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Clinical characteristics of juvenile idiopathic arthritis in an area of central Italy: a population-based study

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Abstract

Background. *Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children and an important cause of short and long-term disability. In a recent systematic review of population based studies, the epidemiology of JIA is variable worldwide with incidence rates ranging between 1.6 and 23.0/100,000, and prevalence rates between 3.8 and 400.0/100.000. We investigate the incidence and describe the characteristics of juvenile idiopathic arthritis in the pediatric population of the central Italy, in the period 2000-2009.*

Methods. *A retrospective study was conducted in the Marche region to identify patients with a diagnosis of juvenile idiopathic arthritis according to ILAR criteria, between January 1, 2000 and December 31, 2009. JIA was classified according to the ILAR criteria, that is, arthritis of unknown etiology that persisted for ≥ 6 weeks with onset before the age of 16 years. The pooled global ascertainment of cases was estimated by capture-recapture methods and two independent information sources of ascertainment of new cases of JIA were considered.*

Results. *We studied 151 patients (56 males, 37.1% and 95 females, 62.9%) meeting the ILAR criteria of juvenile idiopathic arthritis. Mean age at presentation was 6.8 ± 3.7 years for males and 6.0 ± 4.0 years for females (p=0.22). The overall incidence rate was 6.34 per 100,000/year (C.I. 6.26-7.35) and the total incidence rate increase from 2000-2009 was 8.16%. Oligoarthritis was the most common onset type (n=98, 65.0%) with 62.5% of ANA-positive patients in at least two determinations.*

Conclusions. *Our results indicate that juvenile idiopathic arthritis incidence rates in Italy are comparable to previous data from southern Europe, with a higher frequency of oligoarthritis. To the best of our knowledge, this is the first population-based epidemiological study carried out in Italy focusing on the incidence of juvenile idiopathic arthritis.*

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Abbreviations: *ANA: anti-nuclear antibodies; ARA: American Rheumatism Association; CRP: C-reactive protein; ERA: enthesitis-related arthritis; ESR: erythrocyte sedimentation rate; ILAR: International League of Associations for Rheumatology; JIA: juvenile idiopathic arthritis; NSAIDs: non-steroidal anti-inflammatory drugs; RF-: rheumatoid factor negative; RF+: rheumatoid factor positive; sJIA: systemic juvenile idiopathic arthritis*

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children and an important cause of short and long-term disability (1).

According to the International League of Associations for Rheumatology (ILAR) classification, JIA includes all forms of arthritis of unknown etiology beginning before the 16th birthday and persisting for at least 6 weeks (2). On the basis of clinical and laboratory features occurring in the first six months of disease, ILAR identified seven subtypes of JIA: systemic JIA (sJIA), oligoarticular JIA, rheumatoid factor RF-negative (RF-) polyarticular JIA, RF-positive (RF+) polyarticular JIA, enthesitis-related arthritis (ERA), psoriatic arthritis and undifferentiated JIA (1).

The heterogeneity of the disease and the lack of specific diagnostic tests make it difficult to compare different geographic and ethnic groups in terms of incidence, prevalence and disease manifestations. Epidemiologic studies provide useful information about the natural history and outcome of the disease, and contribute to understand the role of environmental and genetic factors for the identification of possible etiologies.

In a recent systematic review of population-based studies, the epidemiology of JIA is variable worldwide, with incidence rates ranging between 1.6 and 23.0/100,000, and prevalence rates between 3.8 and 400.0/100,000 (3).

In Europe, there seems to be a gradient about incidence, with higher figures found in studies from Nordic countries (4) and lower rates reported in studies from Spain, Germany and France (3, 5-7).

However, the geographical differences may also be associated with the type of study and the ascertainment methods used (3). To the best of our knowledge, there are no epidemiologic data from Italy. Table 1 reports all the selected European studies from 1986 to 2011. In this table we report, for each study, the date of publication, the country investigated, the study design, the study period, the diagnostic criteria used, the incidence and prevalence of JIA (3, 8-30).

The aim of our population-based retrospective study was to investigate the incidence, and clinical characteristics of JIA in the pediatric population of Marche, an Italian region of Central Italy, between January 1, 2000, and December 31, 2009.

