

# Growing up with chronic arthritis: the confusing matter of classification

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Disease classification in rheumatology is a matter of debate, in paediatrics between International League Against Rheumatism (ILAR) classification ‘pros and cons’, as well as between paediatric and adult rheumatologists. Indeed, there is no consensus yet about how we should name the disease of adults with juvenile idiopathic arthritis (JIA) in childhood. The non-concordance of adult and paediatric classifications for chronic inflammatory rheumatic diseases is confusing for caregivers, and above all for our patients. Will they be ‘lost in transition’, as phrased by McDonagh and Viner,<sup>1</sup> when their disease stays the same, but gets a new name? Will their treatment be modified according to this new name and the corresponding recommendations for adult disease management? Yes, it is definitely time to think about a thorough modification of the ILAR categories of childhood chronic arthritis.<sup>2</sup>

The ILAR agreed on a classification that comprises all types of idiopathic arthritis in children under the umbrella term of JIA, subdivided into seven categories comprising the systemic, oligoarticular, rheumatoid factor (RF)-negative polyarticular, RF-positive polyarticular, juvenile psoriatic arthritis (jPsA), enthesitis-related arthritis (ERA) and the undifferentiated form.<sup>3</sup> This was the first time that Europeans and Americans agreed to speak the same language. However, since launched, the ILAR classification has been regularly criticised.<sup>4–6</sup> It was revised in 2001, and the reduced emphasis on heredity resulted in a significant decrease in the rates of children with undifferentiated arthritis.<sup>7</sup> Calls for further modifications are nevertheless still numerous.

Martini<sup>8</sup> recognised that dividing patients into groups according to the number of joints involved at disease onset (oligoarticular/polyarticular JIA) was not gathering homogeneous categories; others claimed that strict exclusion criteria of the present classification excluded many authentic juvenile spondyloarthritis from the ERA category,<sup>9–10</sup> the same for the

jPsA category,<sup>11–12</sup> and even the RF-positive polyarticular category.<sup>13</sup> The undifferentiated arthritis group varies markedly in frequency in different reports, because it depends on thorough work-up on heredity and other exclusion criteria.<sup>14–15</sup> Contrary to the intentions of the ILAR, the undifferentiated group in follow-up tends to increase instead of decrease over time.<sup>15</sup>

A new proposal is emerging from Martini and colleagues to define a group composed of young children ≤6 years of age with arthritis and presence of antinuclear antibodies (ANA). Indeed, two important papers from their team showed that the clinical characteristics of ANA-positive young children during the first 2 years after disease onset were very similar despite being classified into different ILAR categories, that is, RF-negative polyarticular, oligoarticular (persistent and extended), jPsA and undifferentiated arthritis, proving at the same time how heterogeneous these categories are.<sup>16–17</sup> However, there are several concerns.

First, we have pointed out that the ANA immunofluorescence test is operator-dependent and still not consensual in terms of threshold of positivity in different laboratories worldwide, even though the aforementioned studies define ANA positivity as two positive immunofluorescence tests at a titre of ≥1/160 on Human Epithelial type 2 (HEp-2) cells at least 3 months apart.<sup>16–17</sup> Second, ANA in JIA still have no identified biological target, and therefore no clear link to aetiology, pathophysiology or treatment option.<sup>18</sup> Most importantly, prospective long-term follow-up of young children with ANA-positive JIA from different cohorts and geographical regions is still lacking. Therefore, ANA should not in our opinion be a classification determinant until more standardisation and evidence for relevance in treatment, disease course or outcome is available.

The clinical entity of psoriatic arthritis (PsA) versus enthesitis and spondyloarthritis

(SpA) in children is mutually exclusive in the ILAR classification, jPsA being restrictive compared with the classification of psoriatic arthritis (CASPAR) criteria. Recent findings of histologically inflamed entheses in dactylitic fingers, suggests that dactylitis and peripheral arthritic involvement often seen in young girls and enthesitis and axial involvement in older boys may be different manifestations of the same disease process.<sup>19</sup> New knowledge has emerged on the role of certain interleukins, and subsequent targeted therapies are developed for PsA in adults.<sup>20</sup> Too strict exclusion criteria for jPsA and ERA may exclude some children and adolescents from access to these treatments, and should therefore be reconsidered in a new ILAR classification.

In the September issue 2016 of *RMD Open*, an elegant article on rheumatic disease classification is presented by Oliveira-Ramos *et al*<sup>14</sup> from Portugal. These authors describe the classification outcome of 426 patients with JIA followed for a mean of 22.5 years into adulthood and reclassified according to the adult classification criteria of chronic inflammatory rheumatic diseases (2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) for rheumatoid arthritis (RA), 1984 modified New York criteria for ankylosing spondylitis, CASPAR criteria for PsA, adult Still's disease, unclassifiable patients (undifferentiated arthritis)). The table is drawn from their data (table 1).

