Onset to First Visit Intervals in Childhood Rheumatic Diseases

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ABSTRACT. ***Objective.*** To determine time intervals between onset of symptoms of a childhood rheumatic disease and first visit to a pediatric rheumatology clinic and to evaluate factors influencing onset to first visit intervals.

Methods. Onset to first visit intervals were analyzed in 836 children representing the 10 most common diseases in a pediatric rheumatology clinic population of 1093.

Results. Among 836 subjects, 469 (56.1%) could identify month of symptom onset. Among patients with juvenile rheumatoid arthritis (JRA) 125 of 195 (64.1%) with pauciarticular, 58 of 105 (55.2%) with polyarticular, and 28 of 36 (77.8%) with systemic subtypes were able to determine time interval between symptom onset and first visit. Month intervals were confidently established in 80 of 250 with a spondyloarthropathy (32.4%), 19 of 52 (36.5%) with psoriatic arthropathy, 65 of 72 (90.3%) with Henoch-Schönlein purpura (HSP), 50 of 56 (89.3%) with Kawasaki disease, 22 of 34 (64.7%) with systemic lupus erythematosus, 13 of 18 (72.2%) with dermatomyositis, and 9 of 18 (50%) with localized scleroderma. Determination of onset was significantly more likely in HSP than in other diagnostic categories except systemic JRA, and more likely in Kawasaki disease than other disease categories except systemic JRA and dermatomyositis. In the group of 469, 287 (61.2%) were seen within 2 months of symptom onset and 447 (95.3%) within 1 year of symptom onset.

Conclusion. Diseases ordinarily typified by an abrupt and acute onset of symptoms were referred most promptly, suggesting that acuity of symptoms at disease onset is the factor that most influences promptness of referral. Prospective studies are required to establish how onset to first visit intervals might influence disease outcomes and to devise best practice referral guidelines. (First Release July 15 2007; J Rheumatol 2007;34:1913–7)

Key Indexing Terms:
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Childhood rheumatic disease outcomes should be favorably influenced by prompt diagnosis, timely referral to a pediatric rheumatology clinical care program, and early treatment. The promptness with which a child is recognized, diagnosed, and referred depends partly on disease and patient characteristics, acumen of the primary healthcare provider, and ease of accessibility to pediatric rheumatology clinical care services.

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Determining the duration between symptom onset and first visit to a pediatric rheumatology clinical care service should help to identify factors that might unfavorably influence onset to first visit intervals and guide approaches to reduce inordinately long delays in accessing pediatric rheumatology services. This analysis was conducted to document intervals between the symptom onset of certain of the most prevalent childhood rheumatic diseases and the child's first visit to a pediatric rheumatology clinic, and to identify factors that correlate with onset to first visit intervals. This information will help to evaluate and guide the provision of pediatric rheumatology clinical care services and resources.

MATERIALS AND METHODS

The study group was derived from a population of 3370 children (age ≤ 18 yrs) referred by a physician, because of a suspected rheumatic disease, to the Pediatric Rheumatic Disease Program, University of Saskatchewan, Saskatoon, during the 24-year period 1981 to 2005.

Since July 1981, data pertaining to all subjects referred via pediatric outpatient, emergency, and in-hospital services 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 management program. A single pediatric rheumatologist (AR) interviewed and examined all subjects and assigned diagnostic labels. Subjects for whom a diagnosis was

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established were assigned to a disease category by applying published or generally accepted diagnostic or classification criteria[1]. For consistency, the term juvenile rheumatoid arthritis (JRA[2]), the nomenclature denoting classification criteria applicable throughout most of the registration period, was retained in favor of juvenile idiopathic arthritis, a current classification system for certain juvenile arthritides[3]. A rheumatic disease was considered a condition ordinarily cared for by a pediatric rheumatologist or a condition for which pediatric rheumatology collaboration or consultation is reasonably requested[4].