Methods

Study design

The population of Region Marche (central Italy), on January 1, 2009 consists of 1,569,578 inhabitants, over an area of 9,366 Km^2, with a population at risk for JIA (0-16 years) of 235,780 (121,766 males, 114,014 females). According to the Italian National Institute of Statistics (ISTAT), the regional population from the 2009 census was taken into account to provide rate denominators (31). In this study we performed a retrospective chart review of diagnoses of JIA according to ILAR criteria between January 1, 2000 and December 31, 2009. JIA cases were classified according to the ILAR criteria, that is, "arthritis of unknown etiology that persisted for $\geq$ 6 weeks with onset before the age of 16 years" (2). Only patients with permanent residence in the Marche region with a diagnosis of JIA during the study period were included. Eleven children were excluded from the study because they did not meet the ILAR criteria. Two independent information sources of ascertainment of new cases of JIA were considered: as primary source, we referred to pediatricians and general practitioners; as secondary source, we referred to departments of pediatrics and rheumatology of public hospitals. Approximately 65% of the general practitioners and 95% of the pediatricians

Table 1 - Incidence and prevalence of JIA in Europe.

Author and date of publication	Study design	Study period	Country	Information Sources	Incidence AIG/100,000	Prevalence AIG/100,000	Diagnostic criteria
Kunnamo I et al. 1986	Prospective	1982-83	Finland	GPs, pediatricians, orthopedic surgeons	19.6	-	ACR
Prieur AM et al. 1987	Retrospective	1982	France	Pediatricians, department of pediatrics, rheumatologists, ophthalmologists, orthopedic surgeons.	1.6	8.6	EULAR
Gäre BA et al. 1987	Population based prospective	1983	Sweden	Pediatric rheumatology clinic and local pediatricians	12.0	56.0	EULAR
Le Gall E et al. 1988	Retrospective	1982	France	Hospitals and private pratictioners	Paris: 1.9 Bretagne: 1.3	Paris: 7.7 Bretagne: 10	EULAR
Gäre BA et al. 1992	Prospective	1988 (P) 1984-88 (I)	Sweden	Hospitals and private pratictioners	10.9	64.1	EULAR
Mielants H et al. 1993	Cross-sectional	1988	Belgium	Questionnaire to student (only 12-18 years), family and clinical, biochemical and radiological examination	-	167.0	EULAR
Symmons D et al. 1996	Retrospective	1990-94	United Kingdom	Centers of pediatric rheumatology	10.0	-	EULAR
Kaipiainen-Seppänen O et al. 1996	Retrospective	1980; 1985;1990	Finland	Hospitals	14	-	ACR
Kiessling U et al. 1998	Population based (Retrospective)	1980-88	East Berlin Germany)	Hospital practitioners	3.5	20.3	EULAR
Moe N et al. 1998	Retrospective	1985-1994 (I) 1994 (P)	Norway	Hospital register (only pediatric department)	22.6	148.1	EULAR
Ozen S et al. 1998	Cross sectional	1998	Turkey	Pediatricians and practitioners	-	64,4	EULAR
Pollet S et al. 2001	Not reported	1999	France	Hospitals and private pratictioners	-	11,2	ILAR
Kaipiainen-Seppänen O et al. 2001	Retrospective	1995	Finland	Hospitals	19.5	-	ACR
Von Koskull ST et al. 2001	Prospective population based	1995	Germany	Pediatricians, orthopaedists, rheumatologists, and private practitioners	6.6	14.8	EULAR
Huemer C et al. 2001	Prospective multicenter (register)	1997-98	Austria	Pediatric rheumatology centers	4.2	-	ACR

Berntson L et al. 2003	Prospective population based	1997-1998	Iceland, Norway, Sweden, Denmark, Finland	Pediatrician with experience in pediatric rheumatology	(15.0 ILAR) (14.0 EULAR)	-	ILAR EULAR
Savolainen E et al. 2003	Prospective	2000	Finland	Health center and hospitals	23.0	-	ILAR
Hanova P et al. 2006	Population based	2002-2003 (I) 2002 (P)	Czech Republic	Rheumatologists and Rheumathology department	13.0	140	ILAR
Danner S et al. 2006	Retrospective	2001	France (Alsace)	Pediatricians, rheumatologists, ophthalmologists, orthopedic surgeons, and physicians involved in physical medicine and rehabilitation	3.2	19.8	ILAR
Pruunsild C et al. 2007	Retrospective Prospective	1995-1997 1998-2000	Estonia	Hospitals	21,7	83.7	ILAR EULAR
Martínez Mengual L et al. 2007	Retrospective	1989-2005 (I) 2005 (P)	Spain	Patients born after 1989 and resident in Asturias	3,5	51.4	ILAR
Riise OR et al. 2008	Prospective Population based	2004-2005	Norway	Practitioners, pediatricians, Rheumathologists and orthopedic surgeons	14.0	-	ILAR
Solau-Gervais E et al. 2010	Retrospective	2006	Alsazia (Wester France)	Pediatricians, rheumathologists	-	15.7	ILAR
Modesto C et al. 2010	Prospective-retrospective, population based	2004-2006	Catalonia (Spain)	Primary care pediatricians, Pediatric rheumathology in hospitalization	6.9	39.7	ILAR
Present study	Retrospective, population based	2000-2009	Italy	Primary care, pediatricians, department of pediatrics	6.3	60	ILAR

