Stressful Life Events Antedating Chronic Childhood Arthritis

Kate M. Neufeld, Chandima P. Karunanayake, Lynn Y. Maenz, and Alan M. Rosenberg

ABSTRACT. ***Objective.*** To investigate associations between antecedent stressful life events and occurrence of juvenile arthritis (JA).

Methods. The study population comprised patients with JA referred to a pediatric rheumatology clinic between 1981 and 2010. A questionnaire, which was developed as a screening tool by the clinic, was completed at the first clinic visit by patients' parents and, for comparison, by parents of unrelated age, sex, geographically, and temporally matched healthy controls. The entire questionnaire captured a broad array of clinical, demographic, psychosocial, and environmental data, including questions about stressful life events from 686 patients with JA and from 1042 controls.

Results. Patients were more likely to have experienced a serious upset (OR 4.81; $p < 0.0001$), a currently ill family member (OR 2.29; $p < 0.0001$), separated parents (OR 1.96; $p < 0.0001$), or difficulties with interpersonal relationships (OR 2.54; $p < 0.0001$) prior to first clinic presentation compared to controls. Children with oligoarticular JA were more likely than controls to have experienced a serious upset (OR 3.46; $p = 0.008$), an ill family member (OR 3.79; CI 2.02, 7.11; $p < 0.0001$), or problems with interpersonal interactions (OR 3.32; $p < 0.0001$). Children with polyarticular JA were more likely to have experienced a serious upset (OR 5.68; $p < 0.0001$), separated parents (OR 2.66; $p = 0.001$), a deceased parent (OR 6.75, $p = 0.017$), or problems with interpersonal relationships (OR 2.39; $p = 0.009$). No significant differences were observed when comparing systemic JA patients to controls.

Conclusion. Strong associations between stressful life events antedating the first clinic visit of patients with JA indicate that life event stresses should be identified and addressed when first encountering and managing children with JA. (J Rheumatol First Release Aug 15 2013; doi:10.3899/jrheum.121505)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS
JUVENILE RHEUMATOID ARTHRITIS
PSYCHOSOCIAL FACTORS
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Juvenile idiopathic arthritis (JIA), like the former juvenile rheumatoid arthritis (JRA) classification, denotes a heterogeneous group of chronic arthritides beginning before age 16 years. Like many rheumatic diseases, the etiologies of chronic forms of juvenile arthritis (JA) are unknown but are believed to have complex origins that include interactions between an array of susceptibility genes and environmental factors[1]. The roles of exogenous antecedent factors influencing the onset of JA also remain unknown, although psychosocial stress[2], infection[3,4,5], and environmental toxicants[6] have each been proposed as possible factors influencing the onset, course and outcomes of arthritis in children.

The role of psychosocial stress in JA is not firmly established; yet there is compelling evidence from earlier retrospective studies that supports a possible association between stressful life events and JA onset[2,7,8,9,10].

Interaction among immune, endocrine, and central nervous system mediators is the cornerstone of neuroendocrine-immune models of disease and the pathogenic process presumed to explain the link between stress and autoimmunity[11]. A peripheral cytokine response is by α1- and β-adrenergic receptors on mononuclear cells[12]. Patients with JA may have exaggerated inflammatory responses to stress since peripheral blood mononuclear cells of children with JA are associated with increased expression of α1-adrenergic receptors[13]. Certain pro-inflammatory cytokine single nucleotide polymorphisms are associated with heightened cytokine production in response to stress so that some individuals might be genetically predisposed to exaggerated stress-induced inflammatory responses[14].

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At the time of a child's first visit to our pediatric rheumatology clinic, a comprehensive questionnaire is completed by the patient's parent, obtaining information about a broad array of clinical, demographic, family history, psychosocial, and environmental variables. The questionnaire asks questions reflecting stressful life events antedating the first clinic presentation. The availability of our large prospectively collected dataset provided an opportunity to further explore potential relationships between antecedent stressful life events and JA.

The objective of this study was to investigate our large database for responses to stressful life event questions from patients with JA and matched controls. The results indicate associations between stressful life events antedating the first clinic visit of certain subsets of JA. These results support the need for future studies that prospectively apply validated, stressful life event measurement tools to precisely define and understand the multifaceted determinants of chronic childhood arthritis.

MATERIALS AND METHODS

The study populations were derived from an inception cohort database comprising all 4185 patients referred by a physician for a suspected rheumatic disease to the Pediatric Rheumatic Disease Clinic, University of Saskatchewan, during the 29 year period from 1981 to 2010. Since July 1981, data pertaining to all subjects referred to the Pediatric Rheumatology Program, University of Saskatchewan (the only pediatric rheumatology program serving the province of Saskatchewan), were prospectively entered into a computerized database. Only one pediatric rheumatologist (AR) interviewed and examined all subjects and assigned diagnostic labels. The study was approved by the University of Saskatchewan's Biomedical Research Ethics Board (Bio #09-75).

JA was defined as arthritis of unknown cause in 1 or more joints beginning before age 16 years and lasting 6 weeks or longer. JA subsets, identified for the purpose of this study, were oligoarticular, polyarticular, and systemic JA. These subsets conform to categories for JRA[15], the nomenclature denoting classification criteria applicable throughout most of the registration period, and correspond to the respective subsets in the current JIA classification system[16]. Diagnosis was made within 6 weeks of first clinic visit. Within our population, children whose diagnosis changed from oligoarticular to psoriatic arthritis (because psoriasis emerged later) or arthritis associated with inflammatory bowel disease (because gastrointestinal manifestations occurred later) were not included in the analysis.

Data were collected using questionnaires completed by a primary caregiver of the referred patients at the time of first visit to the clinic. The questionnaire was developed by our clinic and intended as a screening questionnaire that could help inform future studies. The questionnaire comprised 160 questions capturing information pertaining to a wide array of clinical, demographic, environmental, and psychosocial factors including screening information about stressful life events (Figure 1). For comparison, parents of patients were requested to recruit the parent of a biologically unrelated child of the same age and sex, living in the same neighborhood at approximately the same time to complete the same questionnaire. As a result of this process, a pool of 1042 control subjects was generated (that is, 24.9% of the parents of the total clinic group of 4185 patients arranged for a control subject). From this control pool, control subgroups were generated that were matched for age, sex, year, and geographic region to each of the respective JA subtypes. All eligible controls satisfying matching criteria were incorporated into the respective control groups; there was no sampling of controls as all eligible controls who met the matching criteria were utilized.

Within the entire clinic population of 4185 children, 686 children (16.4%) were diagnosed as having chronic idiopathic arthritis and, of these, 373 were diagnosed with systemic, oligoarticular or polyarticular JA in accord with classification criteria for JRA, the nomenclature applied for most of the data collection period (Figure 2). Not included in this current analysis were subjects who, by current JIA categorizations, would be classified as having psoriatic, enthesitis-related, or undifferentiated JIA. Both the collective JA population and populations stratified for the 3 designated JA subtypes were compared to healthy control populations matched for sex, age, geographic region of residence (corresponding to each of 13 provincial health regions), and time. The sex and age characteristics of the patients and corresponding control groups are shown in Table 1. Children were not matched for ethnicity as numbers of patients and corresponding controls were insufficient to be matched for this criterion.

At the time of the first clinic visit, the following information regarding stressful life event factors was collected: parental separation, death of a parent, illness of a family member, experience with any serious upset or serious loss at about the time of symptom onset, recent death of anyone close to the child (including pets), and any problems getting along with others. More precise details about the stressful event and the amount of time between the stressful event and onset of symptoms were not captured in this screening questionnaire. Social factors that were analyzed for confounder effects included mother's employment outside the home, ethnicity, and rural or urban residency.

Analysis. Data were analyzed using logistic regression analyses, both univariate and multivariate, using SPSS v18.0 and SAS v9.1. A series of bivariable logistic regression models were fitted to determine potential risk factors and confounders that contribute significantly to the prevalence of disease. In each model the dependent variable was a binary outcome, specified as disease group versus healthy controls. We considered models with the following disease groups: (1) entire JA group; (2) oligoarticular JA; (3) rheumatoid factor (RF)-negative polyarticular; (4) RF-positive polyarticular; and (5) systemic JA. Independent variables included in this analysis were information regarding stressful life event factors, including parental separation, death of a parent, illness of a family member, experience with any serious upset or serious loss at about the time of symptom onset, recent death of anyone close to the child (including pets), and any problems getting along with others. Covariates included in the analysis were mother's employment outside the home, ethnicity, live in a city, and rural or urban residency.

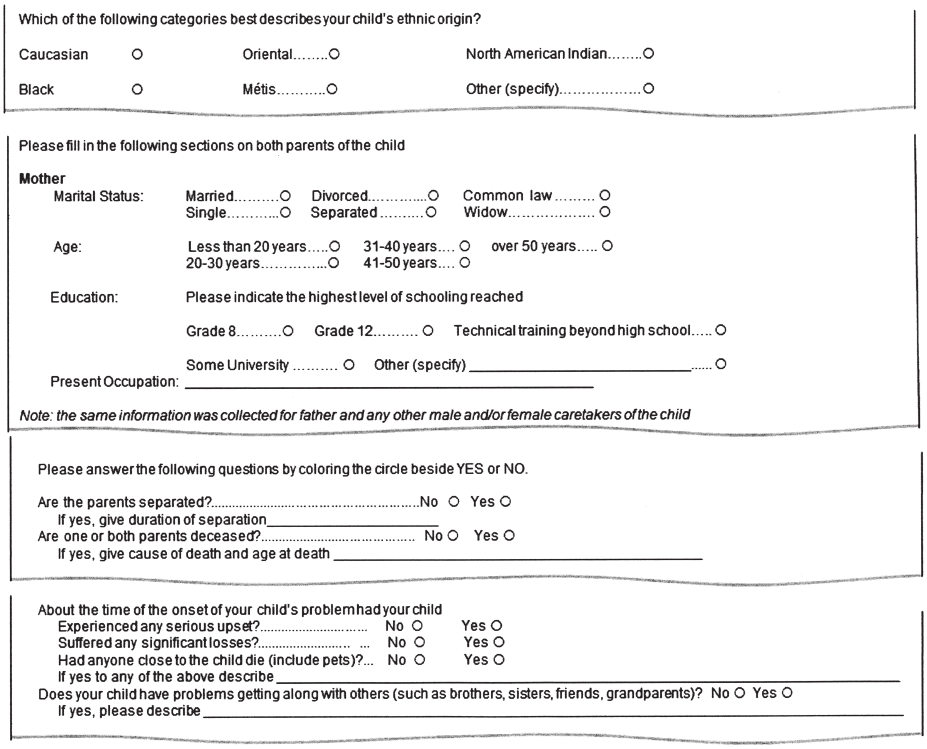
We tested 11 bivariable (one at a time) models for each stressful event factor listed above. After selecting the candidate variables, multivariate models were fitted. The number of interaction terms tested varied for each factor; between 12 and 20 models were tested for each factor.

