Pediatric Rheumatology Review

Juvenile arthritis - Who gets it, where and when? A review of current data on incidence and prevalence

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Received on March 23, 1999; accepted on March 26, 1999.

Clin Exp Rheumatol 1999; 17: 367-374.

Key words:
Juvenile rheumatoid arthritis, juvenile chronic arthritis, epidemiology, incidence, prevalence.

ABSTRACT

Epidemiological studies of chronic arthritis in childhood can provide clues to genetic determinants of disease manifestations and environmental triggers. Available data are difficult to compare, however, because of the heterogeneity of the disease, differences in the classification criteria used for definition and inclusion, and differences in source populations and case ascertainment. Nevertheless, when the data are interpreted according to the methodologies used, geographical and ethnic differences can be found with regard to occurrence rates, age at onset, subgroup distribution and immunological markers. Seasonal variations have been detected in systemic disease. Variations in the incidence of childhood arthritis over time have also been observed, indicating environmental influences on disease frequency, while familial aggregations suggest the presence of genetic factors. These epidemiological data form a challenging puzzle which we hope will provide clues to future understanding of etiologies and cures, with the help of basic scientific research.

Introduction

Epidemiological studies of chronic arthritis in childhood are meaningful to allow the further development/evaluation of criteria for disease classification, description of the natural history and outcome in different disease entities, the identification of early prognostic factors, health care planning and, eventually, the identification of possible etiological factors.

Epidemiology can be defined as "the study of the distribution and determinants of health-related conditions or events in defined populations" (1). A distinction between descriptive and analytical epidemiology is often drawn. In descriptive epidemiology, observations concerning the relationship between a disease and characteristics such as age, sex, race and geographic location are made, i.e. answers are sought to the questions of who gets a disease, where and when. In analytical studies, risk factors and hypothesized causal relationships are examined (1).

Epidemiological research on chronic childhood arthritis has, with few exceptions, been descriptive. The interpretation of published data is complicated because of: (i) the heterogeneity of the disease and the lack of uniform classification criteria; (ii) differences in methodologies for case identification/case ascertainment; and (iii) inadequate definition of study populations.

The purpose of this review is to explore possible differences in the frequency of chronic childhood arthritis and its subtypes among different populations, different geographical areas, and over time, i.e. differences which could point in the direction of underlying genetic and environmental factors. The methodological pitfalls outlined above have therefore to be carefully addressed and are further considered below before the published data is analyzed.

Classification criteria

The revised criteria suggested by the American College of Rheumatology (ACR) in 1977 (2) have been extensively used in North and South America, while European investigators have primarily used the criteria proposed by the European League Against Rheumatism (EULAR) in 1978 (3). Diagnosis and division into subtypes is based in both sets of criteria on clinical examination and no specific diagnostic tests are available.

As shown in Table I, the two sets of criteria are not interchangeable. One confusing issue is that the terminology differs: juvenile rheumatoid arthritis (JRA)

Table I. A comparison of the EULAR (3) classification for juvenile chronic arthritis and the ACR classification of juvenile rheumatoid arthritis (2).

	EULAR	ACR
Age of patients (years)	0-15	0-15
Disease duration for diagnosis	3 months	6 weeks
Onset subtypes (within 6 months of onset)	+	+
List of exclusions	+	+
JAS, IBD and JPsA*	included	excluded
Terminology	JCA	JRA

JAS: juvenile ankylosing spondylitis; IBD: arthropathy associated with inflammatory bowel disease; JPsA: juvenile psoriatic arthropathy.

is used by the ACR and juvenile chronic arthritis (JCA) by EULAR. The main differences which may affect occurrence rates is the required disease duration for diagnosis (6 weeks and 3 months, respectively) and difference in the inclusion of subgroups. The ACR and the EULAR criteria both include the systemic, pauciarticular and polyarticular onset types. In the EULAR criteria, however, juvenile ankylosing spondylitis (JAS), juvenile psoriatic arthritis (JPsA) and arthritis in connection with inflammatory bowel disease (IBD) are also included. An additional complicating factor is that there are no universally accepted criteria for the classification of the latter subgroups, sometimes collected under the "umbrella" term spondyloarthropathies (SpA). In studies where the umbrella term SpA has been used in combination with the ACR criteria for JRA, patients with reactive arthritis, Reiter's syndrome and seronegative arthritis and enthesitis (SEA) syndrome (4) have often been included. The latter groups are not included in the EULAR criteria - thus creating further complications in the interpretation of data.