* Incidence (I), prevalence (P)

Table 2 - Two sources combined ascertainment probabilities

Years	Source 1	Source 2	Both	Total Cases	Estimated Total Cases	95% C.I.	Ascertainment probabilities (%)
2000	5	3	2	6	7.0	4.7-9.3	85.7
2001	7	2	1	8	11.0	4.8-17.2	72.7
2002	17	8	7	18	19.3	16.-22.4	93.5
2003	14	3	2	15	19.0	10.6-27.4	78.9
2004	13	4	4	13	13.0	13.0-13.0	100.0
2005	24	9	8	25	26.8	22.6-31.0	93.4
2006	16	5	5	16	16.0	16.0-16.0	100.0
2007	15	7	4	18	24.6	15.7-33.5	73.2
2008	15	4	3	15	19.0	12.5-25.5	78.9
2009	13	11	7	17	20.0	17.0-23.0	85.0
Pooled (2000-09)	139	56	43	151	180.4	160.9-199.8	83.7

in the Marche region were involved in this study. Combined ascertainment probabilities of the two sources were calculated (Table 2). The pooled global ascertainment of cases was 83.7%, achieved by capture-recapture methods.

Data recorded for each patient included date and place of birth, age at disease onset, gender, ethnicity, subtype of arthritis based on ILAR criteria, symptoms at onset, number of joints involved, laboratory tests results at diagnosis, uveitis (if any) and family history of JIA. Data were collected through a questionnaire and were stored on a password-protected database.

Statistical analysis

We calculated the incidence rate, expressed as cases per 100,000 population per year. 95% incidence rate were estimated assuming a Poisson distribution of incident cases. Differences between proportions of contingency tables were assessed by the chi-square or exact Fisher's tests where appropriate. We compared continuous variables using the Student's t-test, and calculated annual increase rates using a linear regression model. A p value of <0.05 was considered statistically significant. All data analyses were performed using SAS software (SAS Institute, Cary, North Carolina).

Results

In the course of the 10 years of the study, 151 patients, 56 males (37.1%), and 95 females (62.9%), meeting the ILAR criteria of JIA, were identified. The female/male ratio was 1.7. Age at diagnosis ranged from 6 months to 15 years. Mean age ± standard deviation (sd) at onset/presentation was 6.8 ± 3.7 years for males and 6.0 ± 4.0 years for females (p=0.22). Out of the 151 patients meeting ILAR criteria, 94 (69.3%) were 0-4 years old at diagnosis, 45 (16.1%) were 5-9 years, and 41 (14.6%) were > 9 years old. The overall incidence rate was 6.34/100,000 per year (C.I. 6.26-7.35) and the total incidence rate increase from 2000 to 2009 was 8.16%. The annual number of cases, population affected, and changes in incidence rates in the period 2000-2009 are summarized in Table 3.

The crude incidence rate (7.79/100,000, C.I. 4.19-11.39) was highest in 2002, as was the highest annual increase (72.7%). Oligoarthritis was the commonest type of onset (n=98, 65.0%), with 62.5% of

Table 3 - Annual number cases and annual incidence rates of AR (100000 per years): period 2000-2009

Years	No. of incident cases	Population at risk	Rate (per100,000) (95% C.I.)	%	annual increase, %
2000	6	229549	2.61 (0.52-4.71)	4.0	-
2001	8	230004	3.48 (1.07-5.89)	5.3	33.1
2002	18	230970	7.79 (4.19-11.39)	11.9	72.7
2003	15	232968	6.44 (3.18-9.70)	9.9	42.1
2004	13	235610	5.52 (2.52-8.52)	8.6	23.5
2005	25	238647	10.47 (4.08-9.33)	16.6	26.2
2006	16	241823	6.62 (3.37-9.86)	10.6	18.1
2007	18	243948	7.38 (3.97-10.79)	11.9	14.3
2008	15	247114	6.07 (3.00-9.14)	9.9	10.1
2009	17	250210	6.79 (3.56-10.02)	11.3	8.2
Pooled 2000-2009	**151**	**2380843**	**6.34 (6.26-7.35)**	**Period 2000-2009 8.16 %**	

