Pediatric rheumatology

Growth patterns in juvenile rheumatoid arthritis

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Abstract

Objective

To define patterns of growth in juvenile rheumatoid arthritis (JRA) and to evaluate possible associated clinical and laboratory correlates.

Methods

The study population comprised 67 children with JRA who had been followed for 5 years or longer and whose follow-up period did not extend beyond 18 years of age. Height and weight z scores were calculated with reference to age-related standards for each of the annual follow-up intervals and correlated with JRA subtype, the presence of rheumatoid factor (RF), the erythrocyte sedimentation rate (ESR), alkaline phosphatase level (ALP) and medication history.

Results

Initial height-for-age (HAZ) scores for pauciarticular, polyarticular and systemic JRA onset groups (PaJRA, PoJRA and SJRA respectively) were +0.27, -0.07 and +0.40 respectively. A significantly lower HAZ score in the SJRA population compared to the PaJIA population first became apparent at year 2 and the difference was maintained throughout the 9-year follow-up period. A significantly lower HAZ score in the SJRA population compared to the PoJRA population first became apparent at year 6 and the difference was maintained until the ninth year. During the 9-year follow-up period, RF-positive children tended to have negative HAZ scores whereas RF-negative children tended to have positive HAZ scores. The SJRA onset group displayed significantly lower HAZ scores, as compared to the HAZ score at onset, for 7 of the 9 subsequent follow-up intervals. Only 2 patients had heights < 2SD below the mean at final determination. Delay in generalized linear growth occurred predominantly in the SJRA population and to a lesser degree in those with PoJRA associated with RF positivity.

Conclusions

Delay in linear growth occurs in some children with JRA. Patients with pauciarticular and RF-negative polyarticular disease can have growth patterns similar to normal children. Children with RF-positive polyarticular and systemic JRA have more significant growth retardation that occasionally can be sustained and extreme.

Key words

Growth, juvenile arthritis, juvenile idiopathic arthritis, juvenile rheumatoid arthritis.

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Introduction

Localized and generalized disturbances of growth can be prominent adverse consequences of chronic childhood arthritis (1-6). Generalized retardation of linear growth during periods of active disease is particularly characteristic of certain forms of chronic childhood arthritis. Pathophysiological processes that account for the occurrence and severity of growth disturbances in juvenile arthritis are not clearly established. Factors that might contribute to growth suppression associated with childhood arthritis include the degree, extent and duration of disease activity, age at onset, immobility, damage to cartilage, sub-optimal nutrition, and corticosteroid therapy (2, 7-10). Abnormally low concentrations of insulin-like growth factor-1 (IGF-1) and target insensitivity to IGF-1 might also contribute to growth delay during active arthritis (6, 11-15). Earlier and more precise diagnosis of juvenile arthritis and prompt institution of appropriately aggressive treatment might help to minimize growth disturbances. Identification of clinical, biochemical and serologic correlates that could help predict growth impairment in childhood arthritis should aid in guiding the aggressiveness of therapy and help to predict long-term prognosis. This study was undertaken to more thoroughly define longitudinal patterns of growth in a representative population of children with juvenile rheumatoid arthritis (JRA) and to evaluate possible associated clinical and laboratory correlates.

Subjects, materials and methods

Subjects

The study population comprised 67 children who attended the Pediatric Rheumatic Disease Clinic, University of Saskatchewan during the period between 1981 and 1997 inclusive. All subjects had a disease that conformed to the American College of Rheumatology (ACR) classification criteria for the diagnosis of JRA (16). [New classification criteria and nomenclature for chronic childhood arthritides have been proposed (17). This present study population included subjects whose diagnoses corresponded to oligoarticular juvenile idiopathic arthritis (JIA), rheumatoid factor (RF) positive and negative polyarticular JIA, or systemic onset JIA. The study population did not include subjects with enthesitis-related arthritis, or other forms of chronic childhood arthritis. For the purposes of this report the terms pauciarticular, polyarticular and systemic onset JRA will be used as it was this nomenclature that was applicable when all study subjects were first diagnosed]. Additional inclusion requirements were a monitoring period of 5 years or longer that did not extend beyond age 18 years (after which growth would not be expected) and the availability of sufficient clinical and laboratory measurements that had been collected during the follow-up period. Patients with a co-morbid disease that could affect growth were not included; only one patient (a child with Down syndrome) was excluded for this reason.

