Epidemiologic Considerations in Unexplained Pediatric Arthralgia: The Role of Season, School, and Stress

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ABSTRACT. ***Objective.*** To determine demographic and epidemiologic characteristics in children with unexplained joint pain.

Methods. The study population included 730 children (< 18 yrs of age) referred between 1981 and 2007 to the Saskatchewan Pediatric Rheumatology Program, University of Saskatchewan, because of arthralgia. Parents and patients completed a questionnaire at the time of initial presentation, and a diagnosis of unexplained arthralgia was assigned based on clinical assessment. Serum vitamin D levels were measured in 73 patients diagnosed with arthralgia.

Results. Subjects with arthralgia were more likely to report psychosocial stresses including family discord and illness in the family, and to be cared for by a single parent as a consequence of parental separation or death. Significantly more patients reported fall and winter (30%) as the season of symptom onset compared to spring or summer (20%; p = 0.01). Significantly more survey respondents in the arthralgia group reported missing school compared to the control group (62% vs 31%; p = 0.001). Referrals from northern Saskatchewan were significantly more numerous than from southern Saskatchewan (107 vs 45 per 100,000; p < 0.001). Serum vitamin D concentrations measured in a subgroup of patients (n = 73) showed that 62 (82%) were abnormally low, 42% between 50 and 75 nmol/l (insufficient), and 40% < 50 nmol/l (deficient).

Conclusion. Our results suggest an association between psychosocial stress, school absenteeism, vitamin D insufficiency, and unexplained arthralgia in children. (First Release Dec 1 2008; J Rheumatol 2009;36:427–33; doi:10.3899/jrheum.080358)

Key Indexing Terms:
ARTHRALGIA MYALGIA PEDIATRIC RHEUMATIC DISEASES VITAMIN D

Appendicular musculoskeletal pain represents a common reason for referral to pediatricians and pediatric rheumatologists. Unexplained arthralgia represents roughly 20% of all diagnoses comprising our clinic population[1]. Considering the burden of unexplained musculoskeletal pain on patients, families, and healthcare services, research is warranted to understand the origins of this condition and to guide more effective diagnostic, treatment, and prevention strategies.

We undertook a demographic and epidemiological evaluation of a cohort of pediatric patients with arthralgia. Results reveal an association between arthralgia and psychosocial stress and school absenteeism, and a relationship with season that might reflect an association with vitamin D insufficiency.

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Supported by the Pediatric Rheumatic Disease Research Laboratory, Department of Pediatrics, University of Saskatchewan; Institute of Child and Adult Arthritis Research; and Saskatchewan Division of The Arthritis Society. Dr. Matheson is supported by a Canadian Arthritis Network Fellowship.

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Accepted for publication September 17, 2008.

MATERIALS AND METHODS

Subjects and database. The study population was derived from all children referred by a physician because of suspected rheumatic disease to the Pediatric Rheumatic Program, University of Saskatchewan, during the 26-year period July 1981 to June 2007. Data for all subjects referred to the Pediatric Rheumatology Clinic, University of Saskatchewan (the only pediatric rheumatology program serving the province of Saskatchewan), since July 1981 were prospectively recorded in a computer database[2]. All data were analyzed with approval of the University of Saskatchewan's Biomedical Research Ethics Board (#08-53), and the study was conducted in accord with the Saskatchewan Health Information Protection Act.

At first presentation, a parent or guardian completed a questionnaire[1,2] that included self-reported information on the presenting complaint, medical history, schooling, and social history. A parent of the patient was asked to invite the parent of a healthy, unrelated, age and sex matched child from the same neighborhood to complete the same questionnaire, thus approximating a control cohort.