The broad subgroups included in both the ACR and EULAR criteria contain considerable heterogeneity regarding age at onset, sex, the presence of antinuclear antibodies (ANA) and rheumatoid factor (RF), indicating that the subgroups do not have homogenous biological bases. This is further discussed in relation to data from different ethnic groups and geographical areas below.

To overcome the difficulties regarding such variations in classification criteria, the Classification Taskforce of the Pediatric Standing Committee of the International League of Associations for Rheumatology (ILAR) has proposed a system of classification intended to supercede the EULAR and ACR criteria which will hopefully achieve worldwide acceptance (5). The term Juvenile Idiopathic Arthritis is suggested as an umbrella term to indicate that the disease has no known cause. The proposed criteria are more descriptive than those previously used and aim at distinguishing biologically homogenous groups. These criteria will, however, require validation in proper epidemiological and statistical terms and to date no such studies have been published.

Methodologies for case identification and case ascertainment

The optimal epidemiological approach for studying disease occurrence and determinants, i.e. the prospective population-based cohort study, is often not feasible in relatively rare diseases such as JCA/JRA. Large samples are required, and the studies are time-consuming and costly. Thus, other methods of case identification such as practitioner surveys, clinic populations and disease registers have been used. In these studies, however, factors such as general awareness and knowledge of chronic arthritis in childhood, the structure of and access to the country's health care system, and referral patterns may influence the results. Disease-specific registers can be valuable tools, but must cover a sufficiently large and well-defined population, have explicit inclusion criteria to define cases and apply ascertainment mechanisms to detect most cases, as stated by a working group of the World Health Organisation (6). Special methods for case ascertainment such as the capture-mark-recapture approach (7) can offer valuable tools for increasing the accuracy of data.

Definition of study populations

In order to calculate incidence rates and prevalence, well-defined catchment populations are required. In developing countries there may be difficulties in obtaining accurate census data, as discussed by Arguedas *et al.* (8). In countries with diverse health care systems, such as the USA, the catchment population can also be difficult to define (9). In countries where the health care systems are more homogenous and socialised, as in the Nordic countries (10, 11) and the former East Germany (12), the definition of study populations is easier.

Childhood arthritis is referred to as a complex genetic or polygenetic trait in which unknown environmental factors probably also play a substantial role. The clustering of cases in families may indicate a strong genetic influence, while clustering in time and space and secular variation indicate a role for environmental influences. Geographical variations may represent genetic or environmental influences. The same holds true for ethnic differences in disease manifestations. In this review the published data are grouped and analysed in relation to the above parameters. Juvenile arthritis (JA) is used as a collective term for JCA, JRA and SpA, while the specific terms are used as they have been applied in the studies cited.

Who ? Family studies

Early studies on hereditary patterns in JA have shown some family aggregation of cases and a few monozygotic twins concordant for JCA (13-14). Still, the risk for a sibling of a patient with JRA of his also developing JRA does not appear to be very strong (15). In 1994 a North American registry for affected sib-pairs (ASPs) with JRA was established and summary statistics for the disease and demographic variables for the first 71 ASPs have now been published. From the data accumulated in this registry an estimate was made that only about 0.8% of all JRA appear in ASPs. In the 71 sibs registered, 63% were concordant for sex,

76% for JRA onset type, and 79% for course type. There was an unexpectedly high frequency of pauciarticular onset pairs. Seven sets of twins were included, all of whom were concordant for onset and course type, and disease onset was separated by only 3.3 months. In addition, there was a preliminary indication that non-whites were under-represented, perhaps owing to the lower frequency of disease susceptibility alleles in non-white populations. However, ascertainment or detection bias could not be ruled out. In conclusion, this study strengthens the hypothesis that genetic influence plays a role in determining JRA onset type, and mainly in the pauciarticular onset disease (15).

