Conferencial magistral
2º Congreso de la Sociedad Española de Reumatología Pediátrica
Valladolid, 1999

Juvenile Chronic Arthritis – Who gets it, where, when?

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In this talk I will present a review of what we know and what we do not know today about the epidemiology of chronic arthritis in childhood. The review will cover the epidemiology of "idiopathic" juvenile arthritis (JA), including the concepts of juvenile chronic arthritis (JCA), juvenile rheumatoid arthritis (JRA) and spondyloarthropathies (SpA). The terminology I will use is JA as an "umbrella term" for all the concepts, but JRA, JCA, and SpA according to the studies I cite. The different aspects I will cover are:

? Some epidemiological definitions
? Why study epidemiology?
? Methodological considerations
? ? Where does JA occur?
? Who gets chronic arthritis?
? When does JA occur?
? Future epidemiological research

Some epidemiological definitions

Epidemiology can be defined as the study of the distribution and determinants of disease in defined populations (1). In a broader sense it is also a methodological approach to the development of criteria for disease classification, to investigate natural history of disease in different populations and subgroups and the impact of diseases on society (2). Sometimes a distinction between descriptive and analytic epidemiology is made. *Descriptive studies* attempt to estimate incidence, prevalence, morbidity and mortality in relation to basic characteristics such as age, sex race, occupation, social class, place and time. An *analytical study* on the other hand is designed to examine associations and casual relationships. So far epidemiological research in the field of paediatric rheumatology has been mainly descriptive.

Incidence of a disease is defined as the number of new cases occurring in a specific period of time in a defined population. *Prevalence* is the proportion of a population

that is affected by a disease at a particular time. For studying aetiology of a disease incidence is the most important statistic, but prevalence data are often used because they are often easier to obtain.

A useful epidemiological starting point is to compare the occurrence and patterns of disease across the world. If large differences are found this can suggest influences of environmental factors, for example climate, altitude, urbanisation, panorama of infections, diet or socio-economic variation. However, it can also be an effect of genetical differences, where genes linked to a disease may be more frequent among some populations. There is still a lack of reliable incidence data concerning JA from many parts of the world which will be discussed later.

Why study epidemiology?

Epidemiological research in paediatric rheumatology can be useful in order to:

1. Provide the necessary basis for *health care planning* i.e. give data of the frequency of disease and the effects on the society of the disabilities resulting from the disease. In addition the possible gains from various therapeutic interventions can be provided on group level. Today when resources are scarce in most countries in relation to what could be achieved therapeutically this kind of evidence based support in decision making becomes more and more important.
2. *Describe the natural history and outcome* in different disease entities and identify risk factors associated with morbidity and mortality. The current approach to give more aggressive treatment early in the course of disease makes it extremely important to early identify groups of patients who will actually benefit from this approach and groups who will not need it because of an expected more benign disease course.
3. *Identify possible etiologic factors* through descriptive studies from different geographical areas and different ethnical groups. Such studies can provide clues

and generate hypothesis on the impact of environmental and genetic factors on disease occurrence and disease manifestations. Analytical epidemiological studies, such as case-control studies, can then be used to further clarify questions and hypotheses regarding etiologic agents (2, 3).

Methodological considerations

The interpretation of epidemiological data regarding JA is complicated by factors such as:

1. the heterogeneity of the disease and the lack of uniform classification criteria
2. differences in methodologies for case identification and case ascertainment
3. inadequate definition of study populations

1. The *classification criteria* most commonly used are those proposed by American College of Rheumatology (ACR) in 1977 (4) and those by the European League Against Rheumatism (EULAR) in 1978 (5). The criteria suggested by the ACR have been extensively used in North and South America while European investigators have primarily used the criteria proposed by EULAR. Diagnosis and division into subtypes is in both sets of criteria based on clinical examination and no specific diagnostic tests are available. As shown in Table 1 the two sets of criteria are not interchangeable.

Table 1. A comparison of the EULAR classification for juvenile chronic arthritis (JCA) and the ACR classification of juvenile rheumatoid arthritis (JRA).

	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.

One confusing issue is that the terminology differs, juvenile rheumatoid arthritis (JRA) according to ACR and juvenile chronic arthritis (JCA) according to EULAR. The main differences which can effect occurrence rates is the required disease duration for diagnosis (6 weeks and 3 months respectively) and the difference in inclusion of subgroups. ACR and EULAR criteria both include systemic, pauciarticular and polyarticular onset types. In the EULAR criteria 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 is no universally accepted criteria for the classification of the latter subgroups, sometimes collected under the “umbrella“ spondyloarthropathies (SpA). Under the “umbrella“ term SpA when used together with the JRA group, reactive arthritis, Reiter’s syndrome and seronegative arthritis and enthesitis (SEA) syndrome are often included, groups that are not included in the EULAR criteria - thus creating further complications in the interpretation of data.

The broad subgroups included in both ACR and EULAR criteria contain considerable heterogeneity regarding age at onset, sex and the presence of antinuclear antibodies (ANA) and rheumatoid factor (RF) indicating that the subgroups do not have a homogenous biological bases which will be discussed later in relation to data from different ethnic groups and geographical areas. The Classification Taskforce of the Paediatric Standing Committee of the International League of Associations for Rheumatology (ILAR) has recently proposed a system of classification “the Durban criteria“ that can supersede the EULAR and ACR criteria and hopefully achieve world-wide acceptance (6). The term *Idiopathic* Juvenile Arthritis is suggested as an umbrella term to indicate that the disease has no known cause. The proposed

criteria are more descriptive than the formerly used and aim at distinguishing biologically homogenous groups. They do, however, need validation in proper epidemiological and statistical terms and to date no such studies have been published.

2. *Methodologies for case identification and case ascertainment* influence the results in epidemiological studies. Since JA is relatively rare it is time consuming and costly to perform prospective population based cohort studies, since large populations have to be studied over several years to identify enough cases to draw conclusions. Thus other methods of case identification have been used such as; population questionnaires, health care surveys, practitioner surveys, clinic populations, hospital populations and disease registers. Experience has, however, shown that all these methods have their pitfalls. For example, in a study from Australia, where population questionnaires in combination with physical examination of all individuals in the population was performed by a paediatric rheumatologists, it was obvious that the questionnaire was not sensitive enough to identify all cases with JA (7). There is also a risk for a questionnaire not to be specific enough, a history of a swollen knee could have many different explanations, thus leading to an overestimation of the number of cases. The methods relying on cases defined on different levels in the health care system may be biased by access to care, referral patterns and the awareness of rheumatic disease in childhood among medical staff. Hospital based studies will be biased towards more severe cases and mild cases may be missed.
3. *Definition of study populations.* In order to calculate incidence rates and prevalence well defined catchment populations are requiered. In developing countries there may be difficulties in obtaining accurate census data In countries with diverse health care systems such as the USA the catchment population can also be difficult to define. In countries where the health care systems are more homogenous as in the many of the European countries the definition of study population is easier (2,3).

Where?

Incidence

Incidence figures for JCA/JRA from Europe are summarised in Table 2 and from the American continent in Table 3. The difficulties in interpretation discussed above are shown by the wide range in the incidence figures, from 1.3 to 22.6 per 100 000 children below 16 years of age (8, 13)! However, when studies that apply similar methodologies with well defined populations and thorough ascertainment procedures the incidence figures show less variance 10 - 18.2 per 100 000 (9,10, 12, 17, 18).

Table 2. Incidence of juvenile arthritis from different geographical areas in Europe presented from north to south.

Country Reference	Catchment Population (<16 years)	Type of survey Year	Criteria	Annual Incidence rate /100, 000 (95 % confidenceinterval)
Norway Moe & Rygg, 1997 (8)	48, 215	Registry covering defined geographical area, retrospective,1985-94	EULAR	**22.6**
Finland Kunnamo et al, 1986 (9)	148,362	General population prospective, 1982	ARA >3 months	**19.6** (13.1-28.2) **18.2** (10.8-28.7)
Sweden Andersson Gäre & Fasth, 1992 (10)	389,976	General population prospective, 1984-88	EULAR	**8.3-13.7** (max-min) **10.9** (9.4-12.4) (average)
Germany Kiessling et al, 1998 (11)	247,906	Paediatrician/Paediatric Rheumatology Centre, retrospective 1980-88	EULAR (SpA not included)	**5.3-2.3** (max-min) **3.5** (2.8-4.4) (average)
United Kingdom Symmons et al, 1996 (12)	92,374 60,963	Registry, Paediatric Rheumatology Centres prospective, 1990-94	EULAR	**10** (7-13) **10** (6-14)
France Prieur et al, 1987 (13)	964,284 +618,136	Practitioner surveys, retrospective 1981-82	EULAR	**1.3-1.8**

In the study from Costa Rica the same method and inclusion criteria were used as in the Swedish study but the incidence figures differ, 10.9 and 5.4, confidence limits just “touch“, which may be indicates true differences owing to environmental or genetic differences. The lower figures from Canada 3-5.3 per 100 000 (15-16), emanate from paediatric rheumatology centres and referral bias may influence the figures since milder cases may not have been referred and thus not included. The low figure from France 1.3-1.8 (13), may be an effect of difficulties in case ascertainment. The method used was practitioner questionnaires, where some physicians did not respond and thus cases can have been missed. In Europe a falling north to south gradient in incidence can be seen, with the highest incidence in northern Norway, 22.6 per 100 000 and the lowest in France, 1.3-1.8 per 100 000. On the other hand the differences in methodologies discussed before make it difficult

to draw any definite conclusions. However, true genetic and environmental factors may have influenced the figures. For example, the prevalence of HLA B 27 is known to be high among the general population on northern Norway which increases the risk of HLA B 27 associated arthritis.

No similar north/south gradient is found in the figures from the American continent. On the other hand, ethnic differences are seen which will be further discussed later.

Table 3. Incidence of juvenile arthritis according to geographical areas and ethnicity on the American Continent

Country Reference	Catchment population	Type of survey Years	Criteria	**Annual Incidence/100,000** (95 % confidence interval)	Race* (where stated)
USA, Alaska Boyer et al, 1988 (14)	1,627	Registry covering defined area, retrospective, 1970-82	ARA spondyloarthropathy	**5** **24** 47 (males)	Inupiat Eskimo
Canada Hill, 1977 (15)	610,000	Paediatric rheumatology centre, retrospective	-	**3** **7** **0**	Caucasian Can Indian Chinese
Canada Oen et al, 1995 (16)	274,958	Registry, paediatric rheumatology centre retrospective, 1975-92	ARA	**5.3** (average) **18.1** (1986) **9.4** (1986)	mixed Can Indian Caucasian
USA, Minnesota Towner et al, 1983 (17)	12,643-16,749	Paediatric rheumatology centre, retrospective, 1960-70	ARA EULAR	**13.9** (9.9-18.8) **10.5** (7.4-15.3)	Caucasian
USA, Minnesota Peterson et al, 1996 (18)	-	General population retrospective, 1960-93	ARA	**15.0** (1960-69) **14.1** (1970-79) **7.8** (1980-93)	Caucasian
USA, Baltimore Hochberg et al, 1983 (19)	15,186	Paediatric clinic retrospective, 1979-80	ARA	**7** (0.8-23.8)	AA
Costa Rica Arguedas et al, 1998 (20)	350,000	Paediatric clinic defined area, prospective, 1993-95	EULAR	**6.8** (4.1-9.6)	Hispanic+AI Mixed

Prevalence

Prevalence figures for JCA show, just as incidence figures a wide range 8- 400 per 100 000 (7, 13). The highest figures are found in studies where questionnaires have been used in combination with physical examination. This method gives the possibility to identify all cases in a defined population. On the hand it is laborious and time consuming and the population to be surveyed can not be too large. Thus few cases are identified and the confidence limits become wide as shown in Table 4. Thus for example the confidence limits in the study by Manners and Towner overlap although the prevalence differs from 400 to 84 per 100 000 (7, 17).

Table 4. Prevalence of juvenile chronic arthritis according to geographical location in studies using population questionnaires in combination with clinical examination.

Country Reference	No. of cases	**Prevalence/100,000** (95% conf. intervals)
Australia Manners et al, 1996 (7)	9	**400** (140-664)
Belgium Mielants et al, 1993 (21)	5 (definite)	**167**
Turkey Ozen et al, 1998 (22)	30	**64**

In studies where health care organisations in co-operation with practitioners have been used in patient identification the prevalence figures range from 31 to 148, table 5. Larger populations have been surveyed and confidence intervals are closer. Interestingly the prevalence seems to be lower in for example Costa Rica than in northern Norway. Again, this could be attributable to both environmental factors such as climate, diet and differences in infectious panorama and genetic factors. As mentioned before the frequency of HLA B27 is high in the general population in northern Norway.

Table 5. Prevalence of juvenile chronic arthritis according to geographical location in studies using surveys in health care organisations together with practitioners.

Country Reference	No. of cases	**Prevalence**/100 000 (95% conf. Intervals)
Norway Moe & Rygg, 1997 (8)	71	**148**
Sweden Andersson Gäre & Fasth, 1992 (10)	334	**86** (77-96)
USA, Minn Towner et al., 1983 (17)	11	**84** (46-140)
Costa Rica Areguedas et al, 1998 (20)	110	**31** (26-37)

Who?

Age and sex distribution

The occurrence of JA differs with *age and sex* as illustrated in Table 6 from a Swedish population based epidemiological study (9).

Table 6. Incidence and average annual incidence rates (per 100,000) of JCA by age and sex in south-western Sweden, 1984 through 1988.

Age	n/ 5 years	Incidence rate/year	Girls inc. rate/year	Boys inc. rate/year
0-3	60	12.5	**18.3**	6.9
4-7	48	10.5	11.7	9.3
8-11	52	10.6	12.6	8.8
12-15	53	10.3	14.1	**6.4**
Total	213	10.9	14.3	7.9

An overall predominance of girls 2-3:1 is found in most epidemiological studies with mainly Caucasian population. Girls predominate mainly in pauci- and polyarticular arthritis and JpsA, while distribution is more even in the systemic group. According to older studies JAS is much more frequent among boys 4-6:1, while more recent data suggest less marked differences with boy/girl ratios between 2:1 to 3:1. Interestingly, a predominance of boys rather than girls has been noted in JA in recent reports from parts of the world not dominated by Caucasian population, India, Turkey and Singapore (22- 24). From South Africa an equal sex ratio has been reported (25).

As shown in Table 2 a bimodal pattern for *age of onset* was found for girls but not for boys. In studies from other parts of the world, Costa Rica, India and Africa, the

pattern for age of onset differs, i.e. no early peak is found mainly due to the fact that very few girls with ANA positive arthritis are found.

Incidence in relation to ethnic groups

In the figures incidence figures presented from Europe in table 2 the population is mainly Caucasian as in most of the studies from North America and the incidence ranges from roughly 10 to 20 per 100 000. But, as shown in Table 3, Hill (15) noted a higher incidence of JRA among Canadian Indians than among Caucasians and no cases were found in the Chinese population. High incidence figures among Canadian Indians have later been confirmed by Oen et al (16). Boyer et al (15) has reported a low incidence of JRA but a very high incidence of SpA among Inupiat and Yupik Eskimos. Probably the high incidence of SpA is linked to a high frequency of HLA B27 in the Eskimo populations, in analogy with the high incidence of JCA in northern Norway. A lower occurrence of JCA among Hispanic children can be suspected when comparing the study from Costa Rica with studies from Europe and North America. Mainly very few ANA positive young girls with pauciarticular arthritis are found in the Costa Rican study, a group which is dominating in the studies with Caucasian population. In conclusion there seems to be differences in occurrence rates and disease patterns among different ethnic groups which favours genetic differences.

In *family studies* some family aggregation of cases has been found and a few monocygotic twins concordant for JA have been identified, but on the whole the risk for a sibling to develop JA is not very strong. From a North American registry of siblings with JA it could be calculated that 0.8% of all JRA appears in siblings (26). Pauciarticular JRA was over represented. Thus this study strengthens that genetic influence plays a role in determining JRA onset type, especially in pauciarticular disease.

When?

Environmental triggers, such as infections could be supported by clusters of occurrence in time and space. Cyclical patterns of incidence of JCA/JRA have been reported in studies from Sweden (10), Canada (16) and Minnesota, USA (18). A decline in incidence of JRA was found in the study from Minnesota, while no such trend was found in a long term study from Finland (29). A seasonal patterns in the incidence of systemic JRA has been shown in some studies but not in others. A cluster of JCA in relation to influenza A infections was reported by Prithcard (30) from United Kingdom.

As shown in this presentation chronic arthritis in childhood is a divers concept where disease manifestations differ in relation to geography, time and genetics. This together with differences in terminology, criteria and methodology have too long hindered scientific communication. Hopefully international consensus on definitions and classifications will facilitate scientific communication in this field in the future. Clearly defined epidemiological studies together with basic research could help us to answer the questions who gets arthritis, when and where and hopefully also why - which may finally also lead us to find cures.

References

1. Last JM: A Dictionary of Epidemiology. 3rd ed., New York, Oxford University Press, 1995: 55-6.
2. Silman AJ, Hochberg MC: Scope of epidemiology. In Silman AJ & Hochberg MC (eds) Epidemiology of the Rheumatic diseses. Oxford: Oxford University Press, 1993: 1-2
3. Andersson Gäre: Epidemiology. In Ballière's Clinical Rheumatology 1998; 12: 191-208

