, Minnesota residents who fulfilled 1977 American College of Rheumatology criteria for juvenile rheumatoid arthritis (JRA), now denoted as JIA, in 1960-1993[13]. From this cohort, the patients with medical record data present at ≥ 30 years of age (41/65, 63%) as of December 31, 2012 were included in this study. The Rochester Epidemiology Project (REP) provided access to death certificates and to inpatient and outpatient health records from all health

providers in Olmsted County including the Mayo Clinic, Olmsted Medical Center and their affiliated hospitals[14]. Patient data was collected via medical record review and augmented with telephone interview if the patient was able to be contacted from available demographic information (25/41, 61%). Each of the 41 JIA patients was matched to a randomly selected control subject without JIA from the Rochester, Minnesota population, who was age 30 years in the same calendar year and of the same sex as the case. Data on controls was collected via medical record review. This study was approved by the Institutional Review Boards of the Mayo Clinic and the Olmsted Medical Center. Four patients out of the original participant group were deceased. One of the deceased had medical records present at age 40 and was included in the study. The remainder died prior to the age of 30 (3/65, 9%, age range 18-29) and were not included in the denominator for the study, but death certificates/ medical records were reviewed and included in the discussion below.

Cohort 2

Cohort 2 was established at Oslo University Hospital (OUH) in Oslo, Norway. The participant group was comprised of a previously described cohort of 373 patients who were first referred to OUH from 1980 through 1985 and diagnosed with JRA[4, 15, 16]. Patients evaluated after a median of 29 years disease duration (170/373, 46%) were included in the study[6, 17]. Evaluation at 29 years consisted of one of the following: a mailed questionnaire about cardiovascular comorbidity/risk factors if the patient did not have active disease at prior 15 and 23 year follow-up (86/170; 51%), or an extended clinical exam with interview if the patient did have active disease at 15 and/or 23 year follow-up (84/170; 49%). The data obtained were compared to a control group of 91 age and sex matched individuals randomly selected from the Norwegian population register who also participated in a clinical examination including an interview about cardiovascular comorbidity and risk factors. Twenty-five patients out of the original participant group (25/373, 7%, age range 13-42) were deceased at the time of 29 year follow up and were not included in the denominator for the study, but death certificates/medical records were reviewed at a later date and included in the discussion below.

Data Collection

Data collected for both cohorts included the presence of CVD, risk factors for CVD, use of an antihypertensive medication, and/or use of an antilipemic medication. CVD was defined as a prior clinical diagnosis (or patient report via telephone interview) of coronary artery disease, angina, atherosclerosis, congestive heart failure, myocardial infarction, peripheral artery disease, arterial thrombotic event, stroke, or sudden cardiac death. Risk factors for CVD were defined as a prior clinical diagnosis (or patient report via telephone interview) of hypertension, hyperlipidemia, diabetes mellitus, ever smokers, or family history of CVD (defined as myocardial infarction for cohort 1 and myocardial infarction, hypertension, ischemic stroke, diabetes mellitus, hypercholesterolemia, or angina pectoris for cohort 2) in a first degree relative (male < 55 years of age, female < 65 years of age). Blood pressure, lipids and body mass index values closest to age 30 years (± 5 years) were collected from the medical record for cohort 1.

Statistical Analysis

Descriptive statistics (means, percentages, etc.) were used to summarize the data. Characteristics of cases and controls were compared using chi-square and rank sum tests. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). P-values < 0.05 were considered significant.

RESULTS

Cohort 1 was comprised of 41 (68% female) patients with JIA and follow-up at ≥30 years of age. Mean age at follow-up was 45.8 years. Cohort 2 was comprised of 170 (78% female) patients with JIA and 29 year follow-up. Mean age at follow-up was 37.6 years. JRA subtype at diagnosis was similar in both groups with 30 (73%) pauciarticular, 8 (20%) polyarticular and 3 (7%) systemic in cohort 1 and 111 (65%) pauciarticular, 42 (25%) polyarticular and 17 (10%) systemic in cohort 2 (p=0.63).

In cohort 1, 3 patients (7%) had CVD, compared to 1 control (2%; p = 0.31; Table 1). Of these, 1 patient had CVD prior to age 30 with ages at time of CVD diagnosis ranging from 21-39 years. Types of CVD included 1 patient with venous and arterial thrombosis, 1 patient with coronary artery disease and myocardial infarction, and 1 patient with angina pectoris. The original JRA subtype for these patients included 2 pauciarticular and 1 polyarticular. Family history of CVD was present in 6 patients (15%) compared to 1 control (2%; p=0.048). No differences between JIA and controls were found for hypertension, hyperlipidemia, use of antihypertensive medication, use of antilipemic medication, diabetes mellitus, and smoking (ever).