Diagnosis and case definition. All subjects were evaluated by only one pediatric rheumatologist (AMR), who assigned the diagnosis. Subjects for whom a rheumatologic diagnosis could be established were assigned to a disease category by applying published or generally accepted diagnostic criteria, as described[1]. The group of subjects who presented with unexplained appendicular arthralgia, for whom a rheumatologic diagnosis could

not be established, comprised subjects classified as having unexplained joint pain. The presence of joint hypermobility and pes planus were not exclusion criteria; however, patients diagnosed with patellofemoral syndrome, unexplained limb pain, fibromyalgia, growing pains, and isolated unexplained axial skeleton pain were excluded. Appendicular joint pain was defined as symptoms of pain without associated clinical or, when available, laboratory or radiographic evidence of an underlying disease. Only those subjects who were permanent residents of Saskatchewan and younger than 18 years of age at presentation were included in the study population. All data and biological samples collected over the 26-year span of the study were anonymized for the purposes of this study.

Demographic and geographic information. Age, sex, and ethnicity were documented for all subjects. Using the first 3 characters [representing the Forward Sortation Area (FSA) code] of the subject's 6-character residential postal code, an individual subject's residence could be identified as urban or rural and as southern (latitude 49° to 52°) or northern (53° to 59°); the province's population of 1 million is divided roughly equally by latitude 52°[3]. The populations for each of Saskatchewan's 49 postal code regions were obtained from the 2001 Canadian census[3].

Symptom onset and associated symptoms. At the first clinic visit subjects were asked to report the month, season, and year of symptom onset. In addition to the primary presenting complaint, the survey also collected information about other symptoms including as examples, fatigue, back pain, joint pain, and muscle pain.

School and stress-related questions. The survey gathered information concerning school that included whether the child was enrolled in school, history of school absenteeism, and peer relationships at school. To assess relationships between stressors and symptom onset, respondents were provided with the statement, "About the time of the onset of your child's problem had your child...". Following the lead-in statement there were 3 questions: "Experienced any serious upset?", "Suffered any significant losses?", and "Had anyone close to the child died (including pets)?". Other potential family and life stressors included whether the parents were separated or deceased (one or both), if another sibling or family member was currently ill, or if the child was not getting along with other family members.

Vitamin D determination. To explore the possibility that seasonal and geographic patterns relating to onset of arthralgia might relate to vitamin D insufficiency, vitamin D analyses were performed retrospectively using a competitive binding enzyme linked immunoassay [EIA; Immunodiagnostic Systems (IDS), Montreal, QC, Canada] and prospectively using high-pressure liquid chromatography/mass spectrometry (HPLC/MS) technology. Using linear regression analysis the relationship between serum 25-hydroxyvitamin D (25(OH)D) concentrations obtained from IDS ELISA compared favorably with HPLC (slope = 1.17, intercept = –8.8, $r^2 = 0.92$); these results are consistent with other published reports comparing EIA and radioimmunoassay to HPLC[4,5]. Data available from DEQAS (Vitamin D External Quality Assessment Scheme) revealed that enzyme immunoassay and HPLC/MS are the 2 most common methods used to measure 25(OH)D[6].

The retrospective 25(OH)D assay was performed using randomly selected, anonymized serum samples that had been collected at presentation and stored at –20°C. Samples were assayed in accord with the manufacturer's instructions; the product insert indicates that this assay provides a cumulative measurement of vitamin D_2 (75%) and vitamin D_3 (100%). The intraassay coefficient of variation is < 8% and between runs is < 10%. Three quality control samples were included on each assay plate and the samples, calibrators, and controls (from DEQAS[6]) were assayed in duplicate. Calibrators, controls, and patient samples were diluted with biotin-labeled 25(OH)D (1:40) and incubated in microtiter wells coated with sheep 25(OH)D antibody for 2 h at room temperature. After aspiration and washing, horseradish peroxidase-labeled avidin was added and bound selectively to complexed biotin. Color was developed using a chromogenic substrate, tetramethylbenzidine, and hydrogen peroxide. The absorbance was read at 450 nm using an ELx800 microplate reader (Bio-Tek Instruments, Winooski, VT, USA); the color intensity was inversely proportional to the concentration of 25(OH)D. Prospective assessment of 25(OH)D levels was performed by the Saskatchewan Provincial Service Laboratory, Regina, Saskatchewan, by HPLC/MS using a PE Sciex API 4000 HPLC/MS. For this assay, vitamin D was extracted from serum or heparinized plasma using ethanol and a 10:1 mixture of hexane: dichloromethane. Following complete evaporation, the sample was reconstituted in methanol. The mobile phase for the assay was 20 mM ammonium acetate with 0.05% formic acid and 100% methanol. An Eclipse XDB-C8 instrument (5 µm, 4.6 × 150 mm) with a C8 guard column was utilized. Only the total vitamin D level (vitamin D_2 and vitamin D_3) was reported, with a limit of detection of 3 nmol/l.

