Dunlop-Dottridge Lecture

What’s in a Name? That Which We Call JIA, by Any Other Name, Would It Still Be the Same Childhood Arthritis?

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ABSTRACT. Disease classification remains one of the great debates in rheumatology. The age-old question of being a lumper or a splitter is now complicated by the principles underlying precision health, where the aim is for a solution tailored to each individual, technically making every person unique and their own subgroup. Continuing debate swirls over classification and nomenclature in childhood arthritis. This article will provide an unapologetically Canadian lens to the debate and highlight discussions from the recent Dunlop-Dottridge Lectureship at the 2023 Canadian Rheumatology Association Annual Scientific Meeting.

Key Indexing Terms: disease classification, juvenile idiopathic arthritis

Disease classification: The great debate

Classification matters for clinicians and families alike. In the clinic, good classifiers that bring together similar patients may also be good predictors of treatment response and clinical course. A common nomenclature is also required for care-advancing research, where an apples-to-apples comparison is needed between studies and countries. Classification matters not only for treatment but also for access to medications, as the gateway to the approval of new medications are randomized controlled trials on a named patient population. When the names and definitions of that population are in debate, so too is access to medications.

Childhood arthritis: The classification journey

Current classification systems are pragmatic and based mainly on clinical phenotype, which makes sense at the bedside. Phenotypic features used to group patients include age, with 16 years being an arbitrary cut-off between childhood arthritis (juvenile idiopathic arthritis [JIA]) and adult forms of arthritis, and site of inflammation (arthritis vs enthesitis). Basic biologic factors have also been included into current classification schemes with recognized contributors to disease pathogenesis, such as common genetic origins (presence or absence of HLA-B27), innate vs adaptive arms of the immune system (autoinflammatory systemic JIA), and presence or absence of autoantibodies (rheumatoid factor [RF]−positive vs RF-negative polyarthritis).

The original description by Still in 1897, of the disease that bears his name, was one of the first reports of childhood arthritis. In the 1950s, Ansell and Bywaters introduced the age boundary of 16 years to distinguish childhood arthritis from adult forms of the disease. This was followed in the 1970s by parallel but discordant approaches to nomenclature from the different sides of the Atlantic Ocean. The juvenile rheumatoid arthritis (JRA) nomenclature was originated from the American Rheumatism Association, now the American College of Rheumatology (ACR), which is in contrast to the juvenile chronic arthritis (JCA) nomenclature used by the European League Against Rheumatism (EULAR; formerly the European League Against Rheumatism). The ACR JRA classification used a cut-off of 4 affected joints to divide children into pauciarticular (≤ 4 joints) and polyarticular (> 5 joints), and those with systemic arthritis who had fever. The JCA nomenclature proposed by EULAR included 6 subgroups, recognizing 3 additional subgroups with juvenile forms of adult rheumatic disease, including JRA, juvenile psoriatic arthritis (PsA), and juvenile ankylosing spondylitis.

With recognition of the spondylitis subgroup of patients outside of both terminologies with very early onset, a new subgroup termed seronegative enthesopathy and arthropathy was coined in 1982. This potpourri of naming conventions was a big obstacle to worldwide collaborations and advancing knowledge in childhood arthritis. The International League of Associations for Rheumatology (ILAR; formerly the International League Against Rheumatism), brought together the 2 sides of the Atlantic together in 1997 in an attempt to unify the nomenclature and definitions. Canada figures prominently on the classification journey for childhood arthritis and the coining of the first worldwide terminology for childhood arthritis—JIA. This effort brought together key experts from around the world and resulted in the current ILAR terminology of JIA as an umbrella term for children with arthritis that is still in use today.

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The ILAR classification

ILAR criteria stratify patients into 7 mutually exclusive categories: systemic arthritis (systemic JIA [sJIA]), oligoarthritis, RF-negative polyarthritis, RF-positive polyarthritis, PsA, enthesitis-related arthritis (ERA), and undifferentiated arthritis. Figure 1 illustrates the current subgroups within the ILAR classification and the distributions seen in the clinical setting. This clinical phenotype-based classification system recognizes a number of distinguishing characteristics between subgroups, including the presence of extraarticular features, arthritis vs enthesitis, the number of affected joints (polyarthritis vs oligoarthritis), family history, and biologic measures, including the presence/absence of autoantibodies (RF) and HLA-B27. These broad classification features are mirrored in the adult classification systems, with the critical granular details remaining different. All this is layered onto the age boundary of 16 years between childhood and adult arthritis nomenclature.