In cohort 2, 2 patients (1%) had CVD, compared to 0 controls (p = 0.29; Table 1). Types of CVD included 1 patient with myocardial infarction and 1 patient with angina pectoris and myocardial infarction. The original JRA subtype for these patients was polyarticular. Hypertension was present in 14 patients (8%) compared to 2 controls (2%; p = 0.049). Smoking (ever) was present in 90 patients (53%) compared to 36 controls (40%; p = 0.03). No differences between JIA and controls were found regarding use of antihypertensive medication, use of antilipemic medication, family history of CVD, or presence of diabetes mellitus.

Data on BMI, blood pressure and lipid levels were also collected at age 30 (± 5) years in cohort 1. Patients with JIA had significantly lower BMI (mean: 25.1 vs 27.0; p=0.047; Table 2). No differences in blood pressure values between patients with JIA and controls were found. Low-density lipoprotein was somewhat higher in patients with JIA than in controls, but this difference did not reach statistical significance (mean 127.9 vs 110.7; p=0.051). Triglyceride levels were significantly lower in patients with JIA compared to controls (mean 100.3 vs 152.6; p=0.005).

In order to combine the data for cohorts 1 and 2, the follow-up for patients in cohort 1 was truncated at 29 years following date of disease onset. Of the 41 patients with JIA in cohort 1, 30 patients (30/41, 73%) had data meeting this criteria. The combined data are presented in Table 3. Unfortunately, a few CVD events were lost when follow-up was truncated in cohort

1. In this combined cohort, 3 patients (3/200, 2%) with JIA had CVD in comparison to 0 controls (p=0.18). Analysis for the presence of risk factors demonstrated 108 patients (108/200, 54%) with JIA being ever smokers in comparison to 49 controls (49/121, 40%; p=0.019). No statistically significant difference existed between the JIA cohort and control group in regards to CVD events, hypertension, use of antihypertensive medication, use of antilipemic medication, or diabetes mellitus.

Deceased patients did not contribute to clinically apparent CVD events in either cohort. However, CVD events discovered upon review of autopsy reports and death certificates in the deceased patients from each cohort are summarized here. Of those deceased in cohort 1, 1 patient had celiac and hepatic artery thromboses (40 years of age), 1 patient had coronary artery disease and aortic atherosclerosis (19 years of age), and 1 had aortic, cervical, and cranial atherosclerosis (18 years of age). Of those deceased in cohort 2, 1 patient had atherosclerosis of the tibial arteries (24 years of age).

DISCUSSION

To our knowledge, this is the first longitudinal study of patients with JIA evaluating the occurrence of CVD events in adulthood. The data shows there is no increase in CVD events in patients with JIA 29 years following disease onset when compared to the general population. As these cohorts age, it will be informative to evaluate if this baseline risk remains present or a trend toward increasing CVD emerges. A reasonable approach to this evaluation would include repeating this study in 10 years for a decade by decade analysis of the CVD and CVD risk factor trend.

Given the difficulty involved in completing a longitudinal cohort evaluation, other investigators have evaluated surrogate markers of CVD in patients with a diagnosis of JIA. The three primary non-invasive techniques utilized are flow-mediated dilation, carotid intima-media thickness, and pulse wave velocity. These modalities are vascular measures of early atherosclerosis and several investigators have demonstrated these markers to be abnormal or significantly different in patients with JIA in comparison to control groups[17-21]. Coulson *et al* completed a recent review summarizing the literature available on this subject and concluded that while surrogate markers in JIA patients suggest cardiovascular abnormalities, there is an unclear relationship between long-term cardiovascular risk and JIA and further studies are necessary[12]. The current study aimed to fill this void.

CVD risk factors were also assessed in this study and found to be increased in the JIA group as compared to controls in three categories: family history of CVD (cohort 1), hypertension (cohort 2), and ever smokers (cohort 2 and combined cohort). The significance of these findings is unclear as multiple confounding variables exist, such as level of systemic inflammation, disease duration, presence of pro-thrombotic state (as in presence of anti-phospholipid antibodies for example), medication utilization, and degree of physical activity in each patient. Unfortunately, due to the retrospective nature of the review, these data were unable to be collected. Differences in the way CVD family history was defined between the cohorts might explain why this variable was found to be increased (in comparison to

controls) in cohort 1 but not cohort 2. Lifestyle and geographic location differences between the two sites may also account for differences in CVD risk factors between cohorts.

