Dunlop-Dottridge Lecture: The Evolution of JIA

By Rae S. M. Yeung, MD, PhD, FRCPC

The Great Debate is a long-standing highlight of the Canadian Rheumatology Association Annual Scientific Meeting. This year, the debate extended to the Dunlop-Dottridge Lecture, where the topic was the continuing evolution of classification and nomenclature of juvenile idiopathic arthritis (JIA). Good classifiers bring together similar patients in the clinic and for research, where appropriate comparisons are needed between studies and countries, to improve treatment and access to medications. Current classification systems for childhood arthritis are based mainly on clinical phenotype, with a move to incorporate more biology into future disease taxonomies. Features used to currently categorize patients include age (above and below 16 years) and site of inflammation (arthritis versus enthesitis). Basic laboratory findings include genetic underpinnings of disease (HLA-B27), innate versus adaptive arms of the immune system (systemic JIA versus non-systemic JIA), and presence or absence of autoantibodies (rheumatoid factor [RF]). Canada has a storied history in this debate, and the Lectureship showcased Canadian contributions to this journey.

The early descriptions of childhood arthritis were made in the late 1800s by Sir George Frederic Still. The 1970s introduced the great divide, with simultaneous but conflicting approaches to nomenclature from the different sides of the Atlantic. The juvenile rheumatoid arthritis (JRA) nomenclature originated from the precursor of the American College of Rheumatology (ACR), which was in contrast to the Juvenile Chronic Arthritis (JCA) nomenclature used by the European League Against Rheumatism (EULAR). The American JRA classification had 3 subgroups and used the number of affected joints as a cut-off to divide children into pauciarthritis (≤ 4 joints) and polyarthritis (≥ 5 joints) and those with systemic arthritis who had fever. The JCA nomenclature proposed by the Europeans included 6 subgroups, with an additional 3 subgroups corresponding to childhood forms of adult rheumatic disease — juvenile rheumatoid arthritis, juvenile psoriatic arthritis and juvenile ankylosing spondylitis. The International League Against Rheumatism (ILAR), brought the players together in 1997 to unify the nomenclature. Canadians played a prominent role in the efforts at consensus building, resulting in the current JIA terminology. The ILAR criteria stratify patients into seven mutually exclusive categories: systemic arthritis (sJIA), oligoarthritis, RF-negative polyarthritis, RF-positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis, with an age boundary of 16 years between childhood and adult arthritis nomenclature.

Dr. Rae S. M. Yeung provided the Dunlop-Dottridge Lecture on the evolution of JIA at the CRA ASM in February 2023 in Quebec City.

The great debate continues today, with recent proposals by the Pediatric Rheumatology International Trials Organization (PRINTO) to develop a new classification schema. Four PRINTO JIA subgroups are defined: three with adult counterparts (systemic, RF-positive, and enthesitis/spondylitis-related JIA), and one unique to the pediatric population (early-onset antinuclear antibody-positive JIA). Two additional categories for unclassifiable patients are included: Other JIA and Unclassified JIA. Using a Canada-wide inception cohort of children with new onset JIA (ReACCH-OUT study), we evaluated the ILAR and PRINTO classification schemes and compared their alignment with each other. Unfortunately, the two classification systems resulted in significantly different groupings with only two exceptions — those with sJIA and RF+ polyarthritis. Of note, two-thirds of all patients with JIA were not able to be classified under the four PRINTO subgroups.

Advancements in genomics have provided the opportunity to integrate biology and clinical phenotype in classification. The dramatic increase in the number of data points has necessitated the use of machine learning and artificial intelligence approaches for pattern recognition, allowing big data to inform the classification system. Using a computational biology approach, we identified 5 unique subgroups of patients among children with JIA (excluding sJIA). The resulting patient taxonomy was able to resolve differences

between patient subgroups better when compared to current ILAR and PRINTO nomenclature. In most subgroups, the clinical and biologic measures of disease activity and inflammation were directly correlated. But importantly, in two subgroups, clinically well-looking children had extremely high levels of pro-inflammatory cytokines. These subgroups of children with subclinical disease activity had a worrisome disease trajectory, with increased disease activity at follow-up, pointing to the contribution of expanded biologic measures to improve the identification of children at high risk for poor outcomes.

Research networks have been formed across the globe to integrate biology into classification schemes towards this promise of precision medicine. The Canadian-led Understanding Childhood Arthritis Network (UCAN) was formed for this purpose, as were other research consortia around the globe. These groups together with others in the international pediatric rheumatology research community agreed to a set of principles for collaboration in childhood arthritis culminating in the 2016 "London Declaration" — recognizing collaborations as the norm, not the exception, when studying JIA. The future is now, for this perfect storm of opportunities to change the tone of the great classification debate.

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AWARDS, APPOINTMENTS, ACCOLADES

Dr. Sean Hamilton – *CRA Master Award*

I am humbled to receive a 2023 CRA Master Award and wish to thank the CRA and my local rheumatology peers in Newfoundland and Labrador (NL) for their nomination. It is my assumption this award recognizes my clinical contribution to the people of NL, and my educational contribution to the medical students and postgraduate medical trainees of Memorial University of Newfoundland and Labrador.

I'll be retiring in June 2023 after thirty-six years in practice, and as I now pass the torch to my younger colleagues, the demographics dictate that there is much more to accomplish in rheumatic health care delivery in our province. The median age in NL in 1987 — the year I began practice — was 28 years, making us the youngest province in Canada, and as I leave in 2023, that median age is 48 — the oldest province in Canada. The total population is unchanged; the number of rheumatologists is the same.

I leave with confidence in the next generation, and locally I am witnessing strong leadership for the path forward.

To the Rheumatology Community, I wish you well.