The role of age

There are some interesting observations about the epidemiology of childhood arthritis. Starting with age of onset of disease, it is clear that age of onset under 1 year of age is extremely rare. Interestingly, the patterns are also different for those with sJIA compared to those with all other types of JIA (Figure 2). For those with non-sJIA subtypes, there is a peak in very young children between 1 and 4 years of age and a second peak in adolescence. Most patients in the early-onset age group have an oligoarticular phenotype, are commonly antinuclear antibody (ANA) positive, and are at the highest risk of chronic anterior uveitis. This group seems to be unique to childhood, with no correlates in adults. The other subtypes of JIA have loose correlates in adults. The pattern of sJIA is distinct, with the age of onset after the first year equally distributed throughout childhood. The cut-off of 16 years for the JIA classification bookends the top of the age spectrum but can be seen as an arbitrary cut-off, never meant to imply a fundamental difference between childhood and adult arthritis.

Patterns of Joint Involvement

Joint inflammation is the common underlying feature in JIA. In the ILAR classification, the number of affected joints determine disease classification, with the empirical cut-off set at...
4 joints—oligoarthritis with 4 or fewer joints and polyarthritis with more than 4 joints. Clinicians recognize patterns of joint involvement at the bedside, but the ILAR classification systems do not use these patterns.

We used data from a Canada-wide inception cohort of children with new-onset JIA. Data were systematically collected from the Research in Arthritis in Canadian Children, Emphasizing Outcomes (ReACCh-Out) study, that rigorously collected detailed longitudinal clinical data over 5 years, including information on joint inflammation captured on a standard 71-joint homunculus. In this study, we pursued a data-driven strategy, using machine learning to identify measurable clinical variables (ie, joint pattern and degree of localization) in children with newly diagnosed JIA. To characterize hierarchical patterns of joint co-involvements, we applied various machine learning algorithms to identify groups of frequently co-involved joints. We classified each patient into 1 of 7 groups corresponding to their joint involvements—those with predominant pelvic girdle, fingers, wrists, toes, ankles, knees, sternoclavicular joints, and an indistinct pattern (Figure 3). Overall, these patient groups corresponded to clinically meaningful patterns recognized at the bedside and described clinically meaningful subgroups within the ILAR subtypes. For example, children with the pelvic girdle pattern were associated with ERA, those with finger involvement with RF-negative polyarthritis, and those with predominant knee involvement with oligoarthritis. Strikingly, patients remained within their joint pattern grouping throughout the first 5 years of their disease course, regardless of medication use, supporting the stability and validity of this classification approach.

Additionally, those who looked most like their pattern stayed in their pattern. We divided patients up based on how much they look like their assigned patterns of joint involvement. Importantly, from a clinical standpoint, the less recognizable the pattern of joint involvement is, the worse outcomes a patient tends to have. Despite receiving more intense treatment, patterns with nonlocalized joint involvement had significantly slower times to remission. Patients with recognizable patterns respond to treatment but those who do not fit nicely into a category are at the highest risk of not going into clinical remission. Doctors recognize patterns and can treat patterns well, but not when patients do not fit those patterns—reinforcing the importance of pattern recognition at the bedside.

**Expanded role of biology**

Joint inflammation is the common feature underlying JIA. The key role of biology is recognized and included in the ILAR nomenclature, which includes genetics (HLA-B27) and autoantibodies (RF) as classification criteria. Advancements in biotechnology, specifically in genomics, has provided the opportunity to move beyond basic laboratory measures to more deeply characterize the biologic response underlying JIA. The increase in number of data points and data fields has been exponential and increased from the hundreds to the millions, necessitating the aid of computational approaches for pattern recognition.

![Figure 3. Patterns of joint distributions in JIA. Reprinted from Eng et al. JIA: juvenile idiopathic arthritis.](www.jrheum.org)
Unsupervised machine learning allows a hypothesis-free approach to let the data drive pattern recognition to inform the clustering/classification system. In a proof-of-concept study, our team included biologic data (cytokine profiles) with clinical data to aid in patient stratification.13 Interestingly, the most significant patterns, accounting for the most variability among patients, were levels of circulating proinflammatory cytokines. This was followed by standardized measures of disease activity and traditional demographic and laboratory features, including sex, hemoglobin, platelet count, and ANA, all of which are known key differentiating features in JIA. This expanded dataset was able to identify 5 unique subgroups of patients among those with non-sJIA. The resulting patient classifications had an enhanced ability to resolve major differences between patient subpopulations compared to the current ILAR subtypes. These 5 clusters support clinical observations, such as some children with oligoarthritis behave like those with RF-negative polyarthritis and others like PsA, and vice versa.12 There remained significant heterogeneity between as well as within ILAR subtypes when expanded biologic measures were included. The ILAR classification was a good starting point for grouping patients with similar phenotypes and has always been recognized as provisional; efforts continue to identify homogeneous patient groupings and improve classification schemes.

In most cases, the clinical measures of disease activity and biologic measures of inflammation were directly correlated among the subgroups; however, it is striking that for children in 2 of the subgroups, the clinical and biologic measures are discordant, with clinically well-looking children expressing extremely high levels of proinflammatory cytokines. These children had increased measures of disease activity at follow-up compared to at the time of diagnosis, indicating poor response to therapy and poor clinical outcomes. Integrating biologic and clinical information may have the greatest effect on these subgroups of children with subclinical disease activity, where expanded biologic measures may improve clinical decision making.