There are multiple limitations in the completion of this study. These include a relatively small number of patients in cohort 1, a significant number of patients lost to follow-up or unable to be contacted, and the inability to include CVD events discovered on autopsy due to lack of a control group for this subset. This study was also limited by the inability to fully combine the two cohorts due to differences in inclusion criteria and the availability of data collected in a retrospective manner. For example, differences in timing of initial patient accrual resulted in a higher mean age in cohort 1 compared to cohort 2.

Future studies are needed to clarify the relationship between CVD, CVD risk factor development, and JIA. Multi-center collaboration will likely be necessary to achieve the patient volume necessary to document this pattern. Future directions also include stratification by JIA subtype, treatment regimen (including early aggressive treatment and use of biologic medications), presence of anti-phospholipid antibodies, and disease duration.

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ABBREVIATIONS

JRA	juvenile rheumatoid arthritis
JIA	juvenile idiopathic arthritis
RA	rheumatoid arthritis
CVD	cardiovascular disease

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Table 1

Comparison of cardiovascular events and risk factors in Olmsted County (Cohort 1) and Oslo (Cohort 2) cohorts of patients with juvenile idiopathic arthritis and controls.

	Cohort 1			Cohort 2		
Characteristic	**JIA (n = 41)**	**Controls (n = 41)**	***P* Value**	**JIA (n = 170)**	**Controls (n = 91)**	***P* Value**
Current age, years, mean (±SD)	45.8 (± 9.8)	45.9 (± 9.6)	0.97	37.6 (± 4.4)	37.5(± 4.4)	0.99
Sex, female	28 (68%)	28 (68%)	1.0	132 (78%)	71 (78%)	1.0
CVD, ever	3 (7%)	1 (2%)	0.31	2 (1%)	0 (0%)	0.29
Hypertension	12 (29%)	12 (29%)	1.0	14 (8%)	2 (2%)	**0.049**
Use of Antihypertensive Medication, ever	5 (12%)	9 (42%)	0.24	8 (5%)	2 (2%)	0.30
Hyperlipidemia	15 (37%)	16 (39%)	0.82	-	-	-
Use of Antilipemic Medication, ever	6 (15%)	9 (22%)	0.39	3 (2%)	0 (0%)	0.20
Diabetes Mellitus	5 (12%)	2 (5%)	0.24	1 (1%)	1 (1%)	0.20
Family History of CVD*	6 (15%)	1 (2%)	**0.048**	86 (51%)	43 (47%)	0.51
Smoker, ever	21 (51%)	20 (49%)	0.83	90 (53%)	36 (40%)	**0.03**

Values in table are n (%) except where specified.

*Family history defined as myocardial infarction in first degree relative (male < 55, female < 65) for cohort 1 and CVD (myocardial infarction, hypertension, ischemic stroke, diabetes mellitus, hypercholesterolemia or angina pectoris) in first degree relative (male < 55, female < 65) for cohort 2

Table 2

Comparison of cardiovascular risk factors at age 30 years in Olmsted County (Cohort 1) cohort of patients with juvenile idiopathic arthritis and controls.

	JIA		Controls		
Characteristic	**n**	**value**	**n**	**value**	***P* Value**
Body mass index, kg/m^2	39	25.1 (± 5.6)	41	27.0 (± 5.5)	**0.047**
Systolic blood pressure, mmHg	39	118.2 (± 17.9)	41	117.0 (± 16.4)	0.70
Diastolic blood pressure, mmHg	38	72.1 (± 10.4)	41	71.4 (± 12.2)	0.64
Total cholesterol, mg/dL	26	199.1 (± 35.1)	35	192.3 (± 35.1)	0.34
Low-density lipoprotein, mg/dL	20	127.9 (± 37.7)	33	110.7 (± 34.9)	0.051
High density lipoprotein, mg/dL	20	53.9 (± 15.6)	34	52.7 (± 12.4)	0.94
Triglycerides, mg/dL	26	100.3 (± 56.7)	34	152.6 (± 93.3)	**0.005**

Values in table are mean (±SD) except where specified.

Table 3

Comparison of cardiovascular events and risk factors at 29 years of follow-up in Olmsted County (Cohort 1) and Oslo (Cohort 2) cohorts of patients with juvenile idiopathic arthritis and controls combined.

Characteristic	JIA (n = 200)	Controls (n = 121)	*P* Value
CVD, Ever	3 (2%)	0 (0%)	0.18
Hypertension	18 (9%)	5 (4%)	0.10
Use of Antihypertensive Medication, ever	11 (6%)	3 (2%)	0.20
Use of Antilipemic Medication, ever	5 (3%)	1 (1%)	0.28
Diabetes Mellitus	6 (3%)	1 (1%)	0.20
Smoker, Ever	108 (54%)	49 (40%)	**0.019**

Values in table are n (%) except where specified.