Analyses of retrospective and prospective 25(OH)D levels were categorized as deficient (< 50 nmol/l), insufficient (50 to 75 nmol/l), and sufficient (> 75 nmol/l); 25(OH)D data were collected from a total of 73 subjects.

Data analysis. Both the general population and number of cases in each FSA were used to determine the comparative incidence (per 100,000 over the 26-yr study period) in rural, urban, northern, and southern locales. The Statistical Package for Social Sciences Version 15 (SPSS, Chicago, IL, USA) was used for data analyses. For comparison between control and case groups the significance level was set at 0.05 and the confidence interval at 95%. Chi-square analysis was used to assess for significant differences in prevalence rates between groups for demographic, school, and stress related information. Unpaired t tests were performed to assess for difference between groups in 25(OH)D levels, age, and number of associated symptoms.

RESULTS

Burden of disease. Of the 3647 patients referred to the clinic over the 26-year period, 730 had unexplained appendicular joint pain, accounting for 20.0% of all diagnoses.

Epidemiology. Epidemiological and demographic features

Table 1. Demographic characteristics of patients with appendicular joint pain compared with a control cohort.

	Controls, n (%)	Joint Pain, n (%)
Sex		
Male	393 (40.4)	292 (40)
Female	579 (59.6)	438 (60)
Total respondents	972	730
Age		
Mean	10.4 ± 4.3 (SD)	10.4 ± 4.2 (SD)
Median	11	10.9
Ethnicity		
Caucasian	906 (94.4)	591 (89)
Asian	5 (0.5)	5 (0.8)
African American	1 (0.1)	1 (0.2)
First Nations	1 (0.1)	32 (4.8)
Métis	19 (2.0)	14 (2.1)
Other	16 (1.7)	21 (3.2)
Total respondents	948	664
School enrollment		
Yes	834 (87.5)	451 (89.3)
No	119 (12.5)	54 (10.7)
Total respondents	953	505
Geography		
Rural	447 (46.7)	311 (46.7)
Urban	511 (53.3)	419 (57.4)
Total respondents	958	730

of the study subjects and 972 control subjects are presented in Table 1. The sex distribution (60% female, 40% male) was the same in the control and arthralgia groups. Age at presentation (10.4 yrs) was identical for the control and arthralgia groups. Both control and arthralgia groups were comparable with respect to school enrollment and residence in a rural community. Caucasians were the major ethnic group in the 2 categories, representing 94% of the control group and 89% of the arthralgia group. There were significantly more subjects of North American First Nations descent in the arthralgia group (4.8%) compared to the control population (0.1%; p = 0.001), an observation that we believe reflects a control selection bias; First Nations parents were less likely to provide a control subject for their child.

Arthralgia incidence. The average annual incidence of arthralgia referrals was 28 (SD 7) cases per year. Over the 26-year study period, the cumulative number of referrals included 78 per 100,000 among rural residents compared to 75 per 100,000 among urban residents (p = 0.82) and 107 per 100,000 in the northern group compared to 45 per 100,000 in the southern group (p < 0.001).