Onset to first visit intervals were analyzed with reference to diagnostic category; patient age, sex, and ethnicity; whether the patient resided in an urban or rural region; and onset and referral year and season. Ethnicity was categorized as Caucasian, North American Indian (including subjects of mixed Caucasian and North American Indian ancestry), Black, Oriental, and Other. Urban and rural regions were categorized in accord with a definition provided by Statistics Canada (areas with a population concentration < 1000 and a population density of up to 400/km^2, as defined[5]). Year and season of symptom onset were documented at the time of initial presentation from information provided by the primary historian at first visit. Onset information that could not be confidently provided was categorized as unknown. Seasonal categories were designated as March, April, and May (spring); June, July, and August (summer); September, October, and November (fall); and December, January, and February (winter).

First-visit date was the date the patient was first seen in the pediatric rheumatology clinic, which in accord with the clinic protocol occurred within 6 weeks of receiving a request for consultation.

For analytical purposes intervals between symptom onset and first visit were assigned to 4 ordinal categories defined as 0 to 3 months, > 3 months but < 7 months, > 7 months but < 12 months, and ≥ 12 months.

Statistical analysis. Data were analyzed using the Statistical Package for the Social Sciences and Statistical Analytical Software (SPSS Inc.). Differences in the frequencies with which onset month could be determined reliably among groups were analyzed by chi-square. Differences in categories of onset to first visit intervals among diagnostic groups were analyzed by ordinal logistic regression using interval category as the dependent variable and diagnosis as the covariate. Ordinal logistic regression was applied to analyze potential associations between onset to first visit intervals and age, sex, ethnicity, urban/rural residence, and onset and referral year and season. The number of months between symptom onset and first visit were compared using independent samples t tests, assigning Henoch-Schönlein purpura as the reference diagnostic group.

RESULTS

Of the 3370 subjects referred with a suspected rheumatic disease, 1093 (32.4%) had a rheumatic disease, 390 (11.5%) had musculoskeletal conditions associated with nonrheumatic orthopedic conditions, 615 (18.2%) had other nonrheumatic conditions, 1198 (35.6%) had conditions for which a diagnosis had not been established, and, following evaluation, 74 (2.2%) were found to be normal. Of the 1093 with a rheumatic disease, 195 (17.8%) had pauciarticular, 105 (9.6%) polyarticular, and 36 (3.3%) systemic onset JRA; 250 (22.9%) had juvenile ankylosing spondylitis (JAS), probable JAS or the seronegative enthesopathy arthropathy (SEA) syndrome[6]; 52 (4.8%) juvenile psoriatic arthritis (JPsA) or probable JPsA; 72 (6.6%) had Henoch-Schönlein purpura (HSP); 56 (5.1%) Kawasaki disease; 34 (3.1%) systemic lupus erythematosus (SLE); and 18 each (1.7%) had localized scleroderma and dermatomyositis (DM). The remaining 257 patients (23.5%) represented a variety of other rheumatic disease categories that each comprised an insufficient number of patients for effective analysis. Thus, to evaluate onset to first visit intervals the study population comprised 836 patients representing the 10 most prevalent diagnosed rheumatic diseases within the clinic population.

The study group of 836 comprised 473 (56.6%) females and 363 (43.4%) males. The mean age at onset of the group of 623 who could identify onset age was 8.2 ± 4.63 years. 672 were Caucasian (80.4%) and 96 (12.1%) of North American Indian or mixed Caucasian-North American Indian ancestry; the remaining 68 patients (8.1%) represented a variety of other ethnic groups.

Among the 836 patients with one of the 10 most prevalent diagnosed rheumatic diseases, identifying onset month was most likely in HSP, Kawasaki disease, and systemic JRA and least likely in juvenile spondyloarthropathies (SpA) and JPsA. Among patients with JRA, month intervals could be determined in 125 of 195 (64.1%) with pauciarticular, 58 of 105 (55.2%) with polyarticular, and 28 of 36 (77.8%) with systemic onset subtypes. Month intervals were confidently established in 80 of 250 with a SpA (32.4%), 19 of 52 (36.5%) with psoriatic arthropathy, 65 of 72 (90.3%) with HSP, 50 of 56 (89.3%) with Kawasaki disease, 22 of 34 (64.7%) with SLE, 13 of 18 (72.2%) with DM, and 9 of 18 (50%) with localized scleroderma. Precise determination of onset was significantly more likely to occur in HSP than in all other diagnostic categories except systemic JRA (Table 1), and more likely in Kawasaki disease than all other disease categories other than systemic JRA and DM (Table 1). Additional significant differences in ability to identify precise onset month between groups are shown in Table 1.

Of the total group of 469 patients with one of the defined diseases, 287 (61.2%) were seen at the pediatric rheumatic disease clinic within 2 months of symptom onset, 107 (22.8%) between 3 and 6 months, 53 (11.3%) between 7 and 12 months, and 22 (4.7%) after 12 months (Table 2). Thus, 447 patients (95.3%) were seen within 1 year of symptom onset. Of the 22 patients (4.7%) whose first visit was delayed beyond 1 year after onset, 4 (3 with pauciarticular and 1 with polyarticular JRA) were living outside the catchment area at disease onset, were receiving care from a pediatric rheumatology service elsewhere, and relocated more than 1 year after onset. Two patients (1 systemic JRA and 1 DM) had disease onset more than 1 year prior to the initiation of the study in 1981. Three patients (2 polyarticular JRA and 1 SLE) had been followed originally by adult rheumatologists prior to referral to the pediatric service more than 1 year after onset. The remaining 13 patients (2.8% of the study group of 469) were considered to have referral delayed beyond 1 year as a consequence of failure to recognize the need for pediatric rheumatology consultation.

The numbers (%) of patients who could identify an onset

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Table 1. Differences in frequencies in identification of onset month in childhood rheumatic diseases.

Diagnstic Category*	Pauciarticular JRA	Polyarticular JRA	Psoriatic Arthritis	Spondyloarthropathy (n = 250) Yes 80, No 170	SLE	Dermatomyositis	Scleroderma (n = 18) Yes 9, No 9
Systemic (n = 36) Yes 28, No 8	**	$\chi^2 = 5.73$, $p = 0.017$	$\chi^2 = 14.54$, $p < 0.001$	$\chi^2 = 28.06$, $p < 0.001$			$\chi^2 = 4.29$, $p = 0.038$
Pauciarticular JRA (n = 195) Yes 125, No 70			$\chi^2 = 12.83$, $p < 0.001$	$\chi^2 = 45.44$, $p < 0.001$			
Polyarticular JRA (n = 105) Yes 58, No 47			$\chi^2 = 4.87$, $p = 0.27$	$\chi^2 = 16.80$, $p = 0.001$			
Psoriatic arthritis (n = 52) Yes 19, No 33		$\chi^2 = 5.92$, $p = 0.015$					
SLE (n = 34) Yes 22, No 12				$\chi^2 = 13.91$, $p < 0.001$			
Dermatomyositis (n = 18) Yes 13, No 5			$\chi^2 = 6.86$, $p = 0.009$	$\chi^2 = 11.99$, $p = 0.001$			
KD (n = 56) Yes 50, No 6	$\chi^2 = 13.07$, $p < 0.001$	$\chi^2 = 19.17$, $p < 0.001$	$\chi^2 = 32.52$, $p < 0.002$	$\chi^2 = 61.45$, $p < 0.001$	$\chi^2 = 7.89$, $p = 0.005$		$\chi^2 = 15.80$, $p < 0.001$
HSP (n = 72) Yes 65, No 7	$\chi^2 = 17.56$, $p < 0.001$	$\chi^2 = 24.74$, $p < 0.001$	$\chi^2 = 39.90$, $p < 0.001$	$\chi^2 = 76.70$, $p < 0.001$	$\chi^2 = 10.27$, $p = 0.001$	$\chi^2 = 4.06$, $p = 0.044$	$\chi^2 = 15.98$, $p < 0.001$

* Values indicate the number of subjects able to identify onset months (Yes) and those who could not (No) within the total group (n). ** Blank cells indicate no significant difference; frequency differences between spondyloarthropathies and scleroderma (not shown) were not significant. JRA: juvenile rheumatoid arthritis, SLE: systemic lupus erythematosus, KD: Kawasaki disease, HSP: Henoch-Schönlein purpura.

Table 2. Number (%) of patients stratified by diagnosis and onset to first visit interval.

	Total in Category	No. (%) Able to Identify Onset Month	Onset to First Visit Intervals, months 0–2	3–6	7–12	Cumulative ≤ 1 year	> 12
All subjects	836	469 (56.1)	287 (61.2)	107 (22.8)	53 (11.3)	447 (95.3)	22 (4.7)
Pauciarticular JRA	195	125 (64.1)	71 (56.8)	28 (22.4)	19 (15.2)	118 (94.4)	7 (5.6)
Polyarticular JRA	105	58 (55.2)	28 (48.3)	17 (29.3)	11 (19.0)	56 (96.6)	2 (3.4)
Systemic JRA	36	28 (77.8)	20 (71.4)	4 (14.3)	2 (7.1)	26 (92.9)	2 (7.1)
Psoriatic arthritis	52	19 (36.5)	13 (68.4)	3 (15.8)	2 (10.5)	18 (94.17)	1 (5.3)
Spondyloarthropathies	250	80 (32.4)	30 (37.5)	33 (30.8)	12 (15.0)	75 (93.8)	5 (6.3)
SLE	34	22 (64.7)	14 (63.6)	3 (13.6)	2 (9.1)	11 (78.6)	3 (13.6)
Dermatomyositis	18	13 (72.2)	6 (46.2)	6 (46.2)	0	12 (92.3)	1 (7.7)
Localized scleroderma	18	9 (50.0)	2 (22.2)	4 (44.4)	2 (22.2)	8 (88.9)	1 (11.1)
HSP	72	65 (90.3)	57 (87.7)	6 (9.2)	2 (3.1)	65 (100)	0
Kawasaki disease	56	50 (89.3)	46 (92.0)	3 (2.8)	1 (2.0)	50 (100)	0

month and were seen within 12 months of onset were as follows: pauciarticular JRA 118 of 125 (94.4%), polyarticular JRA 56 of 58 (96.6%), systemic JRA 26 of 28 (92.9%), JPsA 18 of 19 (94.7%), juvenile SpA 75 of 80 (93.8%), HSP 65 of 65 (100%), Kawasaki disease 50 of 50 (100%), SLE 19 of 22 (86.4%), DM 12 of 13 (92.3%), and localized scleroderma 8 of 9 (88.9%) (Table 2).

Of the 469 patients, 204 (43.5%) were male and 265 (56.5%) female. Of the 434 who stipulated an ethnic origin, 365 (84.1%) were Caucasian, 54 (12.4%) North American Indian, and 15 (3.5%) were of a variety of other racial/ethnic origins. Of the 464 that stipulated a site of residence, 235 (50.7%) resided in urban areas and 229 (49.4%) in rural areas.

A series of ordinal logistic regression models were utilized to compare each diagnostic category with HSP adjusting for other covariates including age, sex, ethnicity, urban/rural residence, and onset and referral year and season. Using HSP as the reference category in an ordinal logistic regression analysis, there was no significant difference between the onset to first visit interval categories between HSP and Kawasaki disease (ß = 1.71; odds ratio 1.61, 95% confidence interval 0.38 to 6.81), systemic JRA (ß = 0.59; OR 0.53, 95% CI 0.14 to 2.06), PsA (ß = 0.44; OR 0.46, 95% CI 0.10 to 2.07), or SLE (ß = 0.52; OR 0.49, 95% CI 0.11 to 2.21). However, when compared to HSP as the reference diagnosis, significantly longer onset to first visit intervals were observed in pauciarticular JRA (ß = –0.09; OR 0.27, 95% CI 0.10 to 0.69), polyarticular JRA (ß = –0.53; OR 0.17, 95% CI 0.06 to 0.49), SpA (ß = –1.12; OR