Data collection

Information retrieved from patient records included the following: sex, race, date of birth, date of diagnosis, JRA subtype, presence or absence of uveitis, and antinuclear antibody (ANA) and RF test results at first determination. Heights, weights and alkaline phosphatase (ALP) measurements obtained at the initial visit and at approximate annual intervals (12 months ± 4 months) for at least 5 years were retrieved from patient medical records. Heights were obtained using a wall-mounted scale and recorded to the nearest centimeter. Weights were obtained using either a balance arm weight scale or, in more recent years, a digital read-out weight scale and recorded to the nearest one-tenth kilogram. ANA assays were performed as previously described (18). ALP levels were determined by the hospital clinical service laboratory using the method of Bowers and McComb (19) and were interpreted with reference to age-related standards (19, 20). ALP z-scores were calculated by the following formula: [Actual ALP – Average ALP expected for age] / Standard Deviation expected for age.

Hospital clinical service laboratory val-

ues for the erythrocyte sedimentation rate (ESR) were applied as an indicator of disease activity.

Medication profiles were documented for each data entry point.

Height and weight measurements were converted to age-related percentiles and z-scores calculated using EpiInfo 2000 software (Centers for Disease Control, Atlanta, GA) and expressed as height-for-age z scores (HAZ) and weight-for-height z scores (WHZ). The body mass index (BMI) also was calculated using EpiInfo 2000 software. The Statistical Package for the Social Sciences 10.1 (SPSS, Chicago, IL) was used for data analyses. Paired sample t-tests were performed to determine the significance of changes in height and ALP z-scores between groups and within groups over time. Independent sample t-test analyses were applied to evaluate for differences among the 3 JRA subgroups with respect to HAZ and ALP z-score levels. Further stratification of the polyarticular group included analyses comparing RF-positive and RF-negative subgroups and comparing groups of subjects who received and who did not receive systemic corticosteroid therapy. The significance level was set at < 0.05 and confidence intervals at 95%.

Because there was substantial attrition of available data sets after the ninth year post-diagnosis, analyses included data only up to and including the ninth follow-up year.

Results

The characteristics of the study population are summarized in Table I.

At the time of diagnosis, initial HAZ scores for pauciarticular, polyarticular and systemic onset groups were +0.27, -0.07 and +0.40 respectively. Subsequent group-specific HAZ scores, collected at approximate annual intervals for the next 9 years, are shown in Figure 1.

Only at the second year of follow-up was a significant difference in HAZ scores noted between pauciarticular and polyarticular subgroups, with the polyarticular HAZ score being lower ($t = 2.17$; $p = 0.03$; CI = 0.05 – 1.27). A significantly lower HAZ score in the systemic population compared to the pauciarticular population first became apparent at year 2 ($t = 2.41$; $p = 0.02$; CI = 0.14 – 1.61) and the difference was maintained throughout the 9-year follow-up period (at year 9, $t = 2.52$; $p = 0.03$; CI = 0.18 – 2.91). A significantly lower HAZ score in the systemic population compared to the polyarticular population first became apparent at year 6 ($t = 2.80$; $p = .009$; CI = .36 – 2.36) and the difference was maintained until the ninth year ($t = 2.93$; $p = 0.012$; CI = 0.56 – 3.72) .

When the polyarticular group was stratified into RF-positive and RF-negative subgroups, contrasting trends were found (Fig. 2). During the 9-year follow-up period RF-positive children tended to have negative HAZ scores whereas RF-negative children tended to have positive HAZ scores. Although comparison of RF-negative and RF-positive groups showed divergent trends, the differences in HAZ scores were not statistically significant except at year 5 ($t = -2.31$; $p=0.031$; CI = -2.13 – -0.11).

Paired sample t-test analyses did not demonstrate any significant differences in HAZ scores within the pauciarticular and polyarticular subsets. In contrast, the systemic onset group displayed significantly lower HAZ scores, as compared to the HAZ score at onset, for 7 of the 9 subsequent follow-up intervals (at year 1, $t = 5.62$, $p = < 0.001$, CI = 0.47 – 1.09 and at year 9, $t = 3.80$, $p = 0.013$, CI = 0.65 – 3.36; only at years 7 and 8 were the differences not significant).

Systemic steroids were used in this study population at least once in 24 of the 67 patients (35.8%). Two of 27 (7.4%) with pauciarticular JRA received systemic steroids, both for associated iridocyclitis. Of the 29 with polyarticular JRA and the 11 with systemic JRA, 12 (41.4%) and 10 (90.9%) respectively received systemic steroids at some time during their courses. Among the group of 24 children who had received steroids, this therapy was administered only periodically in all subjects. Steroids were being used at 34% of the data entry points. 14 of the 24 taking steroids received intermittent short courses of therapy while the remainder received consecutive therapy for a period ranging from 2 to 7 years (mean 4.1 years).

