A Family History of Psoriasis in a First-degree Relative in Children with JIA: to Include or Exclude?

Mercedes O. Chan, Ross E. Petty, and Jaime Guzman, for the ReACCh-Out Investigators

ABSTRACT. ***Objective.*** To determine the consequences of disregarding first-degree relatives with psoriasis (FRP) as a classification criterion in juvenile idiopathic arthritis (JIA).

Methods. Criteria were examined in children from a prospective cohort with unclassified and psoriatic JIA.

Results. FRP was the most common reason children were unclassified (57/85, 67%); all 57 children could be classified if FRP were disregarded as an exclusion criterion. FRP was a necessary inclusion criterion to classify 11/77 (14.3%) children with psoriatic JIA.

Conclusion. Eliminating FRP as an exclusion criterion, but keeping it as an inclusion criterion in psoriatic JIA simplifies classification, though it is unclear whether the resulting classification would be better. (First Release March 15 2016; J Rheumatol 2016;43:944–7; doi:10.3899/jrheum.150555)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS JUVENILE PSORIATIC ARTHRITIS
CLASSIFICATION PSORIASIS UNDIFFERENTIATED JUVENILE IDIOPATHIC ARTHRITIS

The International League of Associations for Rheumatology (ILAR) classification criteria for juvenile idiopathic arthritis (JIA) uses inclusion and exclusion criteria to define 6 homogeneous categories[1]. Children who cannot be classified into 1 defined category are classified as having "undifferentiated" JIA (UJIA). Using original ILAR criteria[2], UJIA could account for up to 30% of all patients with JIA[3]. The most common reason for this is having as an exclusion criterion a first- or second-degree relative with psoriasis[4]. Following recommendations by Berntson, *et al*[4], the criterion of having a second-degree relative with psoriasis was removed[1]. Thus, current ILAR criteria cite having a first-degree relative as an exclusion criterion for all JIA categories, except juvenile psoriatic arthritis (JPsA).

JPsA classification requires the presence of arthritis and psoriasis, or arthritis and 2 of 3 minor criteria: nail pits or onycholysis; dactylitis; or a first-degree relative with psoriasis (FRP)[1]. In contrast, the adult-oriented ClASsification for Psoriatic ARthritis (CASPAR) criteria classify PsA based on inflammatory articular disease (joint, spine, entheseal) with at least 3 of the following: psoriatic nail changes, dactylitis, rheumatoid factor (RF) negativity, radiographic changes of PsA in the hands and feet, and psoriasis or a family history (FH) of psoriasis up to the second degree[5].

Using the current ILAR criteria, up to 20% of children with JIA may be classified as having UJIA[6,7]. A common reason for this continues to be the exclusion criterion of an FRP[8]. In a single-center pilot study by Chan, *et al*[9] an FRP contributed to the classification of half of patients with UJIA. When this criterion was disregarded, 12 out of 21 patients with UJIA could be classified in a defined category. Further, disregarding this criterion did not affect the classification of children with JPsA. Our current study aimed to confirm these observations in a large multicenter cohort of Canadian children with JIA.

MATERIALS AND METHODS

We retrieved data on all children classified as UJIA or JPsA in the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) cohort. ReACCh-Out recruited 1497 children with JIA diagnosed between 2005 and 2010 at 16 Canadian centers. Data retrieved included basic demographics, history, physical examination, and laboratory features relevant to ILAR classification criteria available at enrollment and the 6-month followup visits.

In the ReACCh-Out study, ILAR category classifications were initