Epidemiology of Juvenile Idiopathic Arthritis in Alsace, France

STÉPHANIE DANNER, CHRISTELLE SORDET, JOELLE TERZIC, LIONEL DONATO, MICHEL VELTEN, MICHEL FISCHBACH, and JEAN SIBILIA

ABSTRACT. ***Objective.*** To determine the incidence, prevalence, and principal characteristics of the different forms of juvenile idiopathic arthritis (JIA) in the region of Alsace, northeastern France, using the new classification of the International League of Associations for Rheumatology (ILAR).

Methods. In 2002 we performed a retrospective epidemiologic study pertaining to the year 2001. The pediatricians, rheumatologists, ophthalmologists, orthopedic surgeons, and physicians involved in functional reeducation in the Alsace region were interviewed, and all patients were classified according to the new ILAR classification using the criteria revised in Durban in 1997.

Results. Among the 361 clinicians contacted, the participation rate was 97.8%. The study identified 67 children followed for JIA in Alsace in 2001, from a total population of 1.8 million inhabitants including 339,095 children under age 16 years. The incidence was calculated to be 3.2 cases/100,000/year and the prevalence 19.8 cases/100,000 children under age 16 years. Among these 67 cases of JIA, the most frequent forms were oligoarthritis (n = 27, 40.3%), polyarthritis without rheumatoid factor (RF; n = 15, 22.4%), and enthesitis related arthritis (n = 12, 17.9%). Other forms, notably systemic arthritis (n = 6, 8.9%) and psoriatic arthritis (n = 3, 4.5%), were more rare and in this study there was no case of polyarthritis with RF. Only 4 patients (6%) were classified in the undifferentiated arthritis group using the new classification. Antinuclear antibodies (ANA; by indirect immunofluorescence, HEp > 1/80) were detected in patients with oligoarthritis (81%) and polyarthritis without RF (79%). Uveitis occurred in 41% of children with oligoarthritis and in 14% of those with polyarthritis without RF.

Conclusion. Our results are comparable to those of other studies carried out in Caucasian populations with regard to incidence and prevalence. This work also highlights the frequent presence of ANA and uveitis in patients with oligoarthritis or polyarthritis without RF. (J Rheumatol 2006;33:1377–81)

Key Indexing Terms:
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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children under age 16 years. However, due to its low incidence and its treatment by different specialists, only a few epidemiologic studies have been performed. These have used quite different diagnostic criteria [i.e., classifications of the American Rheumatology Association (ARA) and the European League Against Rheumatism], making comparisons of the prevalence and incidence of JIA very difficult. In order to harmonize epidemiologic studies of JIA, the International League of Associations for Rheumatology (ILAR) defined a new classification in 1995, the criteria of which were reviewed in Durban in 1997[1] and in Edmonton in 2001[2].

From the Department of Pediatry, Laboratory of Epidemiology, and Department of Rheumatology, CHU Hautepierre, Strasbourg, France.

S. Danner, MD; J. Terzic, MD; M. Fischbach, MD, Department of Pediatry 1; C. Sordet, MD; J. Sibilia, MD, Department of Rheumatology; L. Donato, MD, Department of Pediatry 2; M. Velten, MD, Laboratory of Epidemiology.

Dr. Danner and Dr. Sordet contributed equally to this report.

Address reprint requests to Dr. J. Sibilia, Rheumatology Department, CHU Hautepierre, 67098 Strasbourg Cedex, France.
E-mail: jean.sibilia@wanadoo.fr

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It is essential to better define the epidemiology of this pathology in our countries, on account of the development of new treatments, notably, anti-tumor necrosis factor-α and inhibition of interleukin 1 (IL-1) and IL-6. Consequently, we investigated the incidence, prevalence, and principal characteristics of the different forms of JIA in the French province of Alsace using this new ILAR classification, Durban 1997[1].

MATERIALS AND METHODS

Study. In 2002 we performed a retrospective study pertaining to the period January 1, 2001 to December 31, 2001, in the Alsace region, which has a population of 1.8 million inhabitants including 339,095 children under age 16 years.

Study population. The study population comprised children under age 16 years with JIA according to the ILAR diagnostic criteria who were seen in consultation during the period of the study. We interviewed all clinicians in the Alsace region who treat children under the French healthcare system. This group consisted of rheumatologists (n = 56), pediatricians (n = 135), ophthalmologists (n = 136), orthopedic surgeons (n = 14), and physicians involved in physical medicine and rehabilitation (n = 20). These practitioners were working in hospitals and/or private practice and were recruited using telephone listings for the Bas-Rhin and the Haut-Rhin, the 2 parts of Alsace, and from lists of practitioners provided by the respective hospital services.

Exclusion criteria. Patients were excluded for the following: any type of noninflammatory arthritis; age over 16 years on January 1, 2001; place of residence outside Alsace; or remission without treatment more than 2 years previously.

Study procedure. Clinicians were first contacted by a letter of information enclosing a copy of the new ILAR classification and a questionnaire to fill out for each affected child, and subsequently by telephone. The information collected was reviewed by 2 senior physicians, who analyzed the cases according to the new ILAR criteria.

Data collected include the child's sex, age, form of JIA, age at onset of articular symptoms, family and personal history, antinuclear antibody (ANA), rheumatoid factor (RF), HLA-B27 status, uveitis, and any retardation in growth or in progress at school. Uveitis was confirmed by an ophthalmologic examination but details of ophthalmologic involvement were not recorded in this study. The threshold for antibody positivity was fixed at ≥ 1/80 using indirect immunofluorescence on HEp-2 cells for ANA and at 1/32 by latex test and/or 1/40 on the Waaler-Rose test for RF.

Calculation of incidence and prevalence. Calculations were performed using the latest results from the National Institute of Statistics and Economic Studies for France, dating from 1999.

Statistical analyses. Statistical analyses were performed with Statistica software (version 5.1, StatSoft Inc., Tulsa, OK, USA). Continuous variables were compared by the Kruskal-Wallis nonparametric test and noncontinuous variables by the chi-square test, or by Fisher's exact test if the number of theoretical cases was too low. A probability < 0.05 excluded the null hypothesis in both tests, and differences were considered to be statistically significant for a p value < 0.05. The 95% confidence interval (95% CI) of incidence and prevalence was calculated by the method of Poisson's law.

RESULTS

We interviewed 361 practitioners working in hospitals and/or private practice in Alsace, with a participation of 97.8% (135/135 pediatricians, 56/56 rheumatologists, 133/136 ophthalmologists, 12/14 orthopedic surgeons, and 18/20 physicians involved in functional reeducation).

Prevalence and incidence of JIA. A total of 67 children followed for a form of JIA were included in the study. All were of Caucasian origin, except 8 (5 from North Africa, one from the Pacific, one Turkish, and one of Asiatic origin). On the basis of the cases of JIA occurring during the year of the study, the incidence in Alsace is 3.2 cases/100,000/year (95% CI 1.62; 5.80) and the prevalence 19.8 cases/100,000 (95% CI 19.3; 20.3) children under age 16 years. There may be year to year variation. The distribution of the prevalence of cases according to the form of JIA is given in Figure 1.

Characteristics of patients (Table 1). The age at appearance of the first symptoms was 4.7 years (± 3.2 yrs) in girls, as compared to 7.2 years (± 3.7 yrs) in boys (p = 0.0035), while the mean JIA disease duration was 4.2 years (± 3.7 yrs). Oligoarthritis and polyarthritis without RF were seen more often in girls (p = 0.01), whereas enthesitis related arthritis occurred most often in boys (p = 0.00002).

The uveitis observed during disease development in 13 of the 67 patients (20%) appeared during the first 2 years of the evolution of JIA in 77% (10/13) of cases. This complication was more frequent in girls (p = 0.036) in association with oligoarticular forms of JIA. The age at onset of symptoms was 3.9 years (± 3.8 yrs) in children presenting with uveitis as compared to 6.2 years (± 3.5 yrs) in the absence of uveitis.

ANA were detected above all in patients with oligoarthritis (81% of cases) or polyarthritis without RF (79% of cases), and were found in 85% of the JIA patients with uveitis and 58% of those without uveitis. Rheumatoid factors were detected in only 3.3% of our patients (in one case of enthesitis related arthritis and one of psoriatic arthritis).

Only 2 children had growth failure of 2 SD, while 5 had scholastic retardation (3 children are in a specialized school, and 2 children were held back one year in school).

DISCUSSION

The values of the prevalence and incidence of JIA determined in our study are quite comparable to those reported in the literature. There nevertheless exist important variations, with incidence ranging from 0.83 to 22.6 cases/100,000/year and prevalence from 7.7 to 400 cases/100,000[3-12] (Table 2). Although this large disparity of the results could reflect different environmental or genetic factors, these studies were carried out using different methodologies (retrospective or prospective design, different classifications used, different subject populations interviewed).

In France, only 2 epidemiological surveys of juvenile arthritis have been performed, in 1982[3] and 1999[4], the latter being the only study to have used the ILAR classifications (Table 2). The results of these 2 studies were comparable, although different from ours. A German study has given results that are comparable to ours[5]. By contrast, 2 Scandinavian surveys suggest a higher prevalence of juvenile chronic arthritis, but they did not use the ILAR classifications[6,10], and their methodology was quite different (prospective and retrospective designs, respectively).

Our study was retrospective, but it probably closely reflects the incidence and prevalence of JIA. Indeed, due to the specificity and sometimes the severity of certain forms of JIA, these patients are normally seen in France by at least one of the different types of specialist interviewed, in either a hospital or private practice or both. The participation of 97.8% demonstrates the good motivation of the participants. Only some "minor" forms of JIA, notably of oligoarthritis, might not have been detected using this methodology.

We used the new ILAR classification criteria of 1997[1], which led us to reclassify certain patients. After examination of the cases by 2 senior physicians, 6 children (9%) were reclassified because of the more strict exclusion criteria of the ILAR classification. Two key points of this classification are the notion of psoriasis and the existence of rheumatoid factor. Thus, 4 of the 6 were reassigned to the undifferentiated arthritis group due to family history of psoriasis (n = 3) or the presence of RF without polyarticular involvement (n = 1). The 2 others were placed in the enthesitis related arthritis group because of the appearance of the first symptoms after the age of 8 years in boys who were HLA-B27-positive. The advantage of the ILAR classification is the definition of enthesitis related arthritis; in our study it was the third-largest group. In the literature, only 4 studies have used this new classification of JIA[4-15], whereas other epidemiologic surveys have been

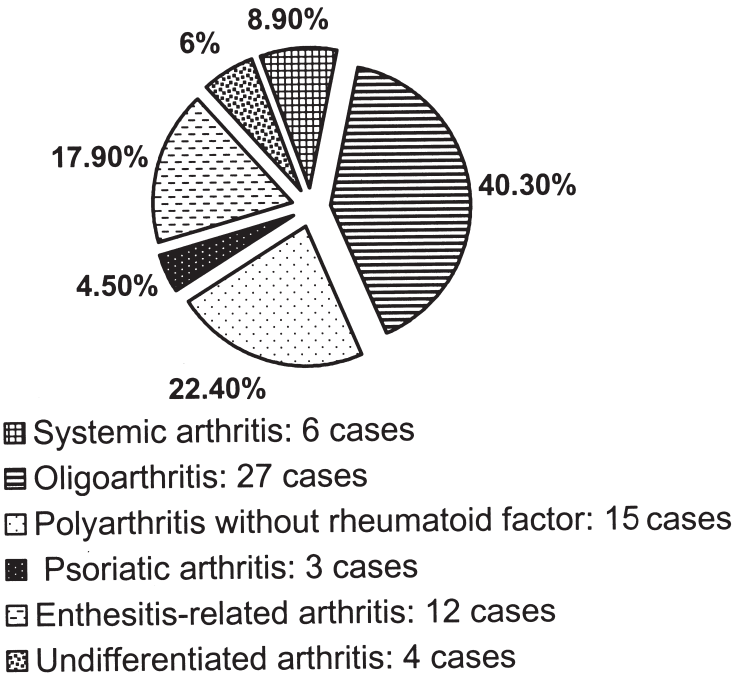

Figure 1. Distribution of the prevalence of cases by form of JIA.

Table 1. Characteristics of the patients with JIA.

Form of JIA	Age at First Symptoms, yrs	Mean Duration of JIA, yrs	M/F	ANA, n = 65 (%)	HLA-B27, n = 59 (%)	RF, n = 60 (%)	Uveitis, n = 67 (%)
Systemic (n = 6)	3.1 (± 1.4)	2.7 (± 3.1)	3/3	0	0	0	0
Oligoarticular (n = 27)	4.2 (± 2.4)	4.1 (± 3.9)	6/21	22/27 (81)	3/24 (12.5)	0	11/27 (41)
Polyarticular, RF– (n = 15)	6.7 (± 1.9)	5.2 (± 4.4)	2/13	11/14 (79)	1/13 (8)	0	2/14 (14)
Psoriatic arthritis (n = 3)	7.0 (± 1)	6.2 (± 3.2)	3/0	0	1/3 (33)	0	0
ERA (n = 12)	9.3 (± 3.3)	2.9 (± 2.5)	12/0	5/11 (45)	8/11 (73)	1/11 (9)	0
Undifferentiated arthritis (n = 4)	10.2 (± 2.8)	6.4 (± 1.7)	1/3	3/4 (75)	1/4 (25)	1/3 (33)	0
Total	5.7 (± 3.6)	4.2 (± 3.7)	27/40	41/65 (63)	14/59 (24)	2/60 (3.3)	13/67 (20)

RF: rheumatoid factor.

Table 2. The prevalence and incidence of JIA reported in the literature.

