Editorial

Are the Number of Joints Involved or the Presence of Psoriasis Still Useful Tools to Identify Homogeneous Disease Entities in Juvenile Idiopathic Arthritis?

Juvenile idiopathic arthritis (JIA) represents a heterogeneous group of disorders of unknown etiology whose classification relies mainly on clinical grounds. A number of classification systems have been developed over the years, the most recent being that proposed by the International League Against Rheumatism (ILAR)[1] (Table 1). This classification has several important features of merit: (1) It has solved the problem of the previous heterogeneity in nomenclature and criteria between Europe and North America. (2) It wisely includes, for each JIA subset, a list of additional features, called descriptors, that may be useful in future studies to better dissect each disease category. (3) It is intended to represent a "work in progress" whose main aim is to find homogeneous disease groups suitable for etiopathogenetic studies[2].

Some of the disease categories identified by the ILAR classification seem indeed to have peculiar features. Systemic arthritis, although probably still a heterogeneous condition, has some distinctive markers that set it apart from the other JIA subsets. It is characterized, with respect to the other JIA forms, not only by prominent systemic features such as high spiking fever, but also by some peculiar aspects of the inflammatory process, such as an apparent major role for interleukin 6 and a marked activation of the macrophage system[3].

On clinical, genetic, and laboratory grounds rheumatoid factor (RF) positive polyarticular JIA is identical to adult RF positive rheumatoid arthritis (RA) and is considered its equivalent in childhood.

Enthesitis related arthritis on several clinical (i.e., enthesitis) and laboratory (i.e., marked increased prevalence of HLA-B27) features is assumed to belong to the spondyloarthropathy group.

Table 1. ILAR classification criteria for juvenile idiopathic arthritis (Durban, 1997)[1].

Systemic
Oligoarthritis
Persistent
Extended
Polyarthritis (RF negative)
Polyarthritis (RF positive)
Psoriatic arthritis
Enthesitis related arthritis

Although the oligoarticular onset category as a whole is probably heterogeneous, by far the largest group of patients is represented by a quite well defined form of JIA. This form, which is typical of children and is not observed in adults, is characterized by an asymmetric arthritis, an early onset (usually before 6 years of age), a female predilection, a high frequency of positive antinuclear antibodies (ANA), and a high risk for developing chronic anterior uveitis. In confirmation that these patients may represent a homogeneous entity, a strong association with some HLA alleles and in particular with DRB1*0801 (DRw8) has been found[4-6]; of interest, correlation with DRw8 is independent from the ethnic group of patients[7]. Patients with these characteristics represent, in Western countries, the great majority of the oligoarthritis group independently from the fact that arthritis remains confined to a few joints (the oligoarticular persistent subgroup) or involves more than 4 joints after the first 6 months of disease (the oligoarticular extended subgroup)[8,9], a feature that occurs in up to 50% of cases[10].

The 2 other JIA categories, polyarticular RF negative and psoriatic, include disease entities that appear more heterogeneous.

Although seronegative polyarticular JIA is found at all ages, 2 peaks are usually observed, one during the first years of life (mainly girls) and the other in the preadolescent age[11], with about half of patients having disease onset before 5 years of age[8,9,12]. About 20 to 40% of patients are ANA positive[8,9,12-14]. ANA positivity is strongly associated with early age at onset; the specificity against the 45 kDa DEK nuclear antigen, which has been found in early-onset, ANA positive oligoarticular disease, has also been observed in ANA positive seronegative polyarticular JIA[15]. Chronic anterior uveitis is observed in seronegative polyarticular disease, with a frequency ranging from 5 to 20%[12,16] and, as in oligoarticular disease, is strongly associated with early age at onset, female sex, and ANA positivity. HLA association studies have provided quite inconsistent results in seronegative polyarthritis as a whole. However, several groups[8,9,12,17] have reported an increase in DRB1*0801 (DRw8) in seronegative polyarticular patients with early age at onset,