4. Brewer EJ, Bass J, Baum J et al: Current proposed revision of JRA criteria. Arthritis Rheum (suppl) 1977; 20: 195-9
5. Wood PH: Nomenclature and classification of arthritis in children. In Munthe E (ed): The care of rheumatic children. Basel, EULAR publishers 1978: 47.
6. Fink CW and the ILAR Task Force for Classification Criteria: A proposal for the development of classification criteria for the idiopathic arthritides of childhood. J Rheumatol 1995; 22:1566-9
7. Manners PJ, Diepeveen: Prevalence of juvenile chronic arthritis in a population of 12-year-old children in urban Australia. Pediatrics 1996; 98: 84-90
8. Moe N, Rygg M: Epidemiology of juvenile chronic arthritis in Northern Norway: A 10-year retrospective study. Clin Exp Rheumatol 1998; 16: 99-101
9. Kunnamo I,Kallio P, Pelkonen P: Incidence of arthritis in urban Finnish children. Arthritis Rheum 1986; 29: 1232-8
10. Andersson Gäre B, Fasth A: Epidemiology of juvenile chronic arthritis in Southwestern Sweden: A 5-year prospective population study. Pediatrics 1992; 90: 950-8
11. Kiessling et al: Incidence and prevalence of juvenile chronic arthritis in East Berlin 1980-88. J Rheumatology 1988; 25: 1837-43
12. Symmons D, Jones M, Osborne J et al., for the Brittish Pediatric Rheumatology Group national Diagnostic Index: Pediatric rheumatology in the United Kingdom. Data from the British Pediatric Rheumatology Group. National Diagnostic Register. J Rheumatol 1996; 23: 1975-80
13. Prieur AM, Le Gall E, Karman F et al: Epidemiologic survey of juvenile chronic arthritis in France. Comparison of data obtained from two different regions. Clin Exp Rheumatol 1987; 5:217-23
14. Boyer GS, Lanier AP, Templin DW: .Prevalence rates of spondyloarthropathies, rheumatoid arthritis, and other rheumatic disorders in an Alaskan Inupiat Eskimo population. J Rheumatol 1988; 15: 678-83
15. Hill R: Juvenile arthritis in various racial groups in British Columbia. Arthritis Rheum 1977; 20 (suppl):162-4
16. Oen K, Fast M, Postl B: Epidemiology of juvenile rheumatoid arthritis in Manitoba, Canada, 1975-92: Cycles in Incidence. J Rheumatol 1995; 22: 745-50
17. Towner SR, Michet CR, Nelson AM: The epidemiology of juvenile arthritis in Rochester, Minnesota 1960-1979. Arthritis Rheum 1983; 1208-13
18. Peterson LS, Mason T, Nelson AM et al: Juvenile rheumatoid arthritis in Rochester, Minnesota 1960-1993. Is the epidemiology changing? Arthritis Rheumat 1996; 39: 1385-90

19. Hochberg MC, Linet MS, Sills EM: The prevalence and Incidence of juvenile rheumatoid arthritis in an urban black population. Am J Public Health 1983; 73:1202-3
20. Arguedas O, Fasth A, Andersson Gäre B, Porras O: Juvenile chronic arthritis in urban San José, Costa Rica: A 2 year prospective study. J Rheumatol 1998; 25: 1844-50
21. Mielants H, Veys EM, Maertens M et al: Prevalence of inflammatory rheumatic diseases in an adolescent urban student population, age12 to 18, in Belgium. Clin Exp Rheumatol 1993; 11: 563-7
22. Ozen S et al: Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: A field study. J Rheumatol 1998; 25: 2445-9
23. Aggrawal A, Mistra R: Juvenile chronic arthritis in India: is it different from that seen in Western countries? Rheumatol Int 1994; 14: 53-6
24. See Y, Koh ET, Boey ML: One hundred and seventy cases of childhood onset rheumatological disease in Singapore. Ann Acad Med Singapore 1998; 27: 496-502
25. Haffejee IE, Raga J, Coovadia HM: Juvenile chronic arthritis in Black and Indian South African children. Sa Mediese Tydskrif 1984; 65: 510-4
26. Ansell BM, Bywaters EGL, Lawrence JS: Familial aggregation and twin studies in Still's disease (juvenile chronic polyarthritis). Rheumatology 1969; 2: 37-61.
27. Baum J, Fink C: Juvenile rheumatoid arhtritis in monozygotic twins: A case report and review of the litterature. Arthritis Rheum 1968; 11: 33-6
28. Moroldo MB, Tague BL, Shear ES, Glass DN, Giannini EH: Juvenile rheumatoid arthrtis in affected sibpairs. Arthritis Rheum 1997; 40: 1962-6
29. Kaipiainen-Seppänen O, Savolainen: A Incidence of chronic rheumatics diseases in Finland during 1980-1990. Clin Exp Rheumatol 1996; 14: 441-4
30. Pritchard MH, Matthews N, Munro J: Antibodies to influenza A in a cluster of children
with juvenile chronic arthritis. Br J Rheum 1988; 27: 176-80