Comparative analysis of children with polyarticular JRA treated with and without steroids showed no statistically significant variance in HAZ scores. As all but 2 with pauciarticular JRA were not treated with steroids and all but 1 of those with systemic JRA were treated with steroids, meaningful comparisons between steroid-treated and steroid non-treated subsets within these two groups were not possible.

Seven of 67 patients (10.4%) had a height <2 SD below the mean on at least 1 occasion. Abnormally low HAZ scores (<2 SD below the mean) in 3 patients were present within the first 3

Table I. Clinical characteristics of study patients.

	Total	Pauciarticular	Polyarticular	Systemic
Number	67	27	29	11
Sex				
Female	50 (75%)	22 (82%)	26 (90%)	2 (18%)
Male	17 (25%)	5 (18%)	3 (10%)	9 (82%)
Onset age (months)				
Mean		56	93	58
Range		18 to 134	13 to 189	6 to 126
Caucasian: North American Indian	58 : 9	27 : 0	20 : 9	11 : 0
Uveitis	11 (16%)	9 (33%)	2 (7%)	0
RF positive	13 (19%)	0	13 (45%)	0
ANA positive	44 (66%)	19 (70%)	25 (86%)	0

RF: rheumatoid factor; ANA: antinuclear antibody.

years of disease and normalized by the fourth year. Only 2 patients, both boys with systemic disease and a history of chronic steroid therapy, had heights < 2 SD below the mean at final determination.

Initial ALP z-scores in the pauciarticular, polyarticular and systemic groups were -0.64, -1.40 and -0.40 respectively. There were no sustained significant differences over the 9-year follow-up period among the three JRA onset subtypes. However, ALP levels were significantly lower in the systemic population as compared to the pauciarticular group at the first, third and fourth follow-up years (respectively, $t = 3.07$, $p = 0.007$; CI = 0.90 – 4.84; $t = 8.00$, $p < 0.001$, CI = 4.81 – 9.05; $t = 2.98$, $p = 0.012$, CI = 0.68 – 4.54). Also, ALP levels were significantly lower in the systemic population at the first and sixth follow-up years as compared to the polyarticular group (respectively, $t = 2.37$, $p = 0.027$, CI = 0.15 – 2.18 and $t = 2.64$, $p = 0.018$, CI = 0.38 – 3.53). The group of polyarticular children with a positive test for RF had significantly higher ALP levels at the fourth, sixth, eighth and ninth follow-up years compared to those who were RF-negative (respectively $t = 2.94$, $p = 0.01$; CI = 0.71 – 4.38; $t = 3.17$, $p = 0.009$, CI = 0.63 – 3.49; $t = 5.08$, $p = 0.007$, CI = 1.25 – 4.28; $t = 2.81$; $p = 0.03$; CI = 0.40 – 4.60) (Fig. 3).

ESR values, as an indicator of disease activity, were significantly higher in the polyarticular group compared to the pauciarticular group only at the first follow-up year ($t = 3.88$; $p = 0.001$; CI = -47.22 – -14.56). When ESR values in the pauciarticular group were compared to those of the systemic group, the latter showed significantly higher values for each of the first 2 years of follow-up but not thereafter ($t = -4.15$; $p = 0.001$; CI = -44.31 – -14.44 and $t = 4.26$; $p = 0.013$; CI = -106.30 – -22.37). There were no significant differences in ESR values between the systemic and polyarticular groups. The RF-positive polyarticular group had significantly higher ESR values only at onset as compared to the RF-negative group ($t = 4.05$; $p = 0.001$; CI = 18.88 – 59.36). No significant differences in BMI were demonstrable among groups at any interval data point.