ANA-positive patients in at least two determinations. Of the 98 children who had oligoarticular JIA onset, only 6 (6.1%) had an extended course after the first 6 months of disease. The second most frequent type of onset was polyarthritis (n=17, 11.3%), with 3 RF+ patients (2.0%) and 6 ANA-positive (4%), in at least two determinations. Of the 18 children (12.0%) who had the systemic disease onset, 3 (16.6%) were ANA-positive. Three patients (2%) had psoriatic arthritis and 4 (2.7%) had enthesitis-related arthritis (ERA). Ten patients (6.7%), who did not fit into any category, were classified as having undifferentiated JIA. Only 11/151 patients (7.3%), 9 with oligoarthritis and 2 with polyarthritis, developed chronic uveitis over the first 7 years of JIA. All had at least two positive ANA tests; their mean age at arthritis onset was 3.5 ± 2.1 years and none developed uveitis before arthritis. The more common symptoms at JIA onset were joint swelling (189 patients, 78.8%), limping (86 patients, 57.0%), joint pain (88 patients: 58.3%), and rash (18 patients, 11.9%). Less frequent symptoms were hepatomegaly and lymphadenopathy (4.6%), splenomegaly (3.3%), and serosities 0.7%.

The most commonly affected joints were the knee (112 patients, 74.1%), the small joints of hands and feet (41 patients, 27.1%), and the wrist (29 patients, 19.2%); hip (15.2%) and elbow joints (10.6%) were affected less frequently. A total of 101 children (66.7%) had an elevated erythrocyte sedimentation rate (ESR); 65 children (43.1%) had elevated C-reactive protein (CRP); elevated neutrophil count and anemia were found in 17 (11.3%) and 14 (9.2%) patients, respectively. RF was found in 16 children (10.6%), of whom 3 had polyarticular JIA, 10 had undifferentiated JIA, 2 had sJIA, and one had psoriatic JIA. HLA-B27 was found in 7 children (4.6%). ANA were detected in 56 patients (37.1%). Most of these patients (n=35, 62.5%) had oligoarticular disease and included 4 boys and 31 girls (p=0.0001). Only 2/151 cases (1.3%) had a family history of autoimmune disease. Growth delay was described in 8 (5.3%) patients. None of the patients had renal amyloidosis or renal disease. No death was recorded during the period of the study.

The clinical and therapeutic characteristics of JIA subtypes (ILAR criteria) are reported in table 4. Notably, oligoarthritis was associated with earlier age at onset and polyarthritis with later age at onset, respectively 5.7 ± 3.8 vs 7.5 ± 3.9 years (p=0.007), and 9.1 ± 3.5 vs 5.9 ± 3.8 years

(p=0.001). In addition, positivity for RF was associated with a later age at presentation: 8.9 ± 3.7 vs 6.0 ± 3.8 years (p=0.004). As regards the frequency distribution of age groups at presentation (0-4, 5-9, 10-16 years), the number of oligoarthritis cases declined with rising age (p=0.005), whereas the number of polyarthritis cases increased with rising age (p=0.001). RF+ patients were more numerous among the 10-16 years old (p=0.003).

When gender and RF were analyzed in relation to ANA, RF and ANA were found to be more common among girls than boys: 47.4% vs 19.6%, p=0.0007, 19.6% vs 5.2%, p=0.006, respectively.

Finally, assessment of the use of medications showed that the 98 patients with oligoarthritis took NSAIDs (n=97, 99.0%), methotrexate (n=24, 24.5%), intra-articular steroid injections (n=35, 35.7%), and biologics (n=4, 4.1%), alone or in combination, whereas the 17 patients with polyarticular JIA used NSAIDs (n=16, 94.1%), methotrexate (n=10, 58.8%), intra-articular steroid injections (n=3, 17.7%) and biologics in (n=2, 11.8%), alone or in combination.

Discussion

JIA is the commonest chronic inflammatory joint disease in pediatric age with an incidence and prevalence variable among different populations throughout the world.