Based on bivariable analysis, variables with $p < 0.20$ became candidates for a multivariable model. Of those, a variable with ≥ 15% missing data was not included in the multivariate logistic regression analysis. All statistically significant ($p < 0.05$) variables were retained in the final multivariable model. The strength of associations is described by odds ratios and their 95% confidence intervals.

RESULTS

The entire JA population (oligoarticular, polyarticular, and systemic JA) consisted of 373 children (33.8% males, 66.2% females; mean age ± SD: 8.1 ± 4.8 yrs). The control group included 987 children (37.1% males, 62.9% females; mean age ± SD: 10.7 ± 4.3 yrs) (Table 1).

Entire JA group. Table 2 shows the univariate and multivariate analyses comparing the JA group to healthy controls. As reported at the time of initial visit to the pediatric rheumatology clinic, children in the JA group were more likely to have experienced stressful events, including



Which of the following categories best describes your child's ethnic origin?

Caucasian O Oriental……O North American Indian……O

Black O Métis……O Other (specify)……O

Please fill in the following sections on both parents of the child

Mother

Marital Status: Married……O Divorced……O Common law……O
Single……O Separated……O Widow……O

Age: Less than 20 years…..O 31-40 years…. O over 50 years….. O
20-30 years……O 41-50 years…. O

Education: Please indicate the highest level of schooling reached

Grade 8……O Grade 12…… O Technical training beyond high school….. O

Some University …… O Other (specify) _____…..O

Present Occupation: _____

Note: the same information was collected for father and any other male and/or female caretakers of the child

Please answer the following questions by coloring the circle beside YES or NO.

Are the parents separated?……No O Yes O
If yes, give duration of separation_____
Are one or both parents deceased?…… No O Yes O
If yes, give cause of death and age at death _____

About the time of the onset of your child's problem had your child
Experienced any serious upset?…… No O Yes O
Suffered any significant losses?…… No O Yes O
Had anyone close to the child die (include pets)?... No O Yes O
If yes to any of the above describe _____
Does your child have problems getting along with others (such as brothers, sisters, friends, grandparents)? No O Yes O
If yes, please describe _____

Figure 1. Selected excerpts from the Pediatric Rheumatic Disease Questionnaire. Representative elements pertinent to the current study are depicted. The questionnaire was designed by our clinic and intended as a screening questionnaire that could help inform future studies. The questionnaire comprised 160 questions and collected demographic characteristics (e.g., age, sex, ethnicity); epidemiologic information (e.g., region of residence and parental marital, health and occupational status); stressful life events; family history; and pregnancy, developmental, immunization, and past medical histories.

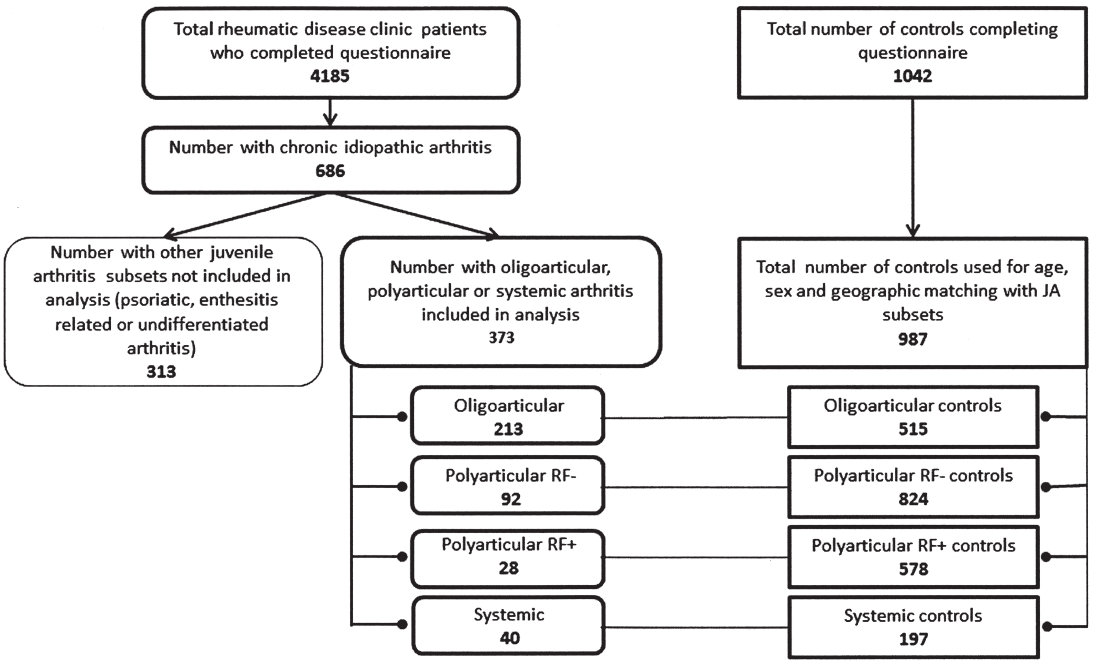


Figure 2. Depiction of the number of children in the juvenile arthritis and control population groups.

Table 1. Characteristics of juvenile arthritis (JA) and corresponding control groups.

	n	Sex M, %; F, %	Age, yrs mean ± SD
Oligoarticular			
Oligoarticular JIA	213	34:66	6.9 ± 4.3
Olligoarticular control	515	35:65	8.5 ± 3.8
Polyarticular			
Polyarticular JIA	120	24:76	10.6 ± 4.7
Polyarticular control	798	24:76	10.7 ± 4.1
Polyarticular RF–			
Polyarticular RF–	92	27:73	9.8 ± 4.8
Polyarticular RF– control	824	27:73	10.6 ± 4.2
Polyarticular RF+			
Polyarticular RF+ JIA	28	14:86	13.2 ± 3.3
Polyarticular RF+ control	578	14:86	13.2 ± 3.1
Systemic			
Systemic JIA	40	60:40	7.4 ± 4.8
Systemic control	197	59:41	9.9 ± 4.3

JIA: juvenile idiopathic arthritis; RF–: rheumatoid factor negative; RF+: rheumatoid factor positive.

separation of parents (OR 1.96; 95% CI 1.31, 2.94; p < 0.001), have a family member currently ill (OR 2.29; 95% CI 1.44, 3.63; p < 0.0001), experienced a serious upset (OR 4.81; 95% CI 2.23, 10.37; p < 0.0001), or had problems getting along with others (OR 2.54; 95% CI 1.63, 3.96; p < 0.0001) (Table 2). Children in the JA group were also more likely to be of aboriginal (North American Indian or Métis) ethnicity (OR 4.96; 95% CI 3.12, 7.88; p < 0.0001) compared to Caucasian or "other" ethnicity and were less likely to have their mother employed outside the home (OR 0.64; 95% CI 0.48, 0.86; p = 0.001) (Table 2). There were no differences between the JA group and healthy controls for the following factors: the death of one or both parents, suffering any significant losses, anyone close to the child died, lived in a city, or rural residence (Table 2).

Multivariate analysis showed significant differences between the JA group and controls for the following factors: separation of parents (OR 1.65; 95% CI 1.02, 2.67; p = 0.042), any member of the family currently ill (OR 1.94; 95% CI 1.16, 3.26; p = 0.012), problems getting along with others (OR 2.37; 95% CI 1.46, 3.85; p = 0.001), and aboriginal ethnicity (OR 2.45; 95% CI 1.34, 4.46; p = 0.004) (Table 2). JA patients were less likely to have a mother employed outside the home (OR 0.65; 95% CI 0.47, 0.90; p = 0.009) compared to controls (Table 2).

Oligoarticular JA subgroup. For the oligoarticular JA subgroup compared to matched controls, patients were more likely to have experienced an ill family member (OR 3.79; 95% CI 2.02, 7.11; p < 0.0001), a serious upset (OR 3.46; 95% CI 1.32, 9.06; p = 0.008), and problems getting along with others (OR 3.32; 95% CI 1.77, 6.21; p < 0.0001) before their first clinic visit (Table 3). Children with oligoarticular JA were also more likely to be of aboriginal ethnicity (OR 2.51; 95% CI 1.23, 5.14; p = 0.009) compared to controls (Table 3). There were no differences between the oligoarticular JA subgroup and healthy controls for the following factors: parents separated, one or both parents deceased, any significant losses, death of anyone close to the child, mother employed outside the home, and rural residence or living in a city (Table 3).

Multivariate analysis showed that any member of the family currently ill (OR 3.16; 95% CI 1.61, 6.22; p = 0.001) and having problems getting along with others (OR 3.42; 95% CI 1.80, 6.52; p < 0.0001) were more likely in the oligoarticular JA subgroup compared to controls (Table 3). There were no differences between the oligoarticular JA subgroup and healthy controls for separated parents and ethnicity (Table 3).

RF-negative polyarticular JA subgroup. For the RF-negative polyarticular JA subgroup compared to matched controls, patients were more likely to have separated parents (OR 2.83; 95% CI 1.52, 5.29; p = 0.001), have experienced a serious upset (OR 8.25; 95% CI 2.66, 25.57; p < 0.0001), and have problems getting along with others (OR 2.72; 95% CI 1.31, 5.66; p = 0.011) before the first clinic visit (Table 4). These patients were less likely to have a mother employed outside the home (OR 0.64; 95% CI 0.48, 0.86; p = 0.003) (Table 4). Children with RF-negative polyarticular JA were also more likely to be of aboriginal ethnicity (OR 9.32; 95% CI 4.91, 17.71; p < 0.0001) compared to controls.

Multivariate analysis supports that RF-negative polyarticular JA patients are more likely to have separated parents (OR 2.45; 95% CI 1.12, 5.41; p = 0.026) and less likely to have a mother employed outside the home (OR 0.50; 95% CI 0.27, 0.91; p = 0.025), and be aboriginal (OR 4.66; 95% CI 1.98, 10.95; p < 0.0001) compared to controls (Table 4).

RF-positive polyarticular JA subgroup. RF-positive polyarthritis was less likely in children who had a mother employed outside the home (OR 0.30; 95% CI 0.11, 0.85; p = 0.016) or those who previously lived in a city (OR 0.34; 95% CI 0.14, 0.84; p = 0.014) (Table 5). Children in this subgroup were also more likely to report being of aboriginal ethnicity (OR 12.24; 95% CI 4.52, 33.20; p < 0.0001) (Table 5). Odds ratio and confidence intervals could not be calculated for certain factors including one or both parents deceased and any significant losses due to low response rate.

Multivariate analysis indicated that children in the RF-positive polyarticular JA subgroup were more likely to be of aboriginal ethnicity (OR 10.80; CI 3.22, 36.29; p < 0.0001) (Table 5). Children with mothers employed outside the home or who have lived in a city showed no significant difference when compared to controls.

Systemic JA subgroup. The only factor significant in the systemic JA subgroup was ethnicity, with 18.4% families reporting aboriginal ethnicity compared to only 5.6% of

Table 2. Comparing psychosocial factors, ethnicity, and rural/urban residency between entire juvenile arthritis (JA) and control groups.

