PATHOGENIC IMPLICATIONS OF AGE OF ONSET IN JUVENILE RHEUMATOID ARTHRITIS

DONITA B. SULLIVAN, JAMES T. CASSIDY, and ROSS E. PETTY

An analysis of age of onset in juvenile rheumatoid arthritis was performed in the last 300 children seen in our clinic. There was a peak age of onset in girls at 1 to 3 years. Distribution of age of onset in boys was bimodal with the first peak at 2 years of age and the second at 9 years. There was no accentuation of frequency in either sex in the 10- to 14-year age group. The distribution of age of onset was bimodal in both monarticular and polyarticular onset of disease, but no particular modal age of onset was seen with systemic onset of disease. It is possible that these data reflect that JRA is not a homogeneous disease, or that there are age-sex related differences in host susceptibility or pathogenic agents.

Previously published reports of children with juvenile rheumatoid arthritis (JRA) have documented the heterogeneity of presentation, course of the disease (1,2), and serologic abnormalities (3–8). In the past, study of age- and sex-dependent variables has helped to elucidate etiologic and pathogenic mechanisms in many diseases; however, there are few studies available that have provided this type of information in JRA. Ansell and Bywaters in 1963 (9) and Laaksonen in 1966 (10) suggested that the age of onset in JRA was bimodal with one peak in the child under 5 and the other in the 10- to 15-year age group. We have been impressed by quite a different distribution of age of onset in 300 children with JRA seen in our clinic. The purpose of this report is to record an analysis of the age and sex incidence of JRA and to correlate this with clinical subtypes of disease. We believe that these data represent important epidemiologic observations in terms of the etiology and pathogenesis of this disease.

MATERIALS AND METHODS

Age of onset of disease was recorded for 300 consecutive children with JRA seen from 1961 to 1973. This series did not include patients first seen on the adult services of this institution with a retrospective determination of age of onset of disease in childhood. For the purposes of the present study, JRA included patients with onset through 14 years of age. Age of onset was defined as the age of appearance of the first symptom or sign consistent with the diagnosis of JRA. The diagnosis of JRA was based upon preliminary criteria established by the American

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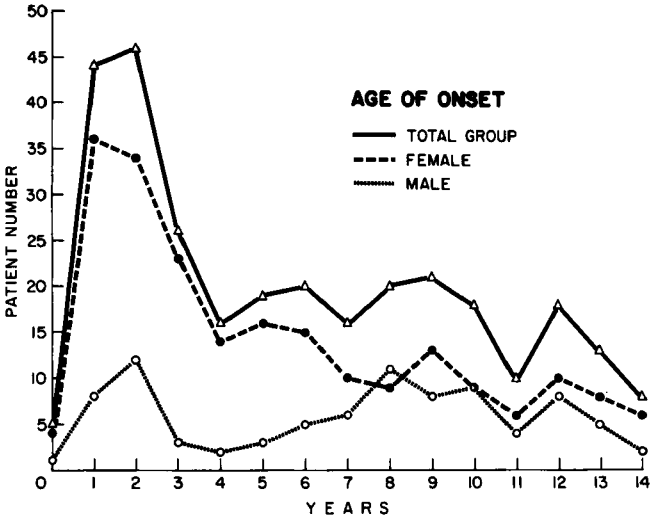

Fig 1. *Age of onset for the total group of children and for females and males separately.*

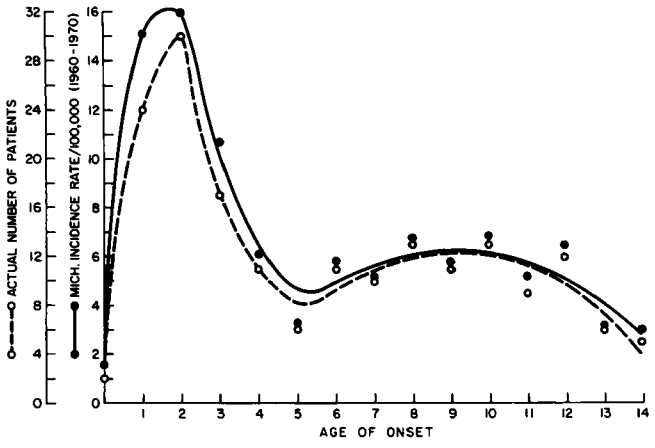

Fig 2. *The incidence rate for children with JRA per 100,000 population in Michigan for the years 1960–1970 and the actual observed number of patients are plotted against age of onset.*

Rheumatism Association (Classification I) (11). Two hundred thirteen children were girls and 87 were boys. Active disease was present at first visit in 91%. The patients' present age ranged from 1 to 21 years with a mean of 10 years.

The children were divided into three groups according to type of onset (12). Those catagorized as having monarticular onset had only one joint involved during the first 4 months of their disease. Children with polyarticular onset had more than two joints objectively involved from the onset or more than four joints present for a minimum of 4 months. Those classified as having systemic onset had prominent manifestations of high fever, rash, lymphadenopathy, hepatosplenomegaly, or serositis in addition to joint involvement. The presence of erosive arthritis was recorded from radiographs of the affected joints.