In the present population-based retrospective study, we evaluated the incidence and the prevalence of JIA among pediatric enrollees of the Marche, an Italian region, during the period 2000-2009. We used ILAR criteria for case identification and estimated the incidence at 6.34 cases per 100,000 for the entire period considered (95% CI: 6.26-7.35). European epidemiologic studies reported a high variability with up to 50-fold differences in JIA prevalence (table 1). The highest incidence rates have been reported in the Nordic Countries with results up to 22.6 per 100.000/year according to ILAR criteria (3, 4).

Studies from southern Europe such as Southern Germany, Spain and France (7, 16, 21, 28) reported lower figures; for this reason a north-south gradient in the incidence of JIA in Europe has been considered (32). However, the observed discrepancies may be related to different classification criteria or to different means of ascertainment, or even to genetic differences and to changes in living conditions over time (30, 33-34). Data from Scandinavia are based on the systematic health visit and may therefore be more accurate in identifying cases. Conversely, studies based on surveys involving practitioners to report JIA cases may come out to be less accurate. Moreover, a tendency to higher incidence rates with the ILAR criteria have been reported, due to the shorter disease duration required for diagnosis (4).

Our incidence figure from the Marche region of 6.34 per 100,000/year is close to a rate of 6.6 per 100,000 and 6.9 per 100,000 reported in two prospective population based studies respectively from Southern Germany and Catalonia (21, 5).

Modesto et al (5) conducted a 3-year (2004-2006) population-based prospective study in Catalunia, a region located in northearstern Spain with a population about four times the one in our study. Interestingly, in the same period, the incidence calculated in our population was similar to that from Catalonia (6.9 per 100,000), with the same ILAR criteria. This finding seems interesting if we consider that retrospective studies, just like ours, often recall lower figures independently from the ascertainment method used. We can speculate that the greater period of observation and the capture recapture method used in our study, resulted in a recruitment of cases similar to a prospective study like that of Modesto. et al (5).

Table 4 - Clinic characteristics of patient with JIA

	Mean age at onset No. of case (%) - mean ± sd		t-test p
Oligoarthritis	Present 98 (64.9) 5.7 ± 3.8	Absent 53 (35.1) 7.5 ± 3.9	0.007
Polyarthritis	Present 17 (11.3) 9.1 ± 3.5	Absent 134 (88.7) 5.9 ± 3.8	0.001
RF positive	Present 16 (10.6) 8.9 ± 3.7	Absent 135 (89.4) 6.0 ± 3.8	0.004
ANA	Present 56 (37.1) 5.7 ± 4.0	Absent 95 (62.9) 6.7 ± 3.8	0.13

	Distribution of JIA frequency in age-groups (years)			Cochran-Armitage Trend test
	0-4 y No. of cases (%)	5-9 y No. of cases (%)	10-16 y No. of cases (%)	P
Oligoarthritis	49 (50.0)	29 (29.6)	20 (20.4)	0.005
Polyarthritis	2 (11.8)	6 (35.3)	9 (52.9)	0.001
RF positive	4 (25.0)	2 (12.5)	10 (62.5)	0.003
ANA positive	30 (53.6)	12 (21.4)	14 (25.0)	0.14

	Characteristics according to ANA		
Gender	Present No. of case %	Absent No. of case %	p
Male Female	11 (19.6) 45 (47.4)	45 (80.4) 50 (52.6)	0.0007
RF	Present No. of case %	Absent No. of case %	p
positive negative	11 (19.6) 45 (80.4)	5 (5.2) 90 (94.7)	0.006
Undifferentiated arthritis	Present No. of case (%) 9 (90.0)	Absent No. of case (%) 1 (10.0)	0.0003

In addition, in previous retrospective studies from Europe (East Berlin, Asturias and Alsace) utilizing the same ILAR criteria (16, 22, 28) lower figures have been found compared to our study.

A lower JIA incidence annual rate of 4.2 per 100,000 has also been reported in Austria in a prospective registry in the '90s but the authors utilized in that case the American Rheumatism Association (ARA) criteria (4).

In accordance with the concept that retrospective studies may underestimate, in such a kind of analysis in which cases were retrieved from general pediatric clinics, Ostergard reported an annual incidence of 6-8 cases per 100,000 from Denmark (35), a figure that is comparable to those from southern Europe and to ours. However, in this study, cases were retrieved only from general pediatric clinics and therefore data could be underestimated.