When? Clusters in time and space and secular trends

A few epidemiological studies supporting the concept of environmental triggers, especially infections, have been published. A cyclical pattern of incidence of JCA 1984 - 1988 was described by Gäre *et al*. in Sweden (10), with a peak in 1986. Oen *et al*. (16) noted a cyclic incidence of JRA with peaks in 1979, 1982, 1986 and 1990-1991. Increases in confirmed *M. pneumonie* infections were concurrent with peaks in the incidence of JRA. Interestingly, there was no consistent variation in the incidence of seronegative spondyloarthropathies. Peterson *et al*. (17) found a cyclic incidence of JRA 1960-1993 in Rochester, Minnesota, with incidence peaks in 1967, 1975 and 1987. In addition, an overall decrease in the incidence of JRA over the last decade was observed, especially in the pauciarticular and systemic onset types. This trend may reflect a change in clinical practice (i.e., the diagnosis of other diseases such as Lyme arthritis) rather than an actual decrease in incidence. In contrast, no decline in the incidence of JRA was found in a population-based study from Finland 1980 - 1990 (18). The incidence peaks in the three former studies do not exactly coincide, which could reflect multiple infectious agents or the influence of geographic location or other environmental factors on JA presentation.

Seasonal variation in the onset of systemic JRA, but no year-to-year variation, has been shown by Lindsley (19) and was confirmed by Peterson *et al.* (17) but not by others (20) The seasonality in the study by Lindsley coincided with the occurrence of enteroviral infections in the same geographic area and this, together with the unique features of systemic disease, are suggestive of an infectious etiology.

A cluster study of children with JCA born in 1963 in the United Kingdom was presented by Pritchard (21). An influenza A strain was present in 1963. The patients were found to have higher antibody levels to this influenza strain than age-matched controls. The patients developed JCA after the appearance of a different type of influenza A in 1977. An interesting hypothesis was posed that the patients developed chronic arthritis because they had been pre-sensitized to influenza A by contact with an earlier strain *in utero*. Such a mechanism could explain why infectious agents are seldom found in relation to the onset of arthritis, even if they play a part in triggering the disease.

Where? Incidence and geographical patterns

Recent incidence figures for JCA and JRA from Europe are summarised in Table II according to a north to south gradient (10-12, 22-25). In Table III the incidence figures for JRA, JCA and SpA from the American continent are presented according to a north to south gradient and ethnicity (8, 16, 26-31). A wide range in incidence can be seen for JCA and JRA: 1.3 to 22.6 per 100,000 children less than 16 years of age. Some of the variance pertains to the methodological differences outlined above and are commented on below, while there is also a possibility of true geographical and ethnic differences.

The wide confidence limits are an effect of the rarity of the disease and point to the necessity of studying large, well-defined populations over a long time period in order to reveal “true” differences. The figures vary less, 10 to 19.2 per 100,000, if studies with similar methodologies are compared, for example prospective studies based on general and well-defined populations (10-11, 17, 24, 30). These studies all emanate from Europe or North America and have a predominantly Caucasian population. In spite of the similar methodology used, the figure from Costa Rica (6.8 per 100,000, ref. 8) falls outside the confidence limits of the Nordic studies (10-11, 22) pointing to a true difference that may pertain to geography or ethnicity or both. The population in the Costa Rican study was mainly Hispanic. One speculation could be that in a warmer climate the milder cases have fewer symptoms and the patients are thus less likely to seek medical attention. The panorama of possible infectious and other environmental triggers may also differ.