An interval incidence rate for this institution by age of onset for JRA was determined for the years 1960 through 1970 for those children in this series living in Michigan. The number of children with onset at each age born in each of the above years was divided by the number of children of that age in each year and the result was expressed as a rate per 100,000.

RESULTS

Distribution of age of onset of disease for these children is shown in Figure 1. For the total group a single large peak at 1–2 years of age is observed. Age of onset for boys, however, shows a bimodal distribution with the first peak at 2 years and the second peak at 9 years. Age of onset for girls does not clearly show a second peak. No accentuation in frequency of onset was seen in either sex at 10–14 years. The age of the patient by sex at the time of the first visit was a normally distributed variable. For girls it was 9.2 years and for boys it was 10.5 years.

Figure 2 shows the incidence rate curve for age of onset for those children living in Michigan and compares it with the actual number of patients seen with onset at each age. The solid black circles and solid line represent the Michigan incidence rate for JRA for children seen at this institution according to age of onset. The open circles and interrupted line represent these same patients expressed as the actual number of children with each age of onset. From 1960 to 1970 the interval incidence rate determined from these data was 9.2 per 100,000 per year. The children at risk in Michigan for each of these years for each of the 15 age groups varied from 119,356 to 198,703. Incidence rate curves for males and females were similar.

A comparison of age of onset curves was also made for Michigan residents who lived within 50 miles of Ann Arbor versus those referred from beyond that distance. These curves were similar except that the curve for children living within the 50-mile radius was somewhat higher at 9 years. The sex distribution in these two populations was nearly identical (71% girls compared to 69%). The type of onset of disease was, however, different. For those within 50 miles, 40% had monarticular onset and 13% systemic; for those beyond 50 miles, 32% had monarticular onset and 25% systemic.

Age of onset of JRA as it relates to type of onset is shown in Figures 3 to 5. One hundred eight children had monarticular onset of disease. Although girls contributed primarily to the large peak of onset at 1 year, it is the boys who appear to have a bimodal distribution of age of onset (Figure 3), eg no boys had

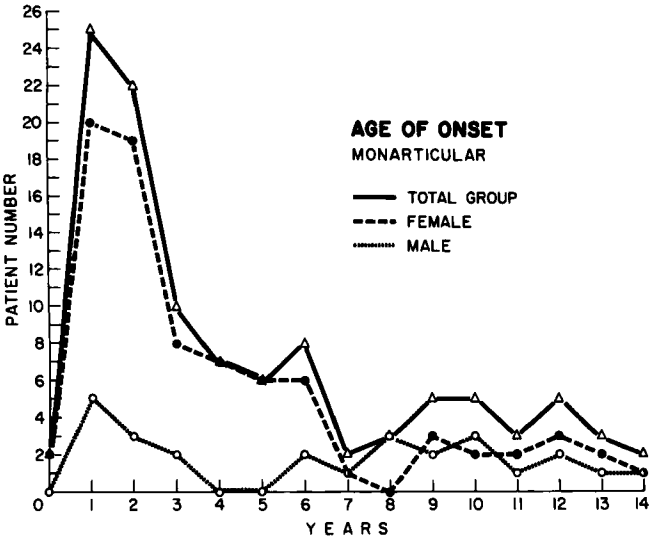

Fig 3. *Age of onset for children with monarticular onset of JRA.*

onset at 4 or 5 years. Polyarticular onset occurred in 137 children. In contrast to the presentation in monarticular disease, a bimodal distribution for the total group is seen. It is notable that both boys and girls contribute to the first peak, although boys contribute relatively more to the second peak (Figure 4).

Fifty-five children had systemic onset of disease. The presence of any particular modal age of onset in systemic onset of disease could not be demonstrated. However, there does appear to be a slightly higher frequency in the younger age group. No particular sex-related peak age is seen (Figure 5). The mean age