A finding of our study was the positive trend of JIA incidence from 2000 to 2009 (+8.16%). This trend may reflect a cyclical pattern of the disease or changes in clinical

practice and not necessarily an increasing incidence. However, as with any study, there is also a possibility of underestimation of cases due to incomplete recruitment of patients.

In line with previous studies, in our study oligoarthritis was found to be the most frequent type of disease even if slightly higher compared to other European series (1, 5, 7, 24, 26-28, 30). Contrary to other epidemiological studies from Europe, in our study ERA has been found less frequent according to ILAR classification (1, 4, 5, 7, 30).

The gender distribution is also in line with data from the literature, as JIA was found to be more frequent in girls than in boys with a significant difference ($p<0.001$). On the other hand, no difference in age at onset between sexes was found.

The age distribution of children with JIA according to the main diagnostic subgroups is illustrated in table 4. The Cochran-Armitage trend test shows that oligoathritis has a peak of onset at 5.7±3.8 years with a trend to decrease significantly with age, whereas polyarthritis has a peak of onset at 9.1±3.5 years with a increasing trend with age. Rheumatoid factor positivity also increases with age.

ANA positivity has been found to be significantly more frequent in the oligoarthritis subgroup, in RF negative children, and in undifferentiated arthritis. A consistent group of girls (47.4%) with a mean age of 5.4 years were ANA positive (Table 4), in accordance with the recent evidence that young ANA positive females may represent a homogeneous group with different characteristics compared to older patients (36).

Uveitis, as noted by others, in our study population developed very early (mean age 3.5 years) and primarily affected the oligoarthritis subgroup (4, 5).

This study has some limitations: as it is common for a retrospective study, clinical follow-up data were incomplete especially for the laboratory and imaging data. The fluctuation of ascertainments during the study period is also a limit. However, to the best of our knowledge, this is the first population-based study evaluating the incidence and the clinical profile of JIA carried out in Italy and also provides a good starting point in understanding the epidemiology of the disease in this country. As in other previous studies of ours (37-41), the goal was to create a JIA registry and to monitor the disease progresses and outcomes.

Conclusion

Our results are in line with prospective studies from the south of Europe that employed the same ILAR criteria. Higher figures are reported in prospective studies from Scandinavia and lower figures in retrospective studies from center-south of Europe. In our study, a slightly higher incidence of the oligoarhritis subgroup has been found compared to other epidemiological studies from Europe.

Ethics approval: The data used in this study were obtained by permission of local authority and gathered in a password protected database.

Consent to participate: We did not required informed consent, because this was a retrospective study coming from an electronic database. Moreover, participants are fully anonymous and the dataset is protect against identity disclosure.

Competing interests: The Authors have no competing interests

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Authors' Contribution: Emma Altobelli participated in the study design, performed the statistical analysis, interpreted the results, participated in the drafting of the manuscript. Valentina Marzetti participated in the acquisition of data and participated in the drafting of the manuscript. Luciana Breda coordinated the acquisition of data and participated in the drafting of the manuscript. Eleonora Miulli, Fabio Filippetti ands Cristina Mancini participated in the acquisition of data. Francesco

Chiarelli, PhD critically revised the manuscript. All authors read and approved the final manuscript.

Riassunto

Caratteristiche cliniche dell'artrite idiopatica giovanile in un'area del centro Italia: uno studio su base di popolazione

Introduzione. L'artrite idiopatica giovanile (AIG) è la più comune malattia reumatica cronica nei bambini ed è una importante causa di disabilità a breve e lungo termine. In una recente revisione sistematica di studi su base di popolazione, si è evidenziato che l'AIG ha una variabilità dei tassi di incidenza 1.6 - 23/100.000 e prevalenza 3.8 - 400/100.000 nel mondo. Nel nostro studio valutiamo l'incidenza e le caratteristiche dell'artrite idiopatica giovanile nella popolazione pediatrica dell'Italia centrale nel periodo 2000-2009.

Metodi. Abbiamo condotto uno studio retrospettivo nella regione Marche per identificare i pazienti con artrite reumatoide giovanile in accordo ai criteri ILAR, durante il periodo 1 gennaio 2000 - 31 dicembre 2009. L'AIG fu classificata in accordo ai criteri ILAR, che consistono in artrite ad eziologia sconosciuta che persiste per più di 6 settimane, con esordio prima dei 16 anni. L'accertamento globale dei casi incidenti fu stimato tramite il metodo cattura-ricattura e due fonti indipendenti di informazione furono usate per l'accertamento dei nuovi casi di AIG.