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0.10, 95% CI 0.04 to 0.25), DM (ß = –1.02; OR 0.11, 95% CI 0.03 to 0.43), and scleroderma (ß = –1.72; OR 0.05, 95% CI 0.01 to 0.35). Systemic onset JRA had significantly shorter onset to first visit intervals than SpA (ß = –1.12; OR 0.18, 95% CI 0.06 to 0.59), DM (ß = –1.02; OR 0.20, 95% CI 0.04 to 0.95), and scleroderma (ß = –1.72; OR 0.10, 95% CI 0.01 to 0.75), but distribution within interval categories did not differ significantly between systemic JRA and the remaining 6 disease categories. Pauciarticular JRA had a significantly shorter onset to first visit interval compared to SpA (ß = –1.02; OR 0.36, 95% CI 0.19 to 0.69). Polyarticular JRA had a longer onset to first visit referral than HSP and Kawasaki disease, but did not differ significantly from other disease categories.

Excluding outlying values (intervals > 12 months) and analyzing month interval as a continuous variable (0–12 months) the mean onset to first visit interval for all subjects was 2.57 months. Within the short onset to first visit interval disease category (≤ 2 months) the mean interval was 0.91 months, for the intermediate category (3–6 months) 4.2 months, and for the late category (7–12 months) 8.7 months.

When onset to first intervals were analyzed as a continuous monthly variable for intervals ≤ 12 months, the following significant differences were found: systemic onset JRA had a significantly shorter onset to first visit interval than polyarticular JRA (t = –2.06; p = 0.043, 95% CI –2.88 to 0.050), SpA (t = –2.08; p = 0.040, 95% CI –2.65 to –0.065), and localized scleroderma (t = –2.38; p = 0.025, 95% CI –5.101 to –0.360), and a significantly longer interval than Kawasaki disease (t = 2.76; p = 0.007, 95% CI 0.412 to 2.566) and HSP (t = 2.06; p = 0.042, 95% CI 0.042 to 1.131). Pauciarticular JRA had a significantly longer interval than Kawasaki disease (t = 5.33; p < 0.001, 95% CI 1.445 to 3.147) and HSP (t = 4.85; p < 0.001, 95% CI 1.150 to 2.726). Polyarticular JRA had a significantly longer interval than Kawasaki disease (t = 6.14; p < 0.001, 95% CI 1.998 to 3.906) and HSP (t = 5.62; p < 0.001, 95% CI 1.680 to 3.508). JPsA had a significantly longer interval than Kawasaki disease (t = 3.57; p = 0.001, 95% CI 0.857 to 3.028) and HSP (t = 2.73; p = 0.008, 95% CI 0.428 to 2.740). SpA had a significantly longer interval than Kawasaki disease (t = 6.4; p < 0.001, 95% CI 1.966 to 3.727) and HSP (t = 5.06; p < 0.001, 95% CI 2.155 to 4.918). SLE had a significantly shorter interval than localized scleroderma (t = 2.61; p = 0.015, 95% CI –4.993 to –0.586) and significantly longer than Kawasaki disease (t = 2.67; p = 0.010, 95% CI 0.064 to 1.072). DM had a significantly shorter interval than localized scleroderma (t = 3.41; p = 0.003, 95% CI –4.579 to –1.087) and significantly longer interval than Kawasaki disease (t = 2.61; p = 0.011, 95% CI 0.323 to 2.451). Localized scleroderma had a significantly longer interval than Kawasaki disease (t = 6.10; p < 0.001, 95% CI 2.835 to 5.605) and HSP (t = 4.92; p < 0.001, 95% CI 2.296 to 5.427).