Factor	Entire JA Population, n (%)	Controls, n (%)	p	OR (95% CI)
Univariate analysis				
Parents separated (n = 1175)*				
Yes	40 (17.0)	89 (9.5)	< 0.001	1.96 (1.31, 2.94)
No	195 (83.0)	851 (90.5)		
One or both parents deceased (n = 1174)				
Yes	3 (1.3)	5 (0.5)	0.212	2.43 (0.58, 10.24)
No	231 (98.7)	935 (99.5)		
Family currently ill (n = 1199)				
Yes	31 (12.9)	58 (6.1)	< 0.0001	2.29 (1.44, 3.63)
No	210 (87.1)	900 (93.9)		
Serious upsets (n = 549)				
Yes	29 (12.4)	9 (2.9)	< 0.0001	4.81 (2.23, 10.37)
No	205 (87.6)	306 (97.1)		
Significant losses (n = 548)				
Yes	6 (2.6)	8 (2.5)	0.968	1.02 (0.35, 2.99)
No	226 (97.4)	308 (97.5)		
Anyone close to the child died (n = 556)				
Yes	20 (8.5)	34 (10.6)	0.397	0.78 (0.44, 1.39)
No	216 (91.5)	286 (89.4)		
Problems getting along with others (n = 1183)				
Yes	35 (14.7)	60 (6.3)	< 0.0001	2.54 (1.63, 3.96)
No	203 (85.3)	885 (93.7)		
Mother employed outside home (n = 1179)				
Yes	130 (55.8)	627 (66.3)	0.003	0.64 (0.48, 0.86)
No	103 (44.2)	319 (33.7)		
Ethnic groups (n = 1294)				
Aboriginal	48 (14.9)	33 (3.4)	< 0.0001	4.96 (3.12, 7.88)
Caucasian or other	275 (85.1)	938 (96.6)		
Urban/rural residence (n = 1340)				
Rural	176 (47.3)	478 (49.4)	0.498	0.92 (0.73, 1.17)
Urban	196 (52.7)	490 (50.6)		
Lived in a city (n = 1251)				
Yes	134 (49.3)	494 (50.5)	0.727	0.95 (0.73, 1.25)
No	138 (50.7)	485 (49.5)		
Multivariate analysis				
Parents separated			0.042	1.65 (1.02, 2.67)
Member of family ill			0.012	1.94 (1.16, 3.26)
Mother employed outside home			0.009	0.65 (0.47, 0.90)
Problems getting along with others			0.001	2.37 (1.46, 3.85)
Aboriginal			0.004	2.45 (1.34, 4.46)

* n values in left column = (number of patients with JA plus number of controls) minus missing data.

families in the control group for univariate analysis (OR 3.78; 95% CI 1.36, 10.49; p = 0.007). All other factors showed no differences between groups for univariate and multivariate analyses (Table 6).

All multivariate models shown in Tables 2 to 6 were investigated for combinations of 2 way interactions with factors having $p < 0.2$, as selected from the bivariable analyses excluding variables with ≥ 15% missing data. No 2-way interactions were significant at the 5% significant level.

DISCUSSION

The results of our assessment of responses to screening stressful life event questions from a large JA inception cohort database suggest an association between stressful events and the early stages of certain subtypes of JA. In particular, serious upsets, illness in the family, and problems with interpersonal relationships were significant stressful life events antedating the first clinic visit of oligoarticular JA. Experiencing a serious upset was also significant prior to the first clinic visit for seronegative polyarticular JA. Systemic and RF+ polyarticular JA subtypes, however, did not show the same stressful life events correlations, indicating that the association of stressful events preceding the onset JA is not generalizable to all JA subtypes. The seropositive polyarticular subset has an older onset age. The

Table 3. Comparing psychosocial factors, ethnicity, and urban/rural residency between oligoarticular juvenile arthritis (JA) and control groups.

Factor	Oligoarticular JA, n (%)	Controls, n (%)	p	OR (95% CI)
Univariate analysis				
Parents separated (n = 631)*				
Yes	18 (13.0)	39 (7.9)	0.063	1.75 (0.96, 3.16)
No	120 (87.0)	454 (92.1)		
One or both parents deceased (n = 631)				
Yes	1 (0.7)	2 (0.4)	0.630	1.79 (0.16, 19.91)
No	137 (99.3)	491 (99.6)		
Member of family ill (n = 639)				
Yes	21 (14.9)	22 (4.4)	< 0.0001	3.79 (2.02, 7.11)
No	120 (85.1)	476 (95.6)		
Serious upsets (n = 283)				
Yes	17 (12.7)	6 (4.0)	0.008	3.46 (1.32, 9.06)
No	117 (87.3)	143 (96.0)		
Significant losses (n = 284)				
Yes	3 (2.2)	3 (2.0)	0.903	1.11 (0.22, 5.57)
No	132 (97.8)	146 (98.0)		
Anyone close to the child died (n = 286)				
Yes	9 (6.6)	15 (10.1)	0.287	0.63 (0.26, 1.49)
No	128 (93.4)	134 (89.9)		
Problems getting along with others (n = 627)				
Yes	20 (14.6)	24 (4.9)	< 0.0001	3.32 (1.77, 6.21)
No	117 (85.4)	466 (95.1)		
Mother employed outside home (n = 634)				
Yes	84 (60.9)	322 (64.9)	0.381	0.84 (0.57, 1.24)
No	54 (39.1)	174 (35.1)		
Ethnic groups (n = 694)				
Aboriginal	15 (8.0)	17 (3.4)	0.009	2.51 (1.23, 5.14)
Caucasian or other	172 (92.0)	490 (96.6)		
Lived in a city (n = 664)				
Yes	85 (55.6)	274 (53.6)	0.673	1.08 (0.75, 1.55)
No	68 (44.4)	237 (46.4)		
Urban/rural residence (n = 719)				
Rural	89 (41.8)	236 (46.6)	0.232	0.82 (0.59, 1.13)
Urban	124 (58.2)	270 (53.4)		
Multivariate analysis				
Parents separated			0.230	1.52 (0.77, 2.99)
Member of family ill			0.001	3.16 (1.61, 6.22)
Problems getting along with others			< 0.0001	3.42 (1.80, 6.52)
Aboriginal			0.792	1.14 (0.42, 3.14)

