

Advances and Challenges in the Classification of Childhood Arthritis

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Abstract: The most appropriate classification of childhood arthritis remains controversial. Several efforts have been made over the years to devise classification systems that identify homogeneous subgroups within the disease spectrum. Although widely used, the International League of Associations for Rheumatology (ILAR) classification has shown major limitations as it was found to have failed its primary goal of identifying homogeneous disease categories. Furthermore, its use of the count of affected joints and of the presence of psoriatic features to define individual disease subsets has been criticized. A novel classification system has been proposed by the Pediatric Rheumatology International Trials Organization (PRINTO) through expert consensus. The preliminary scheme is currently being scrutinized by means a large-scale data collection aimed to formulate an evidence-based classification, whose results will likely be available in 2024. The development of a clinicobiologic classification has been tried in a proof-of-concept study by integrating meaningful biologic and clinical characteristics, including levels of proinflammatory cytokines and measures of disease activity, that defined indicators or composite variables capable of identifying homogeneous patient subgroups by cluster analysis. The current advance in biotechnology, especially genomics, proteomics and transcriptomics, may pave the way to the future identification of well-defined clusters of patients that will inform a biology-based and data-driven classification system. However, any attempt to defining biologic subtypes should be combined with precise clinical and prognostic data in order to devise a rational classification that facilitates the progress towards personalized management of children with JIA. Furthermore, the observed variability in the prevalence of disease subtypes across geographic areas and ethnic groups must be taken into account to develop a classification that is applicable on a global scale.

Keywords: Juvenile idiopathic arthritis, Childhood arthritis, Pediatric rheumatology, Classification.

INTRODUCTION

The classification of childhood arthritis is one of the most debated topics in the field of pediatric rheumatology. A great deal of work has been performed over the years to improve existing criteria, but the optimal scheme is still uncertain. The aim of the present article is to review the classifications proposed for childhood arthritis and to provide an update on the ongoing efforts aimed to revise current criteria. Furthermore, the importance of resolving the classification issue in order to design appropriate research studies and to promote the development of better treatment strategies is discussed. The classification criteria for childhood-onset arthritis proposed over the years is presented in the Table 1 to give an insight on how the disease concept and categorization have evolved.

THE HISTORICAL ACR AND EULAR CLASSIFICATIONS

Historically, the first classification systems were proposed separately in the 1970s by the American college of Rheumatology (ACR) in North America [1]

and by the European League Against Rheumatism (EULAR) in Europe [2], based on the increased understanding of the range of arthritides in children and the associated extra-articular features. The two sets of criteria established a framework for outlining this heterogeneous group of conditions by setting the age limit and the minimum disease duration requested for making the diagnosis and by describing precisely the characteristics of arthritis and extraarticular features. A definition for arthritis was provided, as the presence of swelling or effusion or, if swelling was absent or not detectable, as the coexistence of two or more among tenderness or pain on motion, limitation of range of motion, and increased heat, thus highlighting the importance of a proper physical examination. Furthermore, the cut-off of 4 affected joints to divide children into pauciartthritis or oligoarthritis (≤ 4 affected joints) and polyarthritis (> 5 affected joints) was chosen. However, the two classifications differed in many aspects, including the nomenclature for the disease (juvenile rheumatoid arthritis, JRA, for the ACR and juvenile chronic arthritis, JCA, for the EULAR), the minimum duration of arthritis necessary for diagnosis (six weeks in ACR criteria and three months in EULAR criteria), the recognition of the subsets of juvenile ankylosing spondylitis, juvenile psoriatic arthritis and arthropathies associated with inflammatory bowel disease by EULAR criteria, and the need to demonstrate rheumatoid factor (RF) positivity for

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Table 1: Evolution of the Nomenclature of Childhood Arthritis

	ACR classification	EULAR classification		Vancouver criteria	ILAR classification	PRINTO classification (provisional)
Year	1977	1978	1982	1989		
Disease name	Juvenile rheumatoid arthritis	Juvenile chronic arthritis			Juvenile idiopathic arthritis	Juvenile idiopathic arthritis
Categories	Systemic onset	Systemic			Systemic arthritis	Systemic JIA
	Polyarthritis	Juvenile rheumatoid arthritis (RF-positive)			RF-positive polyarthritis	RF-positive JIA
		Polyarticular			RF-negative polyarthritis	Early-onset ANA-positive JIA
	Oligoarthritis (pauciarticular disease)	Pauciarticular			Oligoarthritis (extended or persistent)	
		Juvenile ankylosing spondylitis	SEA syndrome		Enthesitis-related arthritis	Enthesitis-spondylitis-related JIA
		Juvenile psoriatic arthritis		Juvenile psoriatic arthritis	Psoriatic arthritis	
					Undifferentiated arthritis	Other/unclassified JIA