Females were significantly more likely than males to have onset to first visit intervals of 3–6 or 7–12 months (chi-square = 8.37; p = 0.039); no sex difference was noted in the 1–2 month or > 1 year categories. With respect to onset to first visit interval categories, no significant differences were observed between Caucasian and North American Indian subjects, urban or rural residence, patient age or sex, or year or season of referral.

DISCUSSION

Prompt referral of a child with a suspected rheumatic disease to a pediatric rheumatology service would be expected to improve patient care and outcomes by facilitating early diagnosis and treatment. The optimal interval times between the onset of symptoms and first visit to a pediatric rheumatology clinical care service have not been established. In our clinical population the urgency with which a child was referred reflected predominantly the acuity of the clinical manifestations; Kawasaki disease, HSP, and systemic JRA were generally referred significantly more promptly than in patients with other diseases, an observation that likely reflects the acuity of the presenting features. Thus, diseases ordinarily typified by an abrupt and acute onset of symptoms were referred most promptly, suggesting that acuity of symptoms at disease onset is the factor that most influences promptness of referral. Intervals were not influenced by geography, ethnicity, or time of year.

Childhood rheumatic diseases comprise a collection of uncommon conditions that, as a group, lack organ, system, or etiology specificity, and call for advanced diagnostic tools and increasingly complex treatment regimens. Consequently, primary care family physicians or pediatricians would not ordinarily become adept in diagnosing and managing most childhood rheumatic diseases without pediatric rheumatology collaboration. In the clinic population from which this study group was derived, 96.5% of patients were referred to the pediatric rheumatology program by either a family physician (77.0%) or primary care pediatrician (19.5%)[1].

In an earlier survey of primary care pediatricians and family physicians, more than 90% of practitioners referred patients with JRA for subspecialty care[7]. Factors influencing the decision to refer were a refractory clinical course, symptom severity, and parental request. In our study, the brief onset to first visit intervals suggested that almost all patients were referred so promptly that refractoriness of clinical course would not likely have been a factor. Acuity and severity of symptoms appeared to influence the significantly more prompt referral of systemic JRA, Kawasaki disease, and HSP.

Guidelines for the type of patients who ought to be referred to a pediatric rheumatology clinical care program have been proposed[4], but recommendations that guide the timing of referral after onset of symptoms have not been

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introduced. For certain conditions such as Kawasaki disease, immediate referral for specialized care is always required to ensure prompt treatment that might favorably influence outcomes. However, Kawasaki disease is a condition that is not always referred to a pediatric rheumatology subspecialty service, as care might be provided by general pediatricians in collaboration with pediatric cardiologists. Pediatric rheumatology consultation might be most often sought only when atypical presentations of suspected Kawasaki disease pose a diagnostic challenge or when a child with Kawasaki disease is refractory to conventional first-line therapy. The diagnosis and referral of these more challenging patients might be delayed and thus account for the somewhat longer onset to first visit interval (0.80 months; 5% trimmed 0.49 months) we observed for Kawasaki disease than would ordinarily be considered acceptable for this condition. Similarly, the longer than expected onset to first visit interval for HSP (1.14 months; 5% trimmed 0.63 months) could reflect referral of subjects cared for initially by a primary care physician but who were eventually referred for subspecialty consultation when the course was unusually protracted or complicated.

It is unknown if the intervals for other diagnostic categories are too long and if earlier referral might favorably influence outcomes. For example, it is unknown what minimal interval between onset of pauciarticular JRA and administration of intraarticular steroid therapy is required to minimize adverse outcomes.

Currently, optimal intervals between symptom onset and first clinic visit are unknown. However, future prospective studies that evaluate onset to first visit intervals as a determinate of disease course and outcomes should help establish guidelines for optimizing timeliness of referrals to a pediatric rheumatology subspecialty service. Improving awareness among primary care providers of the frequencies and characteristics of chronic childhood rheumatic diseases should promote earlier recognition and prompt referral to specialized clinical care services.

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