Month and season of symptom onset. Information on season and month of symptom onset could be reliably determined for about half of the patients. Within the arthralgia group, data were available from 392 for season, and 344 for month of symptom onset. Compared to summer (18%), significantly more patients with arthralgia reported fall (29.9%; p = 0.01) and winter (29.1%; p = 0.01) onset (Figure 1A). The onset months of December, January, and October were the most common (Figure 1B).

Schooling and arthralgia. Survey responses relating to school enrollment, the presence of missed school days, and the duration of missed school are shown in Table 2. Similar

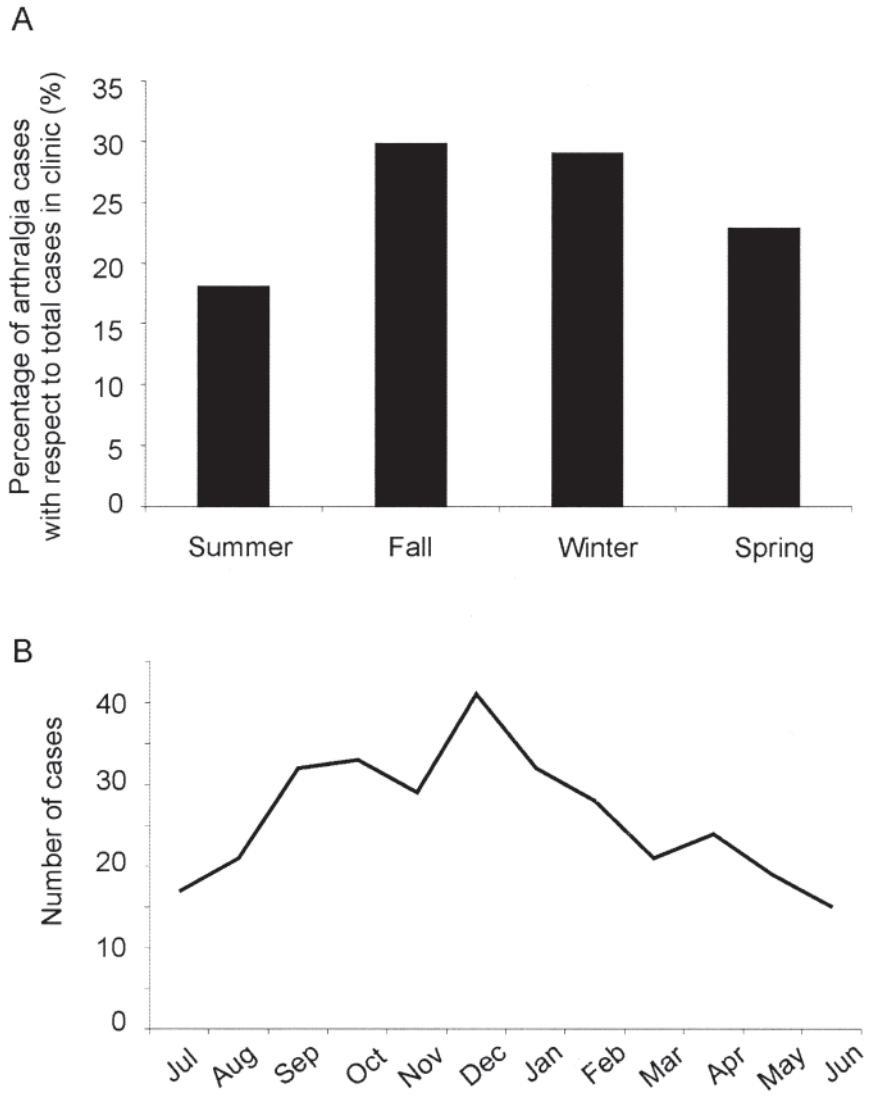

Figure 1. Season of symptom onset of appendicular joint pain presented as a percentage of all cases by season (A) and number of cases by month (B).

percentages of survey respondents in the control (834/953, 85%) and the arthralgia group (451/505, 89.3%) were enrolled in school. Significantly more respondents in the arthralgia group reported missing school compared to the control group (62% vs 31%; p = 0.001). Compared to control patients, significantly more of the arthralgia group had missed more than 2 weeks of school (6% compared to 0.7%; p = 0.001). Survey respondents in the arthralgia group were more likely to not like school (10.8% vs 4.6%; p = 0.001) and were less likely to participate in school related extracurricular activities (83.7% vs 94%; p = 0.001).

Life event stressors and arthralgia. The percentage of survey respondents in the arthralgia group who experienced a serious upset, significant loss, or death near the time of symptom onset is shown in Table 3. In the arthralgia group, 11.6% experienced a serious upset, 6.1% had suffered a significant loss, and 11% had someone close die (including a pet). Other potential causes of stress are shown in Table 4. Compared to the control population, respondents with arthralgia were more likely to report difficulty getting along with a family member (15.6% vs 6.7%; p = 0.001), more likely to report a sibling with a problem or concern (20% vs 9.5%; p = 0.001), and more likely to report an ill family member (17.5% vs 6%; p = 0.001). Respondents with arthralgia were more likely to have separated parents (16% vs 8.6%; p = 0.01) and showed a statistically insignificant higher trend toward having a deceased parent (1.5% vs 0.6%; p = 0.10; Table 3).

Associated symptoms. Subjects with arthralgia were significantly more likely to have associated symptoms than the control group (Table 4). The average number of associated symptoms was significantly greater in the arthralgia group (2.0 ± SD 1.5) than in the control group (0.3 ± SD 0.7; p < 0.001). After joint pain (79.5%), the most common symptoms were muscle pain/weakness (38.9%) and fatigue (29.0%).

Serum vitamin D levels. 25(OH)D levels were retrospectively determined on 42 patients with arthralgia using banked serum samples. The mean serum 25(OH)D level among this group was 59.9 nmol/l (median 57.9 nmol/l, SD 22.8; Figure 2A). For the prospective vitamin D study, levels were meas-

Table 2. Comparison of respondents who reported information about school and extracurricular activities. The denominator in each cell indicates the number of survey respondents in each cohort who completed the survey and were willing to provide a positive or negative response to the question.

Characteristic	Controls, n (%)	Arthralgia Group, n (%)
Missing school		
Yes	267/844 (31)	269/515 (62)*
No	577/844 (68)	206/515 (38)*
Duration school missed†		
Less than 2 weeks	251/257 (98)	229/254 (55)*
More than 2 weeks	6/257 (0.7)	25/254 (6)*
Likes school		
Yes	801/840 (95)	338/435 (89.2)*
No	39/840 (4.6)	47/435 (10.8)*
Extracurricular participation		
Yes	774/825 (94)	349/417 (83.7)*
No	51/825 (6.2)	68/417 (16.3)*

* Chi-square analysis indicated a statistically significant difference compared to the control group (p , 0.001). † Percentages reported for Duration school missed included only those respondents who were indicated as having missed school, and were able to quantify amount (n = 257, 254, for controls, arthralgia group, respectively).

Table 3. Comparison of respondents who reported information about stressful life events. The denominator in each cell indicates the number of survey respondents in each cohort who completed the survey and were willing to provide a positive or negative response to the question.

Patient Feature	Controls, n (%)	Arthralgia Group, n (%)
"About the time of your child's problem had your child..."		
Experienced serious upset?	—	54/466 (11.6)†
Suffered significant loss?	—	28/459 (6.1)†
Had anyone close to them died?	—	47/466 (10.7)†
Problems or concerns with other siblings	89/937 (9.5)	93/465 (20)*
Family member ill	57/945 (6)	83/475 (17.5)*
Problems getting along with family members	62/930 (6.7)	75/482 (15.6)*
Deceased parent(s)	6/930 (0.6)	7/476 (1.5)
Separated parents	8/930 (8.6)	74/466 (16)*

† No statistical comparison was possible. * Chi-square analysis indicated a statistically significant difference compared to control (p = 0.001).

