Review

Juvenile idiopathic arthritis in the world

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ABSTRACT

Juvenile idiopathic arthritis is an heterogeneous condition currently divided into several different categories. Studies have shown important differences in frequency of the various JIA categories in different part of the world. The relative contribution of environmental factors or genetic in explaining these differences remains to be established. A greater JIA-related damage is observed in low-income countries which can be explained by inadequate financial resources and difficulties in health care facilities access. Initiatives to expand the knowledge of paediatric rheumatology all over the world are strongly needed.

Juvenile idiopathic arthritis (JIA) is not a disease but an umbrella term that gather together all arthritis of unknown origin, lasting for more than 6 weeks and with onset before 16 years of age (1). It is the most frequent rheumatologic condition in paediatric age and a relevant cause of short- and long-term disability. The current ILAR (International League Against Rheumatism) classification identifies 7 different types of JIA, based on the symptoms presented during the first six months of disease (2, 3). This classification, proposed at the turn of the last century, provided a useful tool for research but has been criticised during the last 20 years (4-6). The main limitation is that it does not distinguish those forms of chronic arthritis observed both in adults and in children, from those that may be typical of childhood; moreover, the utility of the number of joints affected as classification criteria has been questioned and the existence of a form typical of children and characterized by an early onset and the presence of antinuclear antibodies (ANA) has been suggested (4, 7, 8). An attempt to revise JIA classification is ongoing (9).

Most of the knowledge we have of JIA comes from Western countries while information on developing countries, which in addition have the highest percentage of paediatric population, is scanty. So, taking into account the number of inhabitants and the median age of the population, we lack information on the great majority of children with JIA in the world. Several studies have shown differences in the prevalence of the various ILAR classification JIA categories among different geographic areas (10-17). These include a higher frequency of enthesitis-related arthritis in India, of systemic arthritis in Asia and of ANA-positive JIA in Western countries.

More recently, Consolaro *et al*. (18) performed a systematic analysis on a worldwide basis to assess the prevalence of the various ILAR categories, to gain information on treatment and to assess the disease and health status. They took advantage from the existence of PRINTO (Paediatric Rheumatology International Trials Organisation, www.printo.it) an international network that Nicolino Ruperto and myself founded in 1966 to promote collaborative research in paediatric rheumatic diseases. PRINTO includes 726 paediatric rheumatology centres in 95 countries worldwide including Europe, Middle East, Asia, Africa, Central and South America. Consolaro *et al*. proposed participation in the study to 65 national PRINTO coordinating centres and to one leading paediatric rheumatology centre each in the USA and Canada. Each centre that agreed to participate was then asked to invite qualified centres in its country to join the study.

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The countries involved were divided into eight geographical areas: northern Europe, Western Europe, Southern Europe, Eastern Europe, North America, Latin America, Africa and Middle East, and Southeast Asia. Each centre was asked to enrol up to 100 patients meeting the ILAR criteria for juvenile idiopathic arthritis that were seen consecutively over 6 months.

A total of 9081 patients were enrolled at 130 centres in 49 countries. The results showed a higher prevalence of girls than of boys in all areas, except for Southeast Asia, where boys outnumbered girls. The median age at disease onset was lower in Southern and Northern Europe than in the other areas. Systemic arthritis was more frequent in Southeast Asia, Africa and Middle East and Latin America than in the other areas. Oligoarthritis was more frequent in Southern Europe and less common in Southeast Asia. While the prevalence of rheumatoid factor-negative polyarthritis was highest in North America and lowest in Southeast Asia, rheumatoid factor-positive polyarthritis was more frequent in Latin America and Southeast Asia than in the other areas. Enthesitis-related arthritis showed a very high prevalence in Southeast Asia and a low prevalence in Southern Europe. The prevalence of uveitis was highest in northern and southern Europe and lowest in Latin America, Southeast Asia and Africa and Middle East.

The systematic analysis performed by Consolaro *et al*. confirm previous observations conducted on a national basis on the differences in the prevalence of JIA categories among different geographic areas in the world. Differences in the worldwide distribution of adult rheumatoid arthritis (RA) has also been observed (19) and JIA is a much more heterogeneous condition with respect to RA. As acknowledged by the authors (18) some limitation should be taken into account. Hospital JIA patients may not be not be representative of the entire population in the community. Milder forms of JIA could have been missed either because they were treated in smaller centres or in private practice or, in less developed countries, because of restrictions in the access to health care resources.

The observed differences remains however important and their causes are probably multifactorial, being influenced by genetic and environmental factors. One of the most important differences is the striking high prevalence of enthesitis-related arthritis in South East Asia. This could be related to the high frequency of HLA-B27 in these countries but environmental factors for this as well as for other categories can also play an important role. The microbiome has received much attention for its potential role in the pathogenesis of chronic arthritis (20, 21). Moreover, it is known that environment can modify disease manifestations and severity in patients with the same genotype as it has been shown for familial Mediterranean fever (FMF). In 1974 Schwabe and Peters (22) noted the absence of secondary amyloidosis in a regularly followed cohort of 100 patients of Armenian ancestry with classical FMF living in United states. The mean duration of the disease in these patients was 22.7 years and 44 were above the age of 40 years. Touitou *et al*. (23) demonstrated that country of recruitment, rather than MEFV genotype, is the key risk factor for renal amyloidosis in FMF thus indicating a possible environmental origin of amyloidosis susceptibility. Ozen *et al*. (24) showed that Turkish children with FMF born and raised in Germany express a less severe disease phenotype in comparison with the ones living in Turkey. These findings show that even in diseases where genetic is the major determinant the environment can strongly modify clinical manifestations. It remains therefore to be seen if, for instance, Indian or Taiwanese B-27 positive children born and living in US or Europe would develop enthesitis related arthritis at the same rate and with the same manifestations as those observed in their own country.

Concerning treatment and disease outcome, Consolaro *et al*. found that systemic glucocorticoids were used more commonly in Southeast Asia and Africa and Middle East and less frequently in North America and Western Europe and. On the contrary biological, disease-modifying antirheumatic drugs (bDMARDs) were administered more frequently in Northern Europe and North America than in other geographical areas. Patients living in countries with lower gross domestic product (GDP) had greater disease activity and damage than those living in richer countries. Damage was associated with referral delay.

Limited access to public health facilities as well as lack of adequate financial resources are presumably the causes of these findings. Biological DMARDs are very expensive, and in these countries they are not provided by many public health systems, while just a tiny minority of wealthy patients in private hospitals can afford them. Most patients have to rely on the much less expensive conventional DMARDs (cDMARDs) often given in association. Controlled trials on the efficacy of combination therapy with cDMARDs in JIA are not available but they would be relevant for the vast majority of children living in countries with small GDP.

In low income countries, confronted with major health problems such as poverty, malnutrition and communicable diseases, paediatric rheumatology is much less developed than in Western countries. JIA has a complex diagnosis and management and require chronic care throughout childhood. The lack of paediatric rheumatology care in low-income countries that have the largest paediatric populations represents therefore an important problem.

Several efforts to improve the situation are ongoing (25-29). In the last 20 years the Paediatric Rheumatology European Society (PRES) has also made an effort to diffuse the knowledge of paediatric rheumatic diseases all over the world. Paediatric rheumatology courses have been organised in several extra-European countries and an open access paediatric rheumatology journal has been supported so providing a free source of information and updating for all people interested in childhood rheumatic diseases. Ten years ago PRES launched, in collaboration with the European League Against Rheumatism (EULAR), the EULAR/

PRES Online Course in Paediatric Rheumatology (https://esor.eular.org/enrol/index.php?id=482) that, with a small fee, provides the essential information on diagnosis and treatment of all paediatric rheumatic diseases. The course has been very successful with a lot of participants from all over the world, including many attendees from South East Asia. PRINTO has created a website (https://www.printo.it/pediatric-rheumatology) which provides information in 58 different languages for as many countries on: 1) information for families about the characteristics of paediatric rheumatic diseases; 2) contact details for paediatric rheumatology centres in each given country; 3) the family support associations that can be found in the various countries. It is the most visited family information site on paediatric rheumatic diseases.

In conclusion, there are important differences in the frequency of the various JIA categories in different part of the world. The relative contribution of genetic or environmental factors in explaining these differences remains to be established. In countries with low GDP, JIA causes a greater damage because of inadequate financial resources and difficulties in health care facilities access. Initiatives to expand the knowledge of paediatric rheumatology all over the world are strongly needed.

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