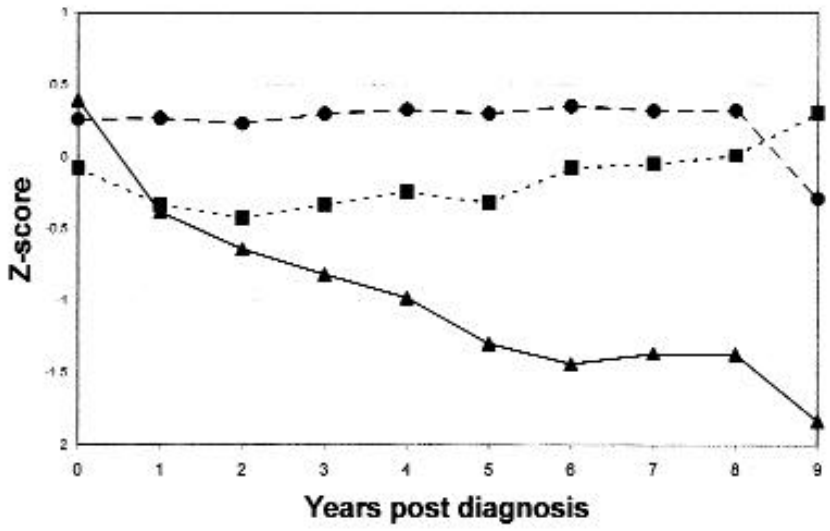

Fig. 1. Height-for-age z scores at onset and for each of the subsequent 9 follow-up years for pauciarticular (●), polyarticular (■) and systemic (▲) onset subtypes. A significant difference in scores between pauciarticular and polyarticular subgroups was noted at year 2. Scores were significantly lower in the systemic subgroup compared to the pauciarticular and polyarticular groups from years 2 to 9 and years 6 to 9, respectively.

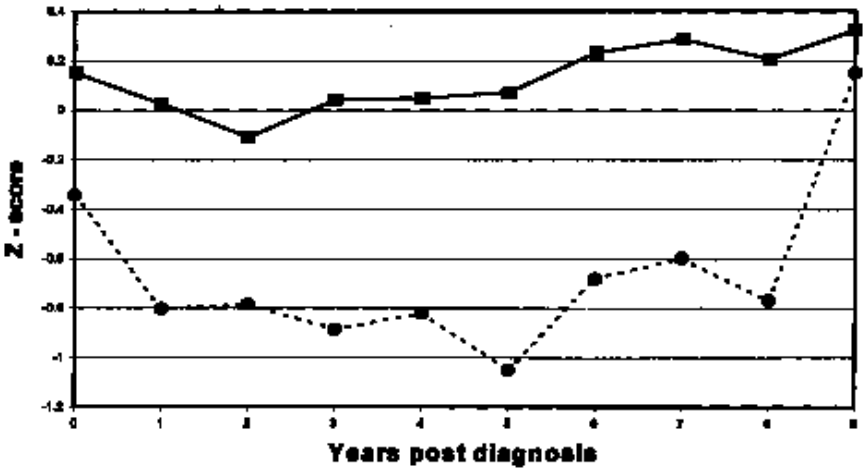

Fig. 2. Height-for-age z scores at onset and for each of the subsequent 9 follow-up years for rheumatoid factor positive (●) and negative (■) polyarticular children. A statistically significant difference was noted only at year 5.

WHZ scores were significantly lower in the polyarticular group as compared to the systemic group at follow-up years 4, 5 and 6 (respectively $t = -2.21$, $p = 0.04$, CI = -2.63 – -0.05; $t = -2.89$; $p = 0.014$; CI = -4.71 – -0.66; $t = -2.89$; $p = 0.02$; CI = -5.47 – -0.71) but not at other data points. No significant difference in WHZ scores between steroid treated and steroid non-treated subjects was noted, suggesting that any observed WHZ differences were independent of steroid use.

Discussion

The results reported here indicate that, among children with JRA, generalized disturbances of growth can occur especially in those with the systemic JRA and, to a lesser degree, polyarticular JRA onset subtypes. These observations are consistent with earlier reports in which growth retardation among systemic and polyarticular subgroups has been demonstrated (1, 3, 4, 7, 22). Among 119 children with chronic arthritis,Ansell and Bywaters (1) noted that retardation of linear growth was associated with a long duration of

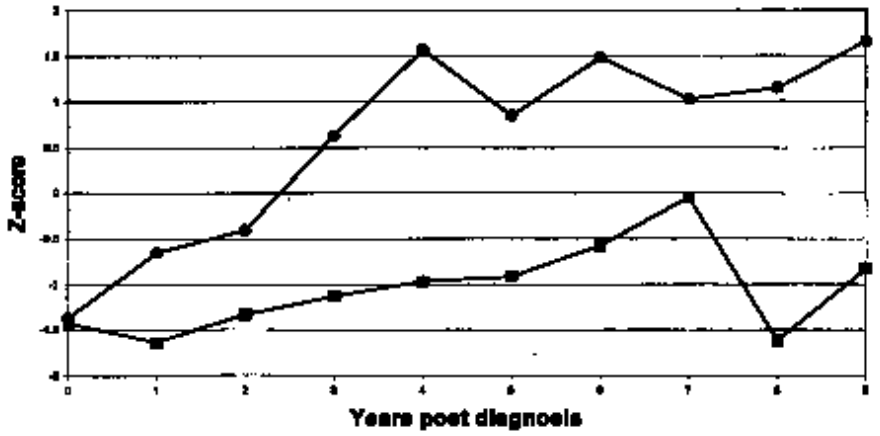

Fig. 3. Alkaline phosphatase (ALP) z scores at onset and for each of the subsequent 9 follow-up years for rheumatoid factor positive (●) and negative (■) polyarticular children. The rheumatoid factor positive subgroup had significantly higher ALP scores at years 4, 6, 8 and 9.