Table 4. Percentage of respondents with additional symptoms. The unexplained musculoskeletal pain group and arthralgia group were compared to the control cohort. The denominator in each cell indicates the number of survey respondents who provided a response for that symptom.

Symptom	Controls Reporting Symptom(s), n (%)	Arthralgia Group Reporting Symptom(s), n (%)
Back pain	43/936 (4.6)	118/478 (24.7)*
Fatigue	37/936 (4)	138/478 (28.9)*
Chest pain	18/936 (2)	68/474 (14.3)*
Joint pain	61/938 (6.5)	385/474 (79.5)*
Muscle pain or weakness	42/939 (4.5)	185/479 (38.6)*
Shortness of breath	47/936 (5)	69/477 (14.5)*
No. of symptoms		
No additional symptoms**	780/936 (83.3)	59/472 (12.5)
1**	104/936 (11.1)	165/472 (35.0)
2**	33/936 (3.5)	105/472 (22.2)
3**	9/936 (1.1)	68/472 (14.4)
4**	5/936 (0.5)	38/472 (8.1)
5**	4/936 (0.4)	24/472 (5.1)
6**	1/936 (0.1)	13/472 (2.8)

* Chi-square analysis indicated a statistically significant difference compared to the control group (p < 0.001). ** Additional symptoms include back pain, joint pain, muscle pain and weakness, fatigue, chest pain, and/or shortness of breath.