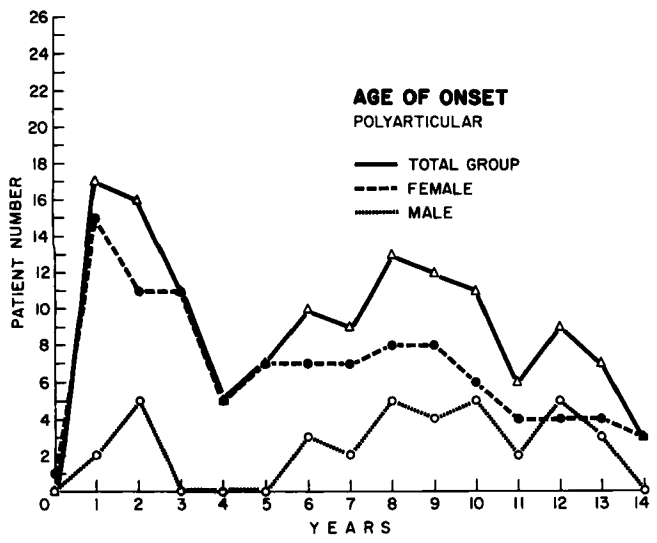

Fig 4. *Age of onset for children with polyarticular onset of JRA.*

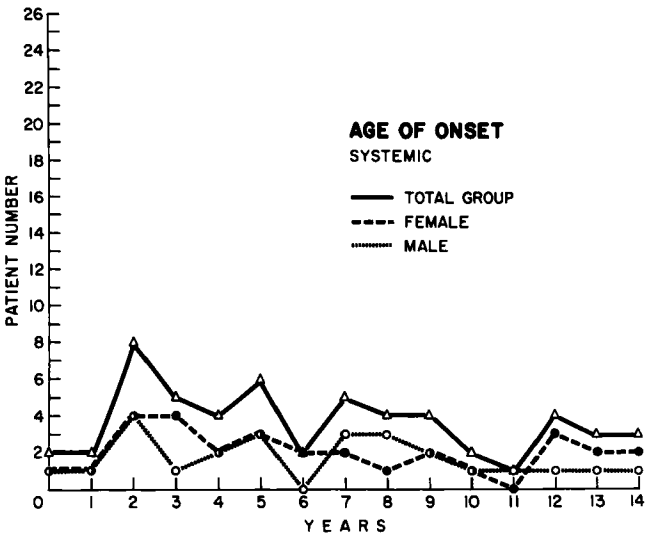

Fig 5. *Age of onset for children with systemic onset of JRA.*

of onset for monarticular onset was 4 years and that for polyarticular or systemic onset of disease was 6 years. Age of onset was significantly related to type of onset of disease ($P < 0.03$). It was also related to erosive articular disease ($P < 0.0001$). The older the child at age of onset of disease, the greater was the frequency of erosive arthritis.

DISCUSSION

Incidence curves for age of onset in JRA were computed by Wood for the years 1947 to 1965 for children seen at Taplow relevant to the population of London and southeastern England (13). His data for females mirrored the general age of onset curve for JRA with one peak at 2–3 years and a second at 5–6 years with relative incidence rates of approximately 0.025 and 0.021% per year respectively. During the age period of 10–15 years the rate for girls was lower at approximately 0.013. Males showed a lower early peak with a rate of 0.010 with a higher rate of 0.015 in the older age range.

Our incidence rates shown in Figure 2 represent minimal estimates as they are based only on children living in the state seen at this referral institution. The fact that the incidence rate curve and the actual age of onset curve are virtually identical strengthens the opinion that our children probably do not represent a group biased in age of onset. In comparing children within a 50-mile radius of Ann Arbor to those beyond that distance, the sex ratio

was found to be nearly identical. On this basis alone, it seems unlikely that a sex-related duration of disease would account for any differences between these groups, or between our series and those of others. There was however a difference in type of onset of disease between these two referral populations. Children coming from within 50 miles tended to have more monarticular disease and those from further away, more systemic type of onset. It seems obvious that the sicker children tend to be referred long distances to a university center.

Examination of the age of onset curves distributed by type of onset could potentially yield more information than the combined curves (Figures 3–5). Girls with polyarticular and monarticular disease comprise the major contribution to the first peak. Both sexes contribute equally to the second peak. Other authors have provided sex-specific ages of onset in JRA, but the numbers of patients in these reports have been too small to analyze (14,15). The data of Ansell and Bywaters suggest a peak incidence for boys between 2 and 4 years with a subsequent gradual increase in occurrence from 9 to 15 years (9). The age-sex specific curves of Laaksonen show a similar distribution for age of onset for both boys and girls (10). In her study there was a slight accentuation in the early years of childhood with a major peak in the 10- to 15-year age period. A partial explanation for this latter phenomenon was the fact that this study included patients who, although they had had onset of disease as children, were first examined as adults. A younger age of onset of children with monarticular disease has also been the experience of other investigators (2,9,16). Bywaters and Ansell found an average age of onset of 6.1 years for children with monarticular disease (16). In the series analyzed by Schaller and Wedgwood, the average age of onset for monarticular disease was 4.9 years, for polyarticular onset 5.5 years, and for systemic disease 6.3 years (2). However Calabro and Marchesano found the youngest mean age of onset in children with systemic disease, 4.6 years, compared to 7.4 years for polyarticular onset and 7.3 years for monarticular disease (1).

Other variables in children with JRA are also distributed according to age of onset. Seropositivity for antinuclear antibodies has been reported previously from this laboratory to be most frequent in the female child with younger age of onset; systemic presentation of JRA was found least often associated with ANA positivity (7). In contrast prevalence of rheumatoid factors was noted to have an increased frequency in children with later age of onset of JRA (4). Rheumatoid factors have been shown to be associated additionally with subcutaneous nodules, erosive joint disease, and a poorer functional class (3–5).

If the age of onset curve for males obtained in this study represents a biologic phenomenon, it strongly suggests that at least two sets of etiologic agents or types of host susceptibility may be involved in JRA: one in the preschool child met in the environment of the home, and the other encountered by the child in the early years of school. Further analysis of these observations reflected in age of onset may underscore epidemiologically important pathogenic mechanisms or host variability in this disease.

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