ANA positivity, and presence of iridocyclitis. As noted, DRB1*0801 is the allele that is more closely associated with early-onset oligoarticular JIA. In the early 1990s[8], an association was reported between seronegative polyarticular JRA and DPB1.0301; this association, at variance with that with DR8, was independent from age at onset and was observed mainly in ANA negative patients. Three main clinical pictures[18] can be observed in polyarticular JIA: (1) a form that resembles adult seronegative RA and is characterized by a symmetric florid synovitis that affects both large and small joints, onset in school age, elevated erythrocyte sedimentation rate (ESR), usually negative ANA, and variable outcome. In this respect it is interesting that the association of DPB1.0301 with ANA negative, late onset seronegative polyarticular JRA has also been reported in adult seronegative RA[19]. (2) A form, also known as "dry synovitis," that is characterized by little palpable synovial thickening, onset in school age, normal or modestly elevated ESR, and ANA negativity[20]. This form is often poorly responsive to treatment and follows a destructive course. The striking differences in the clinical pictures with respect to the other forms of JIA suggest that this subset of "dry synovitis" may also have a different pathogenesis (genetic disease?). (3) A form that resembles early-onset oligoarticular disease in every respect (except for the number of joints affected during the first 6 months of disease). Indeed, it is this form of seronegative polyarticular JIA that is characterized by asymmetric arthritis, early age at onset, female predominance, frequent ANA positivity, elevated risk of developing chronic anterior uveitis, and association with HLA-DRB1.0801. The hypothesis that this latter subset of polyarticular seronegative JIA and early-onset oligoarthritis are the same disease, the former representing a rapid arthritis spread in the latter, is also very strongly supported by studies on the frequency of the various JIA subsets in different ethnic populations. Several studies[21] have indeed shown that early-onset, ANA positive, iridocyclitis-associated oligoarticular arthritis is very rare in many countries, including Costa Rica, India, New Zealand, and South Africa. In these same countries, seronegative polyarticular JIA lacks the early-years onset peak, is rarely ANA positive, and is not associated with chronic anterior uveitis[22,23]. Therefore, in those countries in which ANA positive, early-onset, iridocyclitis-associated oligoarthritis is rare, ANA positive, early-onset, iridocyclitis-associated seronegative polyarthritis is also seldom observed.

Juvenile psoriatic arthritis (PsA) also appears to be quite heterogeneous[24-27]. As in seronegative polyarthritis, age at onset is bimodally distributed, with a first peak occurring during the preschool years (mainly in girls) and a second during mid to late childhood, centering around 10 years of age[25]. In a series of 63 children[28] the median age at onset was 4.5 years in girls and 10.1 years in boys. Patients with early onset have an asymmetric oligoarthritis that may extend; chronic anterior uveitis occurs with a frequency similar to that in early-onset oligoarticular JRA (roughly 20%) and is associated with antinuclear antibodies[24,25]. HLA typing in patients with juvenile PsA of early onset has shown an increase in DRw8[29]. Early-onset juvenile PsA therefore closely resembles early-onset oligoarticular disease, the only difference being a higher reported frequency of dactylitis and of small joint involvement[28]. The older group of patients with juvenile PsA has a male predominance and shares features of enthesitis related arthritis. Finally, in a minority of patients the disease manifests as a symmetric polyarthritis.

In summary, children with the same cluster of features that strongly suggest a common background (asymmetric arthritis, early onset, female predominance, frequent ANA positivity, high risk for chronic anterior uveitis, association with HLA-DR8) are present in different JIA categories (oligoarticular persistent, oligoarticular extended, polyarticular seronegative, and psoriatic). This common cluster of features may be more meaningful to define a homogeneous group of patients than the presence of polyarticular involvement or psoriasis. In other words, the above-mentioned features may define a homogeneous disease entity that is currently classified into different JIA categories.