* n values in left column = (number of patients with JA plus number of controls) minus missing data.

younger onset age in the oligoarticular and seronegative polyarticular subsets could confer more vulnerability to stressful events predisposing to JA, a suggestion consistent with observations that stressful events at a young age are more likely to be associated with later alterations of immune and inflammatory responses[17,18]. Systemic JA, which represents a particularly distinct JA clinical subset, could likely arise from immune and inflammatory pathogenic processes distinctively different from other JA subtypes and might not be influenced by stress. The numbers of subjects in the seropositive polyarticular and systemic JIA groups, which were smaller than the oligoarticular and seronegative polyarticular subsets, might have contributed to the failure to identify life event stressors that might be exposed with larger patient groups.

The observation that stressful life events are important antecedents of inflammatory joint diseases is not new. Paulus Aegineta (625-690 AD) wrote in reference to gout and arthritis: "Sorrow, care, watchfulness, and the other passions of the mind not only excite an attack of the disorder, but also generate a cacochymy either primarily or incidentally"[19]. The role of stress events in the onset of chronic childhood arthritis was first proposed in 1954 from a small prospective study (n = 28) in which it was suggested that emotional factors interacting with hormonal, genetic, traumatic, and infectious influences could lead to the onset

Table 4. Comparing psychosocial factors, ethnicity, and urban/rural residency between rheumatoid factor (RF) negative polyarticular juvenile arthritis (JA) and control groups.

Factor	RF-negative Polyarticular JA, n (%)	Controls, n (%)	p	OR (95% CI)
Univariate analysis				
Parents separated (n = 848)*				
Yes	15 (23.8)	78 (9.9)	0.001	2.83 (1.52, 5.29)
No	48 (76.2)	707 (90.1)		
One or both parents deceased (n = 849)				
Yes	2 (3.2)	5 (0.6)	0.089	5.12 (0.97, 26.94)
No	61 (96.8)	781 (99.4)		
Member of family ill (n = 856)				
Yes	6 (9.8)	49 (6.2)	0.190	1.66 (0.68, 4.05)
No	55 (90.2)	746 (93.8)		
Serious upsets (n = 321)				
Yes	9 (14.1)	5 (1.9)	< 0.0001	8.25 (2.66, 25.57)
No	55 (85.9)	252 (98.1)		
Significant losses (n = 319)				
Yes	3 (4.8)	5 (1.9)	0.189	2.56 (0.60, 11.03)
No	59 (95.2)	252 (98.1)		
Anyone close to the child died (n = 323)				
Yes	9 (14.5)	27 (10.3)	0.348	1.47 (0.65, 3.31)
No	53 (85.5)	234 (89.7)		
Problems getting along with others (n = 849)				
Yes	10 (15.9)	51 (6.5)	0.011	2.72 (1.31, 5.66)
No	53 (84.1)	735 (93.5)		
Mother employed outside home (n = 852)				
Yes	29 (47.5)	525 (66.4)	0.003	0.46 (0.27, 0.78)
No	32 (52.5)	266 (33.6)		
Ethnic groups (n = 887)				
Aboriginal	19 (25.0)	28 (3.5)	< 0.0001	9.32 (4.91, 17.71)
Caucasian or other	57 (75.0)	783 (96.5)		
Urban/rural residence (n = 899)				
Rural	51 (55.4)	395 (48.9)	0.238	1.30 (0.84, 2.00)
Urban	41 (44.6)	412 (51.1)		
Lived in a city (n = 888)				
Yes	29 (40.3)	414 (50.7)	0.089	0.66 (0.40, 1.07)
No	43 (59.7)	402 (49.3)		
Multivariate analysis				
Parents separated			0.026	2.45 (1.12, 5.41)
Any member of the family currently ill			0.603	1.31 (0.47, 3.67)
Mother employed outside the home			0.025	0.50 (0.27, 0.91)
Have problems getting along with others			0.107	2.04 (0.86, 4.88)
Aboriginal			< 0.0001	4.66 (1.98, 10.95)

* n values in left column = (number of patients with JA plus number of controls) minus missing data.

and flares of arthritis in children. The onset of arthritis was associated with "…an emotionally charged event" in one-third of patients and the maternal-child relationship was characterized by "…unusual closeness and intensity", an observation that might pertain to our finding that significantly fewer mothers of children with JA worked outside the home prior to disease onset[7].

A 1968 retrospective study reported by Meyerowitz and colleagues[8], examined 8 pairs of monozygotic twins discordant for chronic arthritis. The study reported that the twin with arthritis had less adequate defenses and had feelings of psychological vulnerability[8]. However, only 3 pairs of twins in the study had onset of arthritis during childhood. In 1972, Heisel, *et al*[9] surveyed 45 children with JA and matched controls for life event changes, including information about the death of a parent, grandparent, sibling or close friend; divorce of parents; or mother beginning to work prior to the onset of JA. The study showed that children who develop JA tend to have recently experienced significantly more changes in their world compared to the matched control group. In 1978, Henoch, *et al*[2] surveyed 88 children with JRA and compared the population to geographically matched children. Of the data on stressful life events (divorce, separation, death, or adoption), 51% occurred near the date of onset of the disease. Children with parents who were divorced, separated, or deceased

Table 5. Comparing psychosocial factors, ethnicity, and urban/rural residency between rheumatoid factor (RF) positive polyarticular juvenile arthritis (JA) and control groups.