Risultati. Abbiamo identificato 151 pazienti (56 maschi, 37.1% e 95 femmine, 62.9%) con i criteri ILAR di artrite idiopatica giovanile. L'età media alla presentazione era di 6.8 ± 3.7 anni per i maschi e 6.0 ± 4.0 per le femmine (p=0.22). Il tasso globale di incidenza era 6.34 per 100.000/anno (I.C. 6.26-7.35); l'incremento totale del tasso di incidenza dal 2000-2009 era 8.16%. L'oligoartrite era il tipo di esordio più comune (n=98, 65.0%) con il 62.5% di ANA-positivi in almeno due determinazioni.

Conclusioni. I nostri risultati indicano che i tassi di incidenza dell'artrite idiopatica giovanile in Italia sono simili a quelli dell'Europa del sud, con una più alta frequenza di oligoartrite. A nostra conoscenza questi sono i primi dati epidemiologici di incidenza su base di popolazione stimati in Italia riguardanti artrite idiopatica giovanile.

References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007; **369**: 767-78.
2. Petty RE, Southwood TR, Manners P et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton 2001. J Rheumatol 2004; **31**: 390-2.
3. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine 2014; **81**: 112-7.
4. Berntson L, Andersson Gäre B, Fasth A, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. J Rheumatol 2003; **30**: 2275-82.
5. Modesto C, Anton J, Rodriguez B et al. Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). Scand J Rheumatol 2010; **39**: 472-9.
6. Oen K. Comparative epidemiology of the rheumatic disease in children. Curr Opin Rheumatol 2000; **12**: 410-4.
7. Danner S, Sordet C, Terzic J et al. Epidemiology of juvenile idiopathic arthritis in Alsace, France. J Rheumatol 2006; **33**: 1377-81.
8. Kunnamo I, Kallio P, Pelkonen P. Incidence of arthritis in urban Finnish children. Arthritis Rheum 1986; **29**: 1232-8.
9. Prieur AM, Le Gall E, Karman F, Edan C, Lasserre O, Goujard J. Epidemiologic survey of juvenile chronic arthritis in France. Comparison of data obtained from two different regions. Clin Exp Rheumatol 1987; **5**: 217-23.
10. Andersson Gäre B, Fasth A, Andersson J, Berglund G, Ekström H, Eriksson M. Incidence and prevalence of juvenile chronic arthritis: a population survey. Ann Rheum Dis 1987; **46**: 277-81.
11. Le Gall E, Karman F, Blayo M, Prieur AM. A comparative epidemiologic study of chronic juvenile arthritis in the western section of Paris and Brittany (1982) [French]. Ann Pédiatr (Paris) 1988; **35**: 547-53.
12. Andersson Gäre B, Fasth A. Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. Pediatrics 1992; **90**: 950-8.
13. Mielants H, Veys EM, Maertens M, et al. Prevalence of inflammatory rheumatic diseases in an adolescent urban student population, age 12 to 18, in Belgium. Clin Exp Rheumatol 1993; **11**: 563-7.