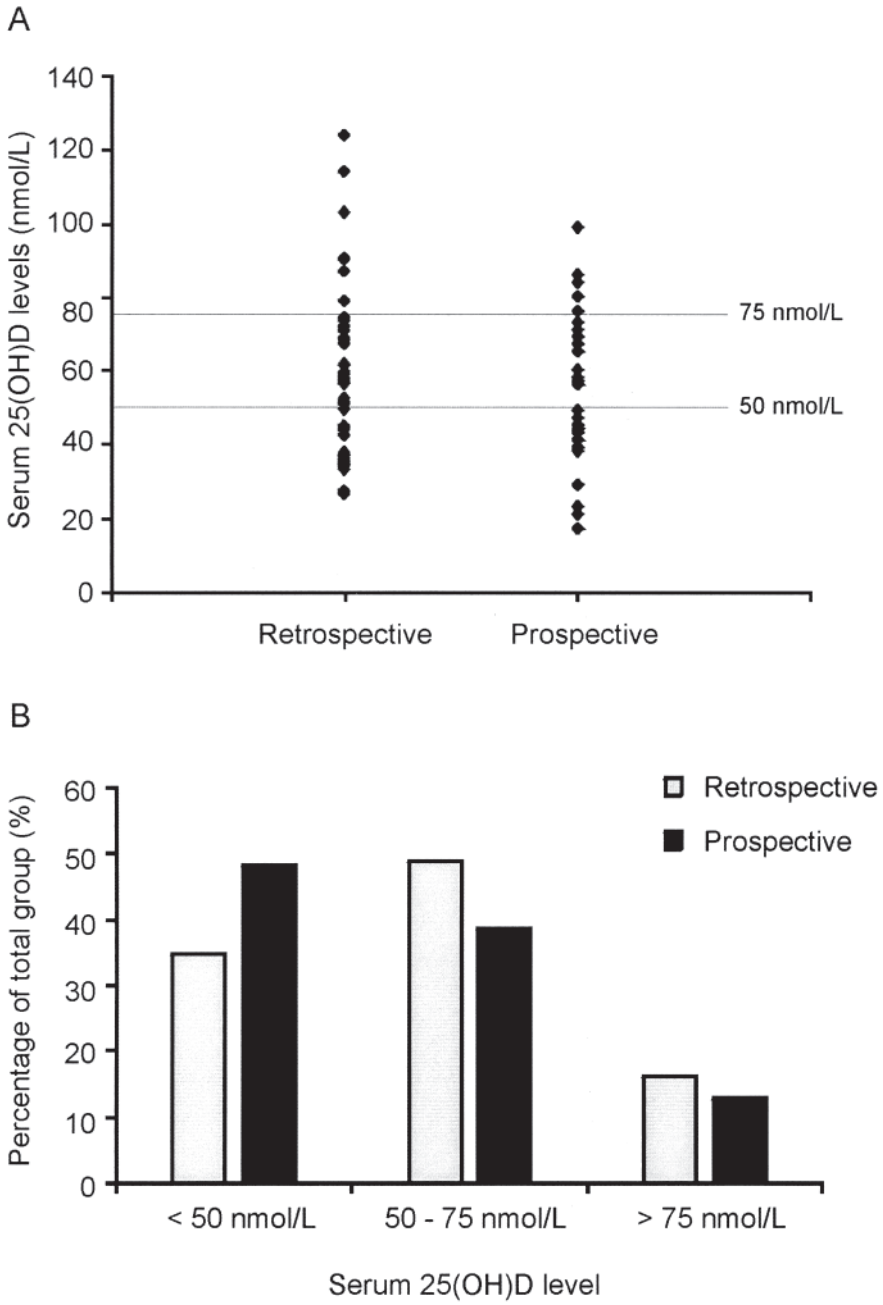

Figure 2. Biochemical determination of serum 25(OH)D concentrations from a group of patients with appendicular joint pain. A. Measurements (nmol/l) were performed on serum samples collected previously (retrospective) or prospectively. B. Percentages of the group that fell within the deficient (< 50 nmol/l), insufficient (50–75 nmol/l), or sufficient (> 75 nmol/l) categories.

ured in 31 patients evaluated at the clinic for arthralgia over the 12-month period February 2007–February 2008. The mean 25(OH)D level in this group was 55.3 nmol/l (median 56 nmol/l, SD 20.5), an insignificant difference (p = 0.372). When combined, the mean 25(OH)D level for all 73 patients was 58 nmol/l (SD 21.9). A significant proportion of the 25(OH)D levels fell into the insufficient or deficient range, with only 13 of 73 patients (18%, 95% CI 10–28) having a vitamin D level > 75 nmol/l. Roughly 40% (95% CI 28–52) of patients had values < 50 nmol/l (deficient), while another 42% (95% CI 31–55) were between 50 and 75 nmol/l (insufficient; Figure 2B).

DISCUSSION

There is limited information on the demographic and epidemiologic characteristics of childhood arthralgia and no substantive indication as to which factors influence the occurrence and course of unexplained musculoskeletal pain

in pediatric populations. Our goal was to characterize demographic and epidemiologic features of arthralgia in a cohort of children.

Our findings show that children with chronic unexplained arthralgia are more likely to report symptom onset during the fall or winter. The higher prevalence of symptom onset during specific seasons would suggest the presence of season-related factors contributing to the onset or worsening of arthralgia symptoms. Potential explanations for winter-associated medical conditions include seasonal pathogens, school attendance, and/or change in temperature and daylight hours. Further, a detailed month of symptom onset analysis (Figure 1A) suggested a bimodal distribution, suggesting the contribution of more than one factor.

One conceivable explanation for the increase in symptom onset during fall and winter months might be related to variations in ultraviolet-B (UV-B) radiation exposure and the resultant decline in vitamin D level. Among infants and adults, musculoskeletal pain is a well recognized feature of vitamin D deficiency[7]. Vitamin D-related decreases in calcium absorption lead to a reduction in bone calcium levels and mineralization, through a parathyroid hormone-mediated imbalance in osteoblast and osteoclast activity[8]. With activity and inflammation the poorly mineralized bone matrix hydrates and expands, causing an outward pressure on the periosteum, leading to pain[9].