The left part of the table confirms what many paediatric rheumatologists believe: the systemic, the RF-positive polyarticular JIA, the ERA and the jPsA categories have their adult counterpart. Then, do we need different words to name them?<sup>2</sup> Although the classifications of adult RA, PsA and SpA also include heterogeneous phenotypes, their treatment strategies are rapidly evolving, and the therapies constantly evaluated. Harmonising the name and the criteria of the disease for the systemic, the RF-positive polyarticular JIA, ERA and jPsA categories between childhood and adult units of care, may allow smoother transfer, and importantly, that they receive the targeted treatments at the right time.

In the right part of the table, the evolution of the RF-negative polyarticular and the oligoarticular groups are shown. Around 15% of the patients classified to have oligoarthritis (persistent and extended) fit SpA classification; almost 40% of the oligoextended and 60% of the RF-negative polyarticular categories fit the criteria for RA, and 24–60% of the oligoarticular categories and RF-negative polyarticular are classified as undifferentiated chronic inflammatory arthritis. Of course, information on ANA status, and detailed clinical presentation at onset in relation to specific outcome categories (RA/SpA/PsA/undifferentiated) would be particularly interesting to look at.

Modification of the JIA classification should be based on knowledge from prospective cohorts and ongoing international registries extending far beyond 10 years follow-up in order to assess adult outcome. In addition, research on genetics and novel disease biomarkers will

**Table 1** Paediatric JIA categories reclassified according to the adult classification criteria of chronic inflammatory rheumatic diseases in individuals with long-term follow-up

Strong correlation between paediatric/adult classifications		Poor correlation between paediatric/adult classifications	
Onset (n)	Long-term follow-up (n)	Onset (n)	Long-term follow-up (n)
Syst JIA (39)	ASD (36) <b>92.3%</b> RA (2) Undiff (1)	RFneg Poly JIA (63)	RA (36) <b>57.1%</b> AS (2) USpA (2) PsA (8) Undiff(15) <b>23.8%</b>
RFpos Poly JIA (68)	RA (65) <b>95.6%</b> AS (1) PsA (1) Undiff (1)	Persist Oligo JIA (66)	RA (4) AS (5) USpA (9) <b>13.6%</b> EnterA (4) PsA (5) Undiff(39) <b>59.1%</b>
ERA (76)	AS (41) USpA (21) <b>86.8%</b> EnterA (4) PsA (6) Undiff (4)	Extend Oligo JIA (54)	RA (21) <b>38.9%</b> AS (2) USpA (10) <b>18.5%</b> EnterA (1) PsA (1) Undiff(19) <b>35.2%</b>
jPsA (13)	PsA (12) <b>92.3%</b> USpA (1)	Undiff (6)	RA (3) AS (1) EnterA (1) Undiff (1)

AS, ankylosing spondylitis; ASD, adult Still's disease; EnterA: enteropathic arthritis; ERA, Enthesitis-Related Arthritis; jPsA : juvenile Psoriatic Arthritis; Persist/Extend Oligo, persistent/extended oligoarticular JIA; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RFneg Poly JIA, rheumatoid factor negative polyarticular JIA; RFpos Poly JIA, rheumatoid factor positive polyarticular JIA; Syst JIA, systemic JIA; USpA, undifferentiated spondyloarthritis; Undiff, undifferentiated arthritis.

hopefully help defining more relevant disease categories. In fact, a recent report from a large consortium on JIA genetics shows that the JIA categories potentially have adult counterparts: the strong associations between RF-positive polyarthritis and specific human leukocyte antigen (HLA) DRB1\* alleles are seen both in children and adults.<sup>21</sup> Interestingly, the combined oligoarthritis and RF-negative polyarthritis categories share the same HLA association with adult seronegative RA.<sup>21</sup>

So how are Oliveira-Ramos *et al*'s results clinically relevant to the up-coming change in ILAR classification? For the caregiver, the nomenclature and classification guide treatment and follow-up strategies. For the patient, receiving the most effective treatment is the main objective. We know that JIA categories change over time in children and may also change in adults, when they are followed closely for features of psoriasis, enthesitis or spondyloarthropathy, or when adult rheumatologists rename the juvenile rheumatic disease. The work of Oliveira-Ramos *et al* is of crucial importance in this time of redefining JIA classification. Further studies of genetic and early clinical characteristics of JIA in children, in order to collect RA, SpA or PsA specific traits,

may be a way to unify the paediatric and adult classifications of rheumatic diseases, for the entire benefit of our children and adolescents. We hope our patients can finally recognise themselves as having the same disease from childhood to adulthood.

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