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; ILAR, International League of Associations for Rheumatology; PRINTO, Pediatric Rheumatology International Trials Organization; SEA, seronegative enthesopathy and arthropathy; RF, rheumatoid factor; JIA, juvenile idiopathic arthritis; ANA, antinuclear antibody.

juvenile rheumatoid arthritis in EULAR classification. This discrepancy introduced many inconsistencies, which were often source of confusion and hampered a reliable comparison of patient series across the two sides of the Atlantic Ocean. Terminology issues were further compounded in 1982 by the recognition of a subgroup of patients with spondylitis features and very early disease onset that was not encompassed by both classifications and was labeled seronegative enthesopathy and arthropathy (SEA) syndrome [3].

THE ILAR CLASSIFICATION

Although the ACR and EULAR classifications helped to shape the distinctive characteristics of the various forms of childhood arthritis, their differences hindered a universal use. To solve this disparity, a Classification Taskforce was established within the Pediatric Standing Committee of the International League of the Associations for Rheumatology (ILAR) in the early 1990s. This group of experts introduced the umbrella term of juvenile idiopathic arthritis (JIA) to identify all forms of childhood arthritis and aimed to eliminate the diversities between the former ACR and EULAR classifications. The Taskforce first gathered in Santiago, Chile in 1995 [4], then in Durban, South Africa in 1997 [5], and finally in Edmonton, Canada in 2001 [6]. The main aim of these efforts was to reach

consensus on defining homogeneous categories within the disease spectrum in order to facilitate research on etiopathogenesis and epidemiology, outcome studies, and treatment trials. Although several elements of the previous criteria were maintained, including the threshold of 16 years to establish the disease onset in the pediatric age, the recognition of a form characterized by the association of arthritis with peculiar systemic extra-articular features and the use of the count of affected joints as classification criterion, the new ILAR criteria introduced exclusions to avoid overlap between categories and to foster homogeneity within the six outlined mutually exclusive categories: these were systemic arthritis, oligoarthritis persistent or extended, RF-negative polyarthritis, RF-positive polyarthritis, psoriatic arthritis, and enthesitis-related arthritis (ERA). A seventh category of “undifferentiated arthritis” was created to accommodate the patients that cannot be placed in any category or fulfil the criteria for more than one category. To gather further information on clinical patterns, several “descriptors” were proposed, such as distribution and course of joint disease, presence of antinuclear antibodies (ANA), occurrence of chronic or acute iridocyclitis, and HLA allele associations. As compared to the former ACR and EULAR systems, the ILAR criteria recognized more in detail the multifaced spectrum of childhood-onset arthritis. The main changes regarded the

subdivision of polyarthritis into a RF-positive and a RF-negative subset, the introduction of the psoriatic arthritis category, and the attribution of the term ERA to the forms of spondyloarthritis with onset in childhood. The ILAR Classification Taskforce decided to exclude inflammatory bowel disease-related arthritis, reactive arthritis, and juvenile ankylosing spondylitis due to the fear that these conditions could contaminate the homogeneity of the outlined categories. When promulgating these criteria, the Classification Taskforce advised that the classification system should be viewed as a work in progress, and pediatric rheumatologists were asked to participate in the process by making their opinions known and by testing the proposed criteria in their patient series.

CRITICISMS TO ILAR CLASSIFICATION

Although the ILAR classification has been widely adopted by clinicians and researchers all over the world, it has been subject to many criticisms and several suggestions for improvement have been raised [7-13]. Some criticisms are general, such as the arbitrary choice of the 16-year cutoff to distinguish childhood arthritis from the adult forms and of the 6-month disease duration to define individual categories. Other regard specific categories. For systemic arthritis, the emerging evidence of the prominent role of autoinflammation mechanisms in its pathogenesis has led to postulate that it sets apart from the JIA spectrum [14, 15]. Moreover, it has been argued that there are patients who present with the same extraarticular manifestations seen in children with classic systemic arthritis, but cannot be classified in this JIA category by ILAR criteria because they never develop arthritis [13]. These patients would meet the criteria for adult-onset Still's disease, which is considered the adult equivalent of systemic JIA and do not require the presence of arthritis for diagnosis [16]. In RF-positive polyarthritis, the addition of the presence of anti-CCP antibodies has been advised to account for the established diagnostic role of these autoantibodies in adult rheumatoid arthritis (RA). Whether positive serology should be prioritized over the number of affected joints is also a matter of debate. RF-negative polyarthritis has been shown to be heterogeneous and to encompass at least two subsets, one characterized by symmetric polyarthritis, onset in school age, and negative ANA, and a second possessing the features of early-onset, ANA-positive oligoarthritis, from which it is only differentiated by a greater number of affected joints [13]. There is, indeed, compelling evidence that