The lower figures from Canada: 3 to 5.3 per 100,000 (16, 28-29), pertain to studies from paediatric rheumatology centres where referral bias could have represented an important factor, i.e. milder cases may have been missed. Selection bias may also have influenced the low figure from France, 1.3 to 1.8 per 100,000, which was based on a questionnaire survey in which a large number of physicians did not respond, thus making ascertainment difficult (25).

The figure from East Berlin in Germany was surprisingly low, 3.5 per 100,000, considering the structure of the country’s health care system, which would facilitate case ascertainment. On the other hand, the study was retrospective in nature, which makes it difficult to evaluate the awareness of rheumatic diseases in children among referring physicians (12). The subgroup distribution was similar to that found in the prospective studies, with a high proportion of pauciarticular disease, which argues against referral bias.

In Europe, the tendency toward a falling north to south gradient in incidence was seen, with the highest incidence rates registered in northern Norway (22.6 per 100,000, ref. 22), and Finland (18.2 per 100,000, ref. 11), while slightly lower figures were found in southern Sweden (10) and Denmark (23), and the lowest rates were found in Germany (3.5 per 100,000, ref. 12) and France (1.3 - 1.8 per 100,000, ref. 25). However, no definite conclusions can be drawn on the basis of this data because of differences in the methodology used between studies, as discussed above.

Table II. Incidence of juvenile arthritis from different geographical areas in Europe, presented from north to south.

Reference	Geographical location	Catchment population (< 16 years)	Type of survey Year	Criteria	Annual incidence rate/100,000 (95 % conf. interval)
Moe & Rygg, 1997 (22)	Norway 2 northernmost counties	48,215	Registry covering defined geographical area Retrospective, 1985 - 1994	EULAR	22.6
Kunnamo *et al.*, 1986 (11)	Finland Helsinki area	148,362	General population Prospective, 1982	ARA > 3 months	19.6 (13.1 - 28.2) 18.2 (10.8 - 28.7)
Kaipiainen-Seppänen & Savolainen,1996 (18)	Finland Helsinki, Tampere, Kuopio regions	275,188 - 264,226	National drug registry + hospital records Retrospective, 1980 - 1990	ARA	13.8 (1980) 15.1 (1985) 13.5 (1990)
Andersson Gäre & Fasth, 1992 (10)	Sweden Southwestern region	389,976	General population Prospective, 1984 - 1988	EULAR	8.3 - 13.7 (max - min) 10.9 (9.4 - 12.4) (ave.)
Östergaard *et al.*, 1988 (23)	Denmark Nordjylland Amt	≈ 100,000	General paediatric clinic Retrospective, 1970 - 1977, 1978 - 1986	ARA > 6 months	6 - 8
Kiessling *et al*., 1998 (12)	Germany East Berlin	247,906	Paediatrician/Paediatric rheumatology centre Retrospective 1980 - 1988	EULAR (SpA not included)	5.3 - 2.3 (max - min) 3.5 (2.8 - 4.4) (ave.)
Symmons *et al*., 1996 (24)	UK Liverpool Canterbury	92,374 60,963	Registry, Paediatric rheumatology centres Prospective, 1990 - 1994	EULAR	10 (7 - 13) 10 (6 - 14)
Prieur *et al*., 1987 (25)	France	964,284 + 618,136	Practitioner surveys Retrospective, 1981 - 1982	EULAR	1.3 - 1.8

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The confidence limits in the Finnish and German studies did not overlap, and would probably not have done so for the Norwegian or French figures either, if they had been calculated. This may indicate that there are true differences pertaining to environmental and/or genetic factors. For example, the prevalence of HLA B27 positivity was high in the general population in northern Norway, which could increase the risk of HLA B27 associated arthritis.

Incidence figures from the North and South American continents did not show any obvious geographical pattern, but there seem to be ethnic differences, which are further discussed below.

Prevalence and geographical patterns

The prevalence of JA from different geographical locations is summarised in Table IV (8, 10, 12, 22, 25, 30-39). The figures show great variation, from 8 per 100,000 to 400 per 100,000 children less than 16 years of age (25, 39), but have to be interpreted carefully because of the differences in methodology used. In addition, most of these studies did not present confidence intervals, and since the numbers of patients and the sizes of the populations on which the prevalence figures were based were small in many of the studies (31, 33, 37, 39), the detection of "true" differences is difficult.

The highest prevalence figures were reported in those studies where population questionnaires in combination with clinical examination by a pediatric rheumatologist were used: 64, 167 and 400 per 100,000 children, respectively (34, 32, 39). These three studies emanated from different parts of the world: Turkey, Belgium and Australia. The Belgian and Australian study populations were small, and when we calculated the confidence intervals for the Australian study from the data given, the figure obtained (95% CI 140-664) was found to overlap with the Belgian figure of 167 per 100,000, thus indicating no actual difference (32, 39). In all three studies, cases were found which had not been previously identified within the health care system, which suggests that some cases will be missed if the health care system alone is relied upon for case identification. On the other hand, Manners *et al.* (39) pointed out that population questionnaires are not the solution for case identification since no question in their questionnaire succeeded in identifying the children with previously undiagnosed JCA. Their conclusion was that only clinical examination supported by a clinical history for both the parent and child can provide a reliable basis for diagnosis.

In two studies from very different geographical locations, Sweden (10) and Costa Rica (8), well-defined populations were prospectively surveyed through health care organisations and practitioners/pediatricians for 5 and 2 years, respectively. The prevalence rates found were 86 (95% CI 77 - 96) in Sweden and 31 (95% CI 25 - 37) in Costa Rica, which supports the hypothesis of a true difference pertaining to genetic and/or envi-

Table III. Incidence of juvenile arthritis according to geographical areas and ethnicity on the American continent.

Reference	Geographical location	Catchment population	Type of survey Years	Criteria	Annual incidence rate/100,000 (95% conf. interval)	Ethnicity* (where stated)
Boyer *et al.*, 1988 (26)	USA Alaska	1,627	Registry covering defined area, Retrospective, 1970-1982	ARA Spondyloarthropathy	5 24 47 (males)	Inupiat Eskimo
Boyer *et al.*, 1990 (27)	USA Alaska	4,343	Registry covering defined area, Retrospective, 1970-1982	ARA Spondyloarthropathy	5 37	Yupik Eskimo
Hill, 1977 (28)	Canada British Columbia	610,000	Pediatric rheumatology centre Retrospective	-	3 7 0	Caucasian Canadian Indian Chinese
Oen *et al.*, 1995 (16)	Canada Manitoba	274,958	Registry, pediatric rheumatology centre Retrospective, 1975-1992	ARA	5.3 (average) 18.1 (1986) 9.4 (1986)	Mixed Canadian Indian Caucasian
Malleson *et al.*, 1996 (29)	Canada (excluding Alberta and Quebec)	4,200,000	Registry, pediatric rheumatology centres Prospective, 1991 - 1993	ARA Spondyloarthropathy JPsA	3.1 (2.7 - 3.7) 1.4 (1.1 - 1.9) 0.3 (0.2 - 0.5)	
Towner *et al.*, 1983 (30)	USA Minnesota	12,643 - 16,749	Pediatric rheumatology centre Retrospective, 1960-1970	ARA EULAR	13.9 (9.9 - 18.8) 10.5 (7.4 - 15.3)	Caucasian
Peterson *et al.*, 1996 (17)	USA Rochester, MN	-	General population Retrospective, 1960 - 1993	ARA	15.0 (1960 - 69) 14.1 (1970 - 79) 7.8 (1980 - 93)	Caucasian
Hochberg *et al.*, 1983 (31)	USA Baltimore	15,186	Pediatric clinic Retrospective, 1979-1980	ARA	7 (0.8 - 23.8)	AA
Arguedas *et al.*, 1998 (8)	Costa Rica	350,000	Pediatric clinic defined area Prospective, 1993-1995	EULAR	6.8 (4.1 - 9.6)	Hispanic + AI mixed

*Ethnicity: AA = Afro - American = AI, American Indian. Where not stated the population was predominantly Caucasian.
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ronmental factors. Differences in disease patterns were also found in these two areas, as will be further discussed below. The remaining studies presented in Table IV were retrospective (12, 22, 25, 31, 35-38) and the data was collected from medical records at different levels of care. Case ascertainment was thus dependent on the structure of the health care systems involved, i.e. the figures could have been influenced by factors such as access to care, the cost of care and referral patterns. However, the figures for countries with homogenous "socialised" medical systems such as Norway (22) and the former East Germany (12) differed, even when patients from all levels of care were identified: 148 per 100,000 in Norway compared to 20 per 100,000 in the former East Germany. The presence of genetic factors is indicated by the high proportion of HLA B27 positive patients in northern Norway (42%), where only one of 78 patients fulfilled the criteria for juvenile ankylosing spondylitis. The prevalence of HLA B27 in the general population in northern Norway was high (22). Unfortunately there was no data on the frequency of HLA B27 in the study from East Berlin, Germany for comparison (12). Other possible influences are climate and the infectious disease panorama.

The low figure reported from a hospital-based study performed in Kuwait was possibly influenced by selection bias, i.e. milder cases may not have been identified (38).

Who and where ? Incidence and prevalence in relation to ethnic groups

The incidence and prevalence of JA (JCA, JRA and SPA) according to ethnicity are shown (where data were available) in Tables III and IV. In the incidence studies from Europe (Table II) the ethnicity was not defined, but since these studies were all derived from the general population, the patients must have been predominantly Caucasian. In the population-based studies with a Caucasian dominance, the incidence rates of JRA and JCA ranged from roughly 10 to 20 per 100,000 children in Europe and North America (10-11, 17-18, 24, 30). In the study by Hill (28), it was noted that the incidence of JRA was higher among Canadian Indians than among Caucasians, while no cases were found among the Chinese population. Oen *et al.* (16) confirmed a high incidence of JRA among Canadian Indian children (18.1 per 100,000) as compared with Caucasian children (9.4) during 1986, one of the incidence peak years men-

Table IV. Prevalence of juvenile arthritis according to geographical location and ethnicity.

Reference	Country/ Ethnicity*	Source	No. of cases	Prevalence/100,000** (95% conf. intervals) JCA	JRA	SpA
Moe & Rygg, 1997 (22)	Norway	Health care organisation + practitioner	71	148		
Andersson Gäre & Fasth, 1992 (10)	Sweden	Health care organisation + practitioner	334	86 (77-96)		
Kiessling *et al*., 1998 (12)	Germany	Practitioner/pediatric rheumatology clinic	28	20† (17-25)		
Mielants *et al*., 1993 (32)	Belgium	Population questionnaire + examination	5 (definite)	167		
Steven, 1992 (33)	UK - Scotland	Practitioner	14	200		
Prieur *et al*., 1987 (25)	France	Practitioner	74	8-10		
Ozen *et al*., 1998 (34)	Turkey	Population questionnaire + examination	30	64		
Boyer *et al*., 1991 (35)	Alaska /NAI	Practitioner	3		83	
Rosenberg, 1990 (36)	Canada	Pediatric rheumatology clinic	115/69		40	24
Oen & Cheang, 1996 (37)	Canada/ Canadian Indian	Pediatric rheumatology clinic	15		45	
Towner *et al*., 1983 (30)	USA	Clinic/total population	11/15	84 (46-140)	113 (69-196)	
Hochberg *et al*., 1983 (31)	USA/AA	Paediatric clinic	4		26 (7-66)	
Arguedas *et al*., 1998 (8)	Costa Rica/ Hispanic + AI	Pediatric clinic/total population	110	31 (26-37)		
Khuffash & Majeed (38)	Kuwait/Arab	Hospital	44		22	
Manners et al, 1996 (39)	Australia	Population questionnaire + examination	9	400 (140-664)††		

*Ethnicity: NAI = North American Indian, AA= Afro American, AI = American Indian. Where not stated the population is predominantly Caucasian
** Prevalence is presented for JCA when EULAR criteria have been used, JRA when the ARA criteria have been used and spondyloarthropathy (SpA) when given separately.
†SpA not included. ††Calculated from data given.
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tioned above. Boyer *et al.* (26, 27) found a low incidence of JRA (5 per 100,000), but an extremely high incidence of SpA among Inupiat and Yupik Eskimos in Alaska (24 and 37 per 100,000, respectively). The prominence of SpA is presumably related to the high frequency of HLA B27 in Eskimo populations (26).
The only figure available for the incidence of JA among Afro-Americans (7 per 100,000) is low compared with Caucasians, but is based on only four cases and the confidence intervals were wide (31).
From Latin America the only data on incidence and prevalence come from the Costa Rican study (8). In spite of the fact that its methodology was similar to the Caucasian population studies cited above, the figures were lower - an incidence of 6.8 and a prevalence of 35 per 100,000 - suggesting a lower occurrence of JRA in the Hispanic population.
There are very few reports on incidence rates from other parts of the world. In a clinic-based recent report from Japan (40) the incidence was very low, 0.83 per 100,000. This may reflect a very low risk of developing arthritis in that population, but could also have reflected at least in part a selection bias. In support of the former theory is the indication that the prevalence of rheumatoid arthritis in adults appears to be lower in Asian populations than in Europe and North America (41).
When the occurrence rates are analysed with the methodology appropriately taken into consideration, there is still a general impression that occurrence rates differ in relation to ethnicity and favour genetic differences. However, ethnicity intermingles with geographical distribution, as well as possible environmental factors.

Who and where? Subgroup, age and sex distribution in relation to geography and ethnic groups

The general clinical picture of JA has been coloured by earlier clinical series

and epidemiological studies in predominantly Caucasian populations. However, now that data are appearing from other parts of the world this picture has to be revised. In Caucasians in Europe, USA and Canada pauciarticular onset disease constitutes more than half of all JA cases, while roughly one quarter have a polyarticular onset and 10% systemic disease. In contrast, a predominance of polyarticular onset disease has been reported from South Africa (42), India (43), Thailand (44), and also among African Americans (45) and Canadian aboriginal populations (46).

IgM RF positivity was more frequently observed in the studies from South Africa (42), India (43) and among African Americans (45): 37%, 19% and 20%, respectively, than in studies from Western countries: 2 - 7% (10, 22, 30). Among Canadian aboriginal groups, RF positive polyarticular disease was found in 56% of the patients (46). The high frequency of RF positivity could be due to genetic factors, but could also be influenced by environmental factors such as polyclonal activation of the immune system caused by frequent concomitant infections.

In recent studies of subgroup distribution from Costa Rica (8), India (43), South Africa (42), Singapore (47), and among African Americans (45), a very small number of ANA positive girls with pauciarticular arthritis and uveitis has been noted, suggesting true differences in disease manifestations pertaining to immunogenetics or environmental factors, or a combination of both. A predominance of males, rather than of girls as in the studies from Western countries (10-11, 22, 30), has been noted in studies from India (43), Turkey (34) and Singapore, (47), while in South Africa an equal sex ratio was found (42).

Conclusions

In conclusion, the increased heterogeneity in the clinical picture of JA and the geographical and ethnic diversity in the occurrence rates of JA, which are becoming obvious now that studies have started to appear from all over the world, certainly underline the need for unifying classification criteria. The differences in terminology, criteria and methodology have too long obscured our possibility for clear scientific communication. The recently proposed ILAR classification criteria (5) hopefully represent a step in the right direction, but as the taskforce itself observed, the criteria "need to be validated under appropriate epidemiological and statistical direction". Geographical and ethnic differences present both a challenge and an opportunity. Clearly defined epidemiologic studies together with basic scientific research will not only help us to predict who may develop JA, where and when, but also why, which may be a prerequisite to finally finding a cure.

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