Factor	RF-positive Polyarticular JA, n (%)	Controls, n (%)	p	OR (95% CI)
Univariate analysis				
Parents separated (n = 500)*				
Yes	0 (0.0)	1 (0.2)	0.975	—
No	14 (100.0)	553 (99.8)		
Member of family ill (n = 576)				
Yes	3 (16.7)	43 (7.7)	0.167	2.39 (0.67, 8.60)
No	15 (83.3)	515 (92.3)		
Serious upsets (n = 214)				
Yes	1 (5.9)	5 (2.5)	0.395	2.40 (0.26, 21.81)
No	16 (94.1)	192 (97.5)		
Significant losses (n = 212)				
Yes	0 (0.0)	5 (2.6)	0.673	—
No	16 (100.0)	191 (97.4)		
Anyone close to the child died (n = 218)				
Yes	2 (11.1)	23 (11.5)	0.659	0.96 (0.21, 4.45)
No	16 (88.9)	177 (88.5)		
Problems getting along with others (n = 574)				
Yes	2 (10.5)	38 (6.8)	0.387	1.60 (0.36, 7.19)
No	17 (89.5)	517 (93.2)		
Mother employed outside home (n = 573)				
Yes	6 (37.5)	370 (66.4)	0.016	0.30 (0.11, 0.85)
No	10 (62.5)	187 (33.6)		
Ethnic groups (n = 594)				
Aboriginal	7 (31.8)	21 (3.7)	< 0.0001	12.24 (4.52, 33.20)
Caucasian or other	15 (68.2)	551 (96.3)		
Urban/rural residence (n = 595)				
Rural	16 (59.3)	248 (43.7)	0.111	1.88 (0.86, 4.12)
Urban	11 (40.7)	320 (56.3)		
Lived in a city (n = 595)				
Yes	7 (30.4)	322 (56.3)	0.014	0.34 (0.14, 0.84)
No	16 (69.6)	250 (43.7)		
Multivariate analysis				
Mother employed outside the home			0.252	0.52 (0.17, 1.60)
Live in a city			0.160	0.42 (0.12, 1.41)
Aboriginal			< 0.0001	10.80 (3.22, 36.29)

* n values in left column = (number of patients with JA plus number of controls) minus missing data.

comprised 28.4% of the JA population and 10.6% of the comparison group.

Only one earlier study reported stressful life events in JA groups stratified by disease subtypes. Vandvik and colleagues[10] reported that, among a group of 106 Norwegian children, both chronic family difficulties and recent stressful life correlated with oligoarticular and polyarticular JA groups.

The clinical course of JA has also been observed to be influenced by major psychosocial stresses[20]. Rimon, *et al* described the role of major life events and chronic minor stresses as a provoking factor in JA and a stronger influence in JA than in adult rheumatoid arthritis (RA)[20].

A strength of our study is the inclusion of substantially larger patient and control populations compared to earlier reports. We acknowledge, however, that there are limitations to the present study, including recall bias due to the use of recalled information from patients' parents at the time of first clinic visit. The questionnaire in our study, designed as a screening tool for a wide array of conditions including stress events, did not include all possible stressful life events and there was no stress scale used to evaluate the relative impact of the various events. Even so, the results are sufficiently striking to warrant future studies designed specifically to address precise antecedent stress events in JA.

Our results suggest that in all subgroups analyzed, North American Indian or Métis representation was significantly higher in the patient population compared to the control group. However, the significance of ethnic differences we observed remains unclear as our patient and control groups were not matched for ethnicity. Thus, we do not know, for example, if parents of children of aboriginal ancestry were

Table 6. Comparing psychosocial factors, ethnicity, and urban/rural residency between systemic juvenile arthritis (JA) and control groups.

Factor	Systemic JRA, n (%)	Controls, n (%)	p	OR (95% CI)
Univariate analysis				
Parents separated (n = 208)*				
Yes	4 (21.1)	18 (9.5)	0.124	2.53 (0.76, 8.45)
No	15 (78.9)	171 (90.5)		
One or both parents deceased (n = 208)				
Yes	0 (0.0)	2 (1.1)	0.825	—
No	19 (100.0)	187 (98.9)		
Member of family ill (n = 213)				
Yes	1 (4.8)	12 (6.3)	0.626	0.75 (0.09, 6.07)
No	20 (95.2)	180 (93.8)		
Serious upsets (n = 72)				
Yes	2 (10.5)	1 (1.9)	0.168	6.12 (0.52, 71.76)
No	17 (89.5)	52 (98.1)		
Significant losses (n = 73)				
Yes	0 (0.0)	4 (7.4)	0.291	—
No	19 (100.0)	50 (92.6)		
Anyone close to the child died (n = 73)				
Yes	0 (0.0)	7 (13.0)	0.109	—
No	19 (100.0)	47 (87.0)		
Have problems getting along with others (n = 211)				
Yes	3 (15.8)	9 (4.7)	0.081	3.81 (0.94, 15.51)
No	16 (84.2)	183 (95.3)		
Mother employed outside home (n = 209)				
Yes	11 (61.1)	119 (62.3)	0.921	0.95 (0.35, 2.56)
No	7 (38.9)	72 (37.7)		
Ethnic groups (n = 233)				
Aboriginal	7 (18.4)	11 (5.6)	0.007	3.78 (1.36, 10.49)
Caucasian	31 (81.6)	184 (94.4)		
Urban/rural residence (n = 235)				
Rural	20 (50.0)	67 (34.4)	0.062	1.91 (0.96, 3.80)
Urban	20 (50.0)	128 (65.6)		
Lived in a city (n = 221)				
Yes	13 (54.2)	124 (62.9)	0.403	0.70 (0.30, 1.63)
No	11 (45.8)	73 (37.1)		
Multivariate analysis				
Parents separated			0.248	2.23 (0.57, 8.71)
Problems getting along with others			0.261	2.59 (0.49, 13.56)
Aboriginal			0.442	1.90 (0.37, 9.78)

* n values in left column = (number of patients with JA plus number of controls) minus missing data.

less likely to solicit a control subject of the same ethnicity. A future study, in which ethnicity and cultural influences on interpreting life events as stressful or not, is required.