Polyarthritis is traditionally defined as the involvement of 5 or more joints during the first 6 months of disease. This criterion has historically been very useful to separate 2 broad categories of arthritis: (1) those that affect mainly large joints in an asymmetrical way (and in which therefore the total number of joints involved may be low); and (2) those that affect both large and small joints in a symmetrical way (and in which the total number of joints is high). However, in a disease characterized by asymmetric arthritis the total number of joints involved may simply be one of the expressions of disease severity. If extended oligoarthritis is considered part of the oligoarticular subgroup, why not include in the same category patients with the same characteristics in which the involvement of 5 or more joints occurs during the first 6 months of disease? Paradoxically, one may run the risk of including the same disease entity in different categories because the fifth joint is affected during the sixth or during the seventh month from onset. In other words, the number of joints involved can be greatly affected by disease severity and therefore may not represent a suitable marker for the definition of a homogeneous JIA subgroup.

Despite the excellent studies to date, PsA remains poorly understood[30]. While RF positive polyarthritis is identical in adults and in children, PsA in children mainly resembles early-onset oligoarticular JIA, while in adults it appears mainly to belong among the seronegative spondyloarthropathies[26]. In adults, the concept of PsA itself is not universally accepted, and there is no universally agreed on definition[30]. Various hypotheses have been considered that

are not mutually exclusive and that in fact may all be true: (1) PsA is a unique, although not yet well characterized, disease entity; (2) psoriasis enhances the susceptibility to arthritis and/or modifies the disease phenotype; and (3) the association of psoriasis and arthritis is coincidental. There is therefore no convincing evidence to date that grouping together patients with arthritis and psoriasis or definite psoriatic features may lead to identification of a homogeneous disease group.

Age at disease onset could have a role in the identification of homogeneous disease entities, since it may somehow be related to the triggering events; early age at onset suggests that the disease is secondary to an altered immunological response to common infectious agents that are encountered very early in life. For instance, we recently found evidence[31] that T cells from patients with early-onset ANA positive oligoarticular JIA are sensitized against epitopes that are shared between the 3 disease-associated HLA antigens[6] and proteins present on Epstein-Barr virus and other herpes viruses; herpes viruses represent a group of infectious agents to which the vast majority of children have already been exposed by 6 years of age.

Thus the encounter with a very diffuse infectious agent (herpes viruses?) during the first years of life could elicit in predisposed individuals (mainly girls, carrying the HLA-DR1*0801 allele) an asymmetric arthritis that may be confined to 4 or fewer joints or, according to disease severity, may spread to involve 5 or more joints either at onset of the disease or later on. Additional features of this abnormal immune response may be the tendency to develop ANA as well as chronic anterior uveitis. The disease may be found in association with psoriasis, and the presence of psoriasis may or may not modify some aspects of the disease phenotype (such as a higher frequency of small joint involvement or the development of dactylitis).

In conclusion, I suggest that: (1) patients belonging to a presumably homogeneous disease entity characterized by early onset, female predilection, frequent ANA positivity, asymmetric arthritis, high risk for chronic iridocyclitis, and association with HLA-DRB1*0801 are currently classified into different JIA categories: oligoarticular persistent, oligoarticular extended, RF negative polyarticular, and psoriatic; and (2) grouping patients according to the number of joints involved or the presence of psoriasis may not lead to identification of homogeneous disease entities suitable for biological studies.

It could therefore be interesting to explore the value of other classification variables (such as age at onset, asymmetry of arthritis at onset, ANA positivity, etc.) and/or their combinations in defining more homogeneous JIA populations, and in differentiating factors related to disease etiology from those related to disease severity or to the possible modifications of disease phenotype induced by psoriasis. In this perspective, the number of joints involved and the presence of psoriasis could be more useful as descriptors than as main classification criteria.

The analysis of patients according to the descriptors in each ILAR JIA category as well as specifically designed prospective studies could be useful to explore this hypothesis.

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