active disease, but that with disease remission a return to normal height was achieved within 2 to 3 years providing epiphyseal growth centers had not fused prematurely. Similarly, in a population of 64 prepubertal children with chronic juvenile arthritis, Saha and colleagues (21) found an initial decrease in patient heights in the first year postdiagnosis but a subsequent increase, suggesting that growth slows prior to treatment but then normalizes to premorbid values with effective control of disease activity. Our data partially support these observations. The pauciarticular population we studied showed relatively stable heights throughout the follow-up period. In contrast, the systemic group showed a progressive decline in heights over time. The polyarticular subset initially showed a modest decline in heights during the first 5 follow-up years, before showing a tendency to normalization. Eighty percent of the subjects in the population reported by Saha and colleagues had oligoarticular disease. Consequently, analyses of data from their population would not reflect the growth disturbances in the systemic or polyarticular subsets, which respectively comprised only 3% and 17% of their study population.

Zak and colleagues (8) assessed the heights of adults with antecedent histories of chronic childhood onset arthritis. Those with heights less than 2 SD below the mean tended to have polyarticular or systemic onset subtypes, exposure to systemic steroid therapy and more functional disability. Seven of the 65 study patients (10.8%) reported by Zak *et al.* had adult heights < 2 SD below the mean. In our population 7 of 67 (10.4%) had a height <2 SD below the mean on at least 1 occasion but only 2 (3.0%) had heights <2 SD below the mean at final determination.

A positive test for rheumatoid factor is considered to be a poor prognostic indicator in JRA (23). In general, our results indicate that heights-for-age values in the polyarticular group tend to be lower than those in the pauciarticular subset although not as low as in the systemic subset. When stratified according to the presence or absence of rheumatoid factor, our seropositive group tended to have lower HAZ scores.

The growth suppressive effects of corticosteroid therapy can be a factor contributing to growth retardation in JRA (10, 24, 25). However, growth delay in JRA, unrelated to steroid treatment, does occur as this study and earlier ones have shown (4, 7, 21). In this present study no significant differences in growth were demonstrable between steroid-treated and steroid-untreated populations, although steroid use in our population was characterized most often by intermittent, low-dose regimens, which are unlikely to substantially suppress growth permanently (26). Polito and colleagues (7), in their study of growth retardation among non-steroid treated children with juvenile arthritis, found growth suppression in the systemic and polyarticular subsets (but not in the pauciarticular subset) that was independent of steroid therapy, an observation consistent with our findings.

The results of the current study indicate that intermittently lower levels of ALP are found within the systemic onset group, which demonstrated substantial growth suppression. However, low ALP levels either in advance of or coincident with documented growth impairment was not found consistently enough in our population to serve as a reliable marker of growth suppression. Earlier studies have suggested no significant differences in ALP levels among children with chronic arthritis (27). Studies that have reported lower levels of bone-specific ALP in children with arthritis have not taken into consideration age-dependent normal values as was done in the present study (20, 28-32). That ALP levels could reflect growth in JRA is suggested by evidence showing increases in ALP coincident with rising height velocities in response to exogenous growth hormone therapy (33). In our study, when the polyarticular group was stratified into RF-positive and RF-negative subsets, analyses revealed that RF-positive patients have significantly higher ALP scores beginning at the fourth follow-up year. Interestingly, higher ALP levels in the RF-positive polyarticular group corresponded with poorer growth, while in the RF-negative subset low ALP levels were associated with normal growth. These observations suggest that different mechanisms of bone metabolism might occur in seropositive and in seronegative polyarticular JRA and support the need for further studies to evaluate differences in bone growth and markers of bone metabolism in JRA subsets.

Our findings confirm that disturbances in generalized linear growth occur in JRA predominantly in those with systemic and rheumatoid factor positive polyarticular onset subtypes. Prospective multicenter and multidisciplinary studies will be required to better define growth patterns in JRA, identify clinical, serological and biochemical corre-

lates and clarify the factors that influence bone growth in the presence of chronic inflammatory joint disease. Elucidation of the pathophysiologic mechanisms of bone growth and metabolism in JRA could help guide the formulation of more rationally conceived and effective monitoring and treatment strategies.

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