We also acknowledge a potential control population selection bias inherent in the study design. It is possible that parents, who were asked to identify a control, might have been less inclined to approach a potential control respondent if the control contact was known to have contended with stressful life experiences. However, the substantial differences between the occurrence of stressful life events in the JA population and in the respective control groups makes it unlikely that selection bias alone, if any occurred, would account for all the observed differences. The questionnaire was not validated and the precise characteristics of the stressful life events were not defined. Further, the timing of the stressful life event in relation to the onset of arthritis was not determined. With the exception of systemic JIA the precise time of onset of other JIA subtypes ordinarily cannot be reliably determined[21]; consequently, identifying influences that definitely predate true disease onset is challenging.

Our observations and those of others suggest associations between antecedent stressful life events and the occurrence of JA. Future prospective studies, using validated data collection tools, to acquire more comprehensive and detailed life event stress data prior to disease onset will be required to more precisely determine the role of stress events in influencing disease occurrence and course. Future

studies would benefit from applying life course epidemiologic approaches in which an array of interacting social, economic, and biologic factors, including stressful events, occurring at various life stages can be evaluated as potential influences on the occurrence and course of future chronic diseases[22].

The results of our research suggest that it could be important, at first clinic visit, to consider life event stresses when evaluating and managing children with chronic arthritis.

REFERENCES

1. Firestein G. Etiology and Pathogenesis of Rheumatoid Arthritis. Philadelphia: W.B. Saunders, 2001.
2. Henoch MJ, Batson JW, Baum J. Psychosocial factors in juvenile rheumatoid arthritis. Arthritis Rheum 1978;21:229-33.
3. Aslan M, Kasapcopur O, Yasar H, Polat E, Saribas S, Cakan H, et al. Do infections trigger juvenile idiopathic arthritis? Rheumatol Int 2011;31:215-20.
4. Kunnamo I. Infections and related risk factors of arthritis in children. A case-control study. Scand J Rheumatol 1987;16:93-9.
5. Pugh MT, Southwood TR, Gaston JS. The role of infection in juvenile chronic arthritis. Br J Rheumatol 1993;32:838-44.
6. Albano SA, Santana-Sahagun E, Weisman MH. Cigarette smoking and rheumatoid arthritis. Semin Arthritis Rheum 2001;31:146-59.
7. Blom GE, Nicholls G. Emotional factors in children with rheumatoid arthritis. Am J Orthopsychiatry 1954;24:588-600; discussion, 600-1.
8. Meyerowitz S, Jacox RF, Hess DW. Monozygotic twins discordant for rheumatoid arthritis: a genetic, clinical and psychological study of 8 sets. Arthritis Rheum 1968;11:1-21.
9. Heisel JS. Life changes as etiologic factors in juvenile rheumatoid arthritis. J Psychosom Res 1972;16:411-20.
10. Vandvik IH, Høyeraal HM, Fagertun H. Chronic family difficulties and stressful life events in recent onset juvenile arthritis. J Rheumatol 1989;16:1088-92.
11. Stojanovich L. Stress and autoimmunity. Autoimmun Rev 2010;9:A271-6.
12. Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, et al. A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci U S A 2003;100:1920-5.
13. Roupe van der Voort C, Heijnen CJ, Wulffraat N, Kuis W, Kavelaars A. Stress induces increases in IL-6 production by leucocytes of patients with the chronic inflammatory disease juvenile rheumatoid arthritis: a putative role for alpha(1)-adrenergic receptors. J Neuroimmunol 2000;110:223-9.
14. Woo P. Cytokine polymorphisms and inflammation. Clin Exp Rheumatol 2000;18:767-71.
15. Brewer EJ, Jr., Bass J, Baum J, Cassidy JT, Fink C, Jacobs J, et al. Current proposed revision of JRA Criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. Arthritis Rheum 1977;20:195-9.
16. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
17. Slopen N, Kubzansky LD, McLaughlin KA, Koenen KC. Childhood adversity and inflammatory processes in youth: A prospective study. Psychoneuroendocrinology 2013;38:188-200.
18. Slopen N, McLaughlin KA, Dunn EC, Koenen KC. Childhood adversity and cell-mediated immunity in young adulthood: Does type and timing matter? Brain Behav Immun 2013;28:63-71.
19. Aegineta P. The Medical Works of Paulus Aegineta, Third Book, translated from the Greek by Francis Adams. London: Truettal, Wurtz, & Co, 1834:354.
20. Rimón R, Belmaker RH, Ebstein R. Psychosomatic aspects of juvenile rheumatoid arthritis. Scand J Rheumatol 1977;6:1-10.
21. Shapiro C, Maenz L, Hossain A, Pahwa P, Rosenberg A. Onset to first visit intervals in childhood rheumatic diseases. J Rheumatol 2007;34:1913-7.
22. Lynch J, Smith GD. A life course approach to chronic disease epidemiology. Annu Rev Public Health 2005;26:1-35.