	Country	Type of Study*	Population Interviewed	Classification	Incidence, per 100,000/yr	Prevalence, per 100,000
Our study	France	R	Hospitals and private practitioners	ILAR	3.2	19.8
Le Gall[3]	France	R	Hospitals and private practitioners	EULAR	Paris: 1.9 Bretagne: 1.3	Paris: 7.7 Bretagne: 10
Pollet[4]	France	R	Hospitals and private practitioners	ILAR	1.6	11.2
Kiessling[5]	Germany	R	Hospital practitioners	EULAR	3.5	20.3
Von Koskull[12]	Germany	P	Hospitals and private practitioners	EULAR	7.5	16.5
Moe[10]	Norway	R	Hospital register	EULAR	22.6	148.1
Andersson Gäre[6]	Sweden	P	Hospitals and private practitioners	EULAR	10.9	64.1
Arguedas[7]	Costa Rica	P	Hospitals and private practitioners	EULAR	6.8	31.4
Peterson[11]	Minnesota, USA	R	Medical register	ARA	11.7	86.1
Manners[9]	Australia	P	Children interviewed and examined by rheumatologists	EULAR	—	400
Fujikawa[8]	Japan	R	Hospital practitioners	ARA	0.83	—

* R: retrospective, P: prospective. ILAR: International League of Associations for Rheumatology, EULAR: European League of Associations Against Rheumatism, ARA: American Rheumatology Association.

based principally on the classifications of the European League of Associations Against Rheumatism and the American Rheumatism Association. The percentage of children in the undifferentiated arthritis group ranged from 9.2% to 37% in these 4 studies.

Proposals have been made with the aim of decreasing the number of unclassified forms of juvenile arthritis without affecting the homogeneity of the other groups[14]. The existence of classifications for "probable psoriatic arthritis" and "arthritis with RF" would have enabled us to avoid placing our 4 children in the "undifferentiated arthritis" group. RF is in fact a discriminative element in this classification, and 2 positive samples at an interval of 3 months are required for it to be considered to be present. This specific confirmation was not carried out in practice in 7 children in our study (one case of enthesitis related arthritis, one undifferentiated arthritis, and 5 oligoarthritis). These 5 cases of oligoarthritis were nevertheless retained in this group in the absence of evolution to a polyarticular form after a mean followup of 3 years and 8 months. If we had excluded these 5 children from the oligoarthritis group, the undifferentiated arthritis group would have been larger, at 13.4%. By comparison, Berntson, *et al*[13] classified 37% of their cases of JIA in the undifferentiated group due to the unknown serological status. Pollet and Salles[4] similarly excluded children with unknown rheumatoid serology, but only 9.2% of them were placed in the undifferentiated arthritis group. The other investigators do not discuss this point[14,15].

Use of the ILAR classification criteria confirms the higher incidence of oligoarthritis. This predominance has been reported in all studies of Caucasian populations[3,4,8-15] and also in Central America[5]. We found no case of polyarthritis with RF. This is probably related to the small size of our sample, since polyarthritis with RF is rare, representing only 1% to 5.8% of cases of JIA in other studies[4,13-18].

ANA were identified in a total of 63% of our patients. This figure is higher than those reported in the literature — in European studies the values range from 25% to 53.7% of cases[3,4,6,10,19,20]. It is, however, difficult to compare our results, which are based on a positivity threshold of 1/80 in indirect immunofluorescence assays, as the threshold employed is usually not indicated in the other reports. RF were detected overall in 3.3% of our patients, but were never associated with polyarthritis or extensive oligoarthritis. This frequency corresponds to those in the literature, which range from 2.7% to 11.5% of cases of JIA.

Uveitis occurred in 20% of our patients during the evolution of their disease, this figure being one of the highest in the literature, although it is comparable to that reported by Kunnamo, *et al* from Finland[20]. Unfortunately, we do not know the incidence of uveitis during the period of our study. In our investigation, the appearance of this complication was correlated with the presence of ANA, as observed in numerous studies in European countries and North America[3,4,6,10,19,21,22]. Our study confirms that rigorous ophthalmologic surveillance must be maintained from the onset of disease, even in the absence of any clinical symptoms and especially in the oligoarticular forms of JIA. Our study has some limitations because it is a retrospective data analysis.

Our study allowed us (1) to determine that the prevalence of JIA is 19 per 100,000 in France, applying the criteria of the ILAR to a Caucasian population; and (2) to confirm the high prevalence of uveitis in these patients, especially in association with ANA, and above all in the oligoarticular and polyarticular forms of JIA without rheumatoid factor.

Better knowledge of JIA is indispensable, notably since it has become possible to use new therapeutic strategies employing basic classical treatments or biotherapy.

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