The proposed PRINTO classification

The Pediatric Rheumatology International Trials Organization (PRINTO) proposed a revision of the ILAR criteria.13 Like the ILAR criteria, the provisional PRINTO classification was developed through expert consensus and considers clinical information together with basic laboratory and imaging data. The initiative aimed to harmonize conditions across the age spectrum and to distinguish conditions limited to children. Currently, 4 PRINTO JIA subgroups are defined: 3 with proposed adult counterparts (systemic, RF-positive, and enthesitis/spondylitis-related [E/SpR] JIA) and 1 unique to the pediatric population (early-onset ANA-positive [EOANA] JIA). Two additional categories for unclassifiable patients are included: other JIA, for those who do not fit any defined category, and unclassified JIA, for those who fit 2 or more defined categories.13

We evaluated the ILAR and PRINTO classification schemes, compared their alignment with each other and with adult arthritis classification systems, and expanded biologically based classification systems14 using over 1200 patients from the ReACCh-OUT study.10 The 2 classification systems resulted in significantly different groupings with 2 exceptions. All patients with systemic arthritis and RF-positive polyarthritis were categorized identically by both the ILAR and PRINTO criteria. Approximately 60% of patients with ERA from the ILAR schema were categorized into the corresponding E/SpR JIA category from the PRINTO schema. The patients assigned to the new EOANA JIA subtype included mainly children with oligoarthritis from the ILAR classification, together with some with RF-negative polyarthritis, PsA, ERA, and undifferentiated arthritis. We identified homogeneity with respect to sex and age of onset among patients with EOANA JIA, but differences remained for the risk of uveitis depending on the original ILAR category. One major concern with the PRINTO proposal was that most patients in the remaining ILAR categories mapped to other JIA, with two-thirds of all patients with JIA unable to be classified under the 4 PRINTO disorders.14

We also evaluated alignment with adult classification schemes. Consistent with the alignment between the ILAR and PRINTO nomenclature, patients with systemic arthritis and RF-positive polyarthritis in both the ILAR and PRINTO classifications mapped nicely to adult-onset Still disease and seropositive rheumatoid arthritis, respectively. Those with PsA from the ILAR groupings mapped nicely to their adult counterparts, but no equivalent groupings were found in the PRINTO classification. Of note, the oligoarthritis ILA subtype and the EOANA JIA PRINTO subtype did not have corresponding subtypes in the adult nomenclature, nor did they align well with any of the expanded biologically based subtypes. As they currently stand, the ILAR system appears to align better with adult arthritis than the PRINTO system,14 but none align well with the expanded biologically based subgroups.

The power of collaboration

As we move to the next chapter and include pathobiology considerations in the next generation of classification schemes, it is clear that like other rare diseases, understanding the family of rare diseases that comprise childhood arthritis will require collaborations. Research networks have been formed across the globe to integrate biology into nomenclature as a starting point toward precision medicine. The Understanding Childhood Arthritis Network (UCAN) is a federation of research networks focused on translational research in childhood arthritis. This Canadian-led effort brings together over 50 countries into a hub-and-spoke model with core centers in Utrecht, Netherlands; Toronto, Canada; and Singapore. Harmonization and standardization are the backbone of the UCAN network, with personalized medicine research projects building on that core foundation. Some of the lessons learned from UCAN include the need to establish minimal core clinical datasets; biologic standard operating protocols to address preanalytical variability in biospecimens; interlaboratory and cross platform validation of techniques and machines; international cohorts and collaborations for discovery and validation of research findings; fair and inclusive participation in our teams and patient cohorts, including equity, diversity and inclusion principles;
and partnerships with our patients, families, industry, and policymakers to share knowledge and transform care.

Similarly, in the United Kingdom, the CLUSTER consortium was formed to bring together established cohorts of children with JIA to enable biomarker-based stratification of patients. In 2016, CLUSTER and UCAN together with PRINTO and the Childhood Arthritis and Rheumatology Research Alliance (CARRA) agreed on a set of principles for collaboration in childhood arthritis. Coining the “London Declaration,” these signatories agreed that we should move forward in a new era of international collaboration and with collaborations as the norm, not the exception, when studying JIA and other rare rheumatic diseases.

Perfect storm of opportunities for the future
There is a merging of opportunities for precision medicine, with rapid advances in machine learning and genomic medicine coupled with a tide of goodwill and international collaborations. The early data showing that biologically based patient groupings are clinically meaningful and provide helpful clues to pathobiology and rationale to guide therapy show promise for the future. As we work together and agree on harmonized approaches to data capture and data generation, this will also apply to naming conventions. These all have practical implications for drug approval and access. Starting with disease names and classifications, now is the time to work together as rheumatologists across the entire age continuum to provide seamless care for our patients.

REFERENCES