Both season and latitude affect the intensity of solar radiation reaching the earth's surface, and UV-B exposure is necessary to photolyze 7-dehydrocholesterol in the skin to vitamin D_3 production. As the UV index does not decline significantly until September-October in Saskatchewan, it is unlikely that vitamin D deficiency would explain the observed increase in symptom onset in early fall. However, the January-February peak of symptom onset we observed in the arthralgia subjects would be consistent with current knowledge about reduced UV-B exposure and low vitamin D levels, since 25(OH)D has been reported to have a half-life of 1 to 2 months in the circulation[10]. A link between vitamin D and unexplained musculoskeletal pain might also explain the higher rate of referral (per capita) from the northern region of the province. The mean vitamin D level for the arthralgia group we studied was 58 nmol/l, with 82% of all subjects being below the currently accepted minimal level of 75 nmol/l[11]. These findings are similar to those reported in comparable adult studies in which between 73% and 90% of all patients presenting to an outpatient clinic for a rheumatologic complaint met the criteria for vitamin D deficiency (< 50 nmol/l)[12,13].

A role for stress has been suggested for the development and exacerbation of certain functional pain syndromes, including headache[14], abdominal pain[15,16], and noncardiac chest pain[17]. Further, psychological stress has been reported to affect outcomes in a number of rheumatologic conditions including juvenile idiopathic arthritis[18] and low back pain[19-21]. In this study we provide support for a possible role for psychological stress in children with unexplained arthralgia, as a substantial number of children with arthralgia reported having experienced a discomforting event around the time of symptom onset (Table 3).

Other research has focused on the influence of specific types of stress on child health, including functional pain. For example, school-related stress might play a role in the seasonal variation of abdominal pain[16]. A busy school schedule, fewer opportunities to participate in outdoor activities, and shorter days could conceivably lead to anxiety, depression, and functional pain. Association between bullying and a variety of health problems of childhood including fatigue, headache, abdominal pain, and medication use has been reported[22,23]. Our cohort of children with unexplained arthralgia was more likely to have school-related stress compared to a group of healthy controls. The arthralgia group was 2 to 3 times more likely to not like school, and to not participate in extracurricular activities (Table 2). In addition, children with arthralgia were 2 times more likely to have missed school, and 10 times more likely to have missed more than 2 weeks of school. Recognizing a symptom onset peak in September-October that coincides with the beginning of school, it is possible that school and school-related stress may contribute to the increase in arthralgia cases during those months.

There are limitations to our data. The cross-sectional design of the study does not permit definitive interpretations regarding cause and effect. More specifically, based on our results we cannot be certain that home or school-related stress precipitates or exacerbates joint pain. A contrasting hypothesis could be that the presence of persistent unexplained arthralgia may lead to anxiety and stress at home or at school. Another potential limitation to this study is bias secondary to information obtained from retrospective self-report. Specifically, the arthralgia group may be attributing a negative quality to an event that would otherwise have been considered innocuous. Although limited, a few pediatric studies assessing the role of stress and negative life events on disease have attempted to eliminate bias using prospective-observational (for common conditions) or within-family or sibling-pairs study designs (for rare conditions)[20,24,25]. An additional limitation of this study was that 25(OH)D measurements were not available from a healthy control cohort of either Saskatchewan or Canadian children for comparison. For this reason, we cannot discount the possibility that the majority of children in our region are deficient in vitamin D and the reported high prevalence of vitamin D insufficiency in our study reflects the general pediatric population. Further research, including documenting vitamin D levels in healthy children, and reassessment of symptoms following supplementation with vitamin D, will

be required to strengthen any link between arthralgia and low vitamin D levels.

We have presented month of symptom onset, and school and stress questionnaire data suggesting that unrecognized seasonal and stress-related factors might contribute to the occurrence of chronic unexplained pediatric arthralgia in some children. Based on our findings we propose that a biopsychosocial model might aid management of pediatric arthralgia. This model would presume that the child's condition is the result of interaction of biological, environmental, psychological, and sociocultural factors. Further studies, including a comparison with appropriate controls and demonstration of alleviation of symptoms with normalization of vitamin D levels, are required to provide support for a putative role for vitamin D insufficiency in the etiopathogenesis of childhood arthralgia.

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