patients with early-onset, ANA-positive JIA constitute a homogeneous subgroup, which is classified inappropriately by the ILAR system in different categories, based on the number of affected joints or the presence of psoriasis or a psoriatic diathesis. This patient subgroup is thought to be homogeneous as it shares several common characteristics, including, beside the early age of onset and the presence of circulating ANA, strong female predilection, asymmetry of arthritis, high risk of development of chronic iridocyclitis, and some HLA associations. It has, then, been suggested that these patients be grouped in a distinctive category of early onset, ANA-positive JIA, irrespective of the number of joints involved or the presence of psoriasis [9, 10, 12]. It is increasingly recognized that this disease entity is unique to children as it does not exist in adults. Notably, the use of the count of affected joints is considered unreliable as classification criterion because standardized joint examination is known to be largely variable across different examiners. Furthermore, ultrasound assessment was found to detect signs of synovitis in joints defined as inactive on physical examination and hence to reclassify as polyarthritis many patients labeled as oligoarthritis on clinical grounds [17]. The ILAR categories whose definition is most challenging is psoriatic arthritis [18, 19]. There is evidence that this form of JIA is not a unique entity, as stated in the ILAR scheme. It appears that the association of psoriasis with arthritis leads to the identification of at least two different groups of patients, one that has the same characteristics as early-onset, ANA-positive JIA, and another that is part of the spectrum of spondyloarthropathies and bears a resemblance to the forms of psoriatic arthritis in adults that belong to the same disease family [13, 18]. However, the diagnosis of psoriatic arthritis cannot be made by ILAR criteria if there is a first-degree relative with an HLA-B27-associated disease or if the arthritis occurs in a boy older than 6 years and HLA-B27 positive. In addition, the coexistence of psoriatic arthritis and ERA would place the patient into the undifferentiated arthritis category. Thus, the ILAR classification excludes children with spondyloarthropathic features from the psoriatic arthritis group. This limitation precludes the identification of those patients who have a form of psoriatic arthritis similar to that seen in adults [13]. As highlighted above, some important forms of the childhood arthritis, such as inflammatory bowel disease-related arthritis, reactive arthritis, and juvenile ankylosing spondylitis are not incorporated within ILAR criteria.

THE PRINTO CRITERIA

A new set of classification criteria for JIA developed through expert consensus has been recently proposed by the Pediatric Rheumatology International Trials Organization (PRINTO) [20]. The general definition of JIA was modified by raising the threshold of age at onset to 18 years, whereas it was maintained that arthritis should persist for at least 6 weeks and diagnosed after the exclusion of other known conditions. This classification delineates the following disease categories: 1) systemic JIA, which is thought to be the pediatric equivalent of adult-onset Still's disease; 2) RF-positive JIA, which is considered identical to seropositive RA; 3) enthesitis/spondylitis-related JIA, which corresponds to the ILAR category of ERA, but whose nomenclature was modified to account for the view that it is a form of undifferentiated spondyloarthritis; 4) early-onset ANA-positive JIA, which is distinctive of children as it does not have a counterpart in adults. All patients who do not meet these definitions are included in two additional categories for unclassifiable patients: other JIA, for those who do not fit any defined category, and unclassified JIA, for those who fit 2 or more defined categories. The proposed criteria are considered provisional, and an international collection of clinical and biologic data is ongoing with the aim to refine the provisional criteria and to devise an evidence-based classification.

COMPARISON OF THE PERFORMANCE OF ILAR AND PRINTO CRITERIA

A recent Canadian study compared the ILAR and PRINTO classification schemes and evaluated their alignment with each other and with adult arthritis classification systems as well as with recently defined clinicobiologic subtypes using 1228 patients from the ReACCh-OUT study [21]. With the exception of patients with systemic arthritis and RF-positive polyarthritis, which were categorized identically by both ILAR and PRINTO criteria, the two classification systems led to markedly divergent groupings. Only 60% of patients with ERA by ILAR classification were categorized into the corresponding PRINTO enthesitis/spondylitis-related JIA category. The new early-onset, ANA-positive JIA subtype outlined in the PRINTO criteria included predominantly children with oligoarthritis by ILAR classification, but also some patients with RF-negative polyarthritis, psoriatic arthritis, ERA, and undifferentiated arthritis. Homogeneity was identified among patients with early-onset, ANA-positive JIA with regard to sex and age, but

differences were recorded for the risk of uveitis in relation on their original ILAR category. A total of 12% of patients were unclassifiable using the ILAR criteria, whereas 63.3% were unclassifiable with PRINTO criteria. Patients with systemic arthritis and RF-positive polyarthritis in both ILAR and PRINTO classifications revealed good correspondence with adult-onset Still disease and seropositive RA, respectively. Patients with psoriatic arthritis from the ILAR groupings mapped well to their adult counterparts, but no equivalent groupings were seen in the PRINTO classification. In line with the notion that the early-onset, ANA positive JIA subtype is unique to children, this category did not have corresponding subtypes in the adult nomenclature. Overall, the ILAR classification was found to align better with adult arthritis than the PRINTO system, but neither of them corresponded satisfactorily to the clinicobiologic subgroups.

TOWARDS A BIOLOGIC CLASSIFICATION

The key relevance of biology is incorporated in the ILAR scheme, which adopts genetics (HLA-B27) and autoantibodies (RF) as classification criteria. The addition of anti-CCP antibodies and ANA in the PRINTO proposal goes along the same line. Approaches that take advantage of new opportunities in clinical and biological phenotyping promise to accelerate progress toward a more rational and precise classification of childhood arthritis. Integration of clinical information with biologic data, especially those yielded by genetic analyses and autoantibody determination, may potentially improve patient stratification and better address disease heterogeneity. It has been suggested that the discovery of distinct molecular signatures may enable identification of patient subgroups amenable to specific mechanism-based intervention [22]. A recent proof-of-concept study explored the value for patient stratification of combining biologic biomarkers (cytokine profiles) with clinical information [23]. Biologic and clinical data were integrated by means of computational technology for data-driven pattern recognition. Meaningful biologic and clinical characteristics defined axes/indicators that identified homogeneous patient subgroups by cluster analysis. Levels of circulating proinflammatory cytokines were found to account for most of the variability among patients. Standardized measures of disease activity and traditional demographic and laboratory features, including sex, hemoglobin, platelet count, and ANA, were the second most powerful differentiating parameters. The expanded dataset led to identify 5

unique subgroups of patients among those with non-systemic JIA. The patient categorization achieved with this methodology proved more capable than the ILAR system to capture major differences between patient subpopulations. Furthermore, the 5 clusters helped to resolve some heterogeneity and disclosed existing homogeneity within ILAR subgroups.

CONCLUSIONS

A precise classification of childhood arthritis is fundamental to drive proper pathogenetic studies and to foster the design of more rational and personalized treatment strategies. Despite two revisions, the ILAR criteria have failed to address the concerns raised about the heterogeneity of some disease categories. Furthermore, they have proved unable to distinguish the forms of childhood arthritis that are unique to the pediatric age group from those that are the same as those seen in adults. In this respect, well-established criteria would facilitate the transition of pediatric patients who enter the late adolescence/early adulthood to the care of adult rheumatologists, who are used to diagnose the majority of their patients with inflammatory arthritis as seronegative or seropositive RA, and may find it difficult to understand the complex categorization of childhood arthritides into six mutually exclusive categories, plus the category of undifferentiated arthritis. It has been conjectured that if certain forms of childhood arthritis were recognized to extend across the age spectrum, then pediatric studies could restrict their focus to pharmacokinetics, pharmacodynamics, and safety, considerably accelerating drug approval for children [24]. The analysis of the clinical and biologic data that are being collected by PRINTO is eagerly awaited with the hope that its results will delineate new homogeneous disease entities and lead to formulate a novel data-driven classification.

Looking at the future, the recent advance in biotechnology, especially genomics, proteomics and transcriptomics, offers the opportunity to characterize more in depth the biologic mechanisms underlying the pathophysiology of JIA [22, 25,26]. The scrutiny of the huge amount of data that will be yielded by the application of the novel research methodologies with the aid of computational approaches based on artificial intelligence and unsupervised machine learning hold the promise to enable adequately powered analyses and to identify appropriate clusters of patients that inform a biology-based and data-driven classification system. A challenging goal is the discrimination between apparently homogeneous clinical phenotypes

that are related to different etiologic factors from those that are truly similar and whose recognition may greatly facilitate downstream mechanistic studies [22]. Future investigations must also consider the global implications of a revised classification system, which should address the observed and still unexplained variability in the prevalence of disease phenotypes, including frequency of uveitis and age at disease onset, among different geographic areas or ethnic groups [27].

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