14. Symmons DP, Jones M, Osborne J, Sills J, Southwood TR, Woo P. Pediatric rheumatology in the United Kingdom: data from the British Pediatric Rheumatology Group National Diagnostic Register. J Rheumatol 1996; **23**: 1975-80.
15. Kaipiainen-Seppanen O, Savolainen A. Incidence of chronic juvenile rheumatic diseases in Finland during 1980-1990. Clin Exp Rheumatol 1996; **14**: 441-4.
16. Kiessling U, Doring E, Listing J, et al. Incidence and prevalence of juvenile chronic arthritis in East Berlin 1980–88. J Rheumatol 1998; **25**: 1837-43.
17. Moe N, Rygg M. Epidemiology of juvenile chronic arthritis in northern Norway: a ten-year retrospective study. Clin Exp Rheumatol 1998; **16**: 99-101.
18. Ozen S, Karaaslan Y, Ozdemir O et al. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study. J Rheumatol 1998; **25**: 2445-9.
19. Pollet S, Salles M [Thèse d'exercice] Epidémiologie de l'arthrite juvenile idiopathique en 1999 dans la région Nord-Pas-de-Calais. Lille: Université du droit et de la santé, 2001; 1 vol., 128 p., Bibliogr. f. 117-128.
20. Kaipiainen-Seppanen O, Savolainen A. Changes in the incidence of juvenile rheumatoid arthritis in Finland. Rheumatology (Oxford) 2001; **40**: 928-32.
21. Von Koskull S, Truckenbrodt H, Holle R, Hörmann A. Incidence and prevalence of juvenile arthritis in an urban population of southern Germany: a prospective study. Ann Rheum Dis 2001; **60**: 940-5.
22. Huemer C, Huemer M, Dorner T et al. Incidence of pediatric rheumatic diseases in a regional population in Austria. J Rheumatol 2001; **28**: 2116-9.
23. Berntson L, Andersson Gäre B, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. J Rheumatol 2003; **30**: 2275-82.
24. Savolainen E, Kaipiainen-Seppänen O, Kröger L, Luosujärvi R. Total incidence and distribution of inflammatory joint diseases in a defined population: results from the Kuopio 2000 arthritis survey. J Rheumatol 2003; **30**: 2460-8.
25. Hanova P, Pavelka K, Dostal C, Holcatova I, Pikhart H. Epidemiology of rheumatoid arthritis, juvenile idiopathic arthritis and gout in two regions of the Czech Republic in a descriptive population-based survey in 2002–2003. Clin Exp Rheumatol 2006; **24**: 499-507.
26. Pruunsild C, Uibo K, Liivamägi H, Tarraste S, Talvik T, Pelkonen P. Prevalence and short-term outcome of juvenile idiopathic arthritis: a population-based study in Estonia. Clin Exp Rheumatol 2007; **25**: 649-53.
27. Pruunsild C, Uibo K, Liivamägi H, Tarraste S, Talvik T, Pelkonen P. Incidence of juvenile idiopathic arthritis in children in Estonia: a prospective population-based study Scand J Rheumatol 2007; **36**: 7-13.
28. Mengual L, Fernández Menéndez JM, Solís Sánchez G, Fernández Díaz M, Fernández González N, Málaga Guerrero S. Epidemiological study of juvenile idiopathic arthritis in the last sixteen years in Asturias (Spain). An Pediatr (Barc) 2007; **66**: 24-30.
29. Riise ØR, Handeland KS, Cvancarova M, et al. Incidence and characteristics of arthritis in Norwegian children: a population-based study. Pediatrics 2008; **121**: 299-306.
30. Solau-Gervais E, Robin C, Gambert C, et al. Prevalence and distribution of juvenile idiopathic arthritis in a region of Western France. Joint Bone Spine 2010; **77**: 47-9.
31. Istituto Nazionale di statistica (ISTAT). Popolazione residente 2011. Available from: http://demo.istat.it/ [Last accessed: 2017, Feb 6].
32. Andersson Gäre B. Juvenile arthritis--who gets it, where and when? A review of current data on incidence and prevalence. Clin Exp Rheumatol 1999; **17**: 367-74.
33. Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis why does it vary so much? J Rheumatol. 2002; **29**: 1520-30.
34. Oen KG, Cheang M. Epidemiology of chronic arthritis in childhood. Semin Arthritis Rheum 1996; **26**: 575-91.
35. Ostergaard PA, Lillquist K, Rosthøj S, Urfe P. Occurrence and types of juvenile rheumatoid arthritis in the County of Jutland 1970-1977 and 1978-1986. Ugeskr Laeger 1988; **150**: 342-61.
36. Ravelli A, Varnier GC, Oliveira S et al. Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. Arthritis Rheum 2011; **63**: 267-75.
37. Breda L, Marzetti V, Gaspari S, Del Torto M, Chiarelli F, Altobelli E. Population-based study

of incidence and clinical characteristics of rheumatic fever in Abruzzo, central Italy 2000-2009. J Pediatr 2012; **160**: 832-6.
38. Altobelli E, Petrocelli R, Verrotti A, Valenti M. Infections and risk of type I diabetes in childhood: a population-based case-control study. Eur J Epidemiol 2003; **18**(5): 425-30.
39. Altobelli E, Petrocelli R, Verrotti A, Chiarelli F, Marziliano C. Genetic and environmental factors affect the onset of type 1 diabetes mellitus. Pediatr Diabetes 2016; **17**(8): 559-66.
40. Altobelli E, Paduano R, Gentile T, et al. Health-related quality of life in children and adolescents with celiac disease: survey of a population from central Italy. Health Qual Life Outcomes 2013; **11**: 204.
41. Blasetti A, Di Giulio C, Tocco AM, et al. Variables associated with severe hypoglycemia in children and adolescents with type 1 diabetes: a population-based study. Pediatr Diabetes 2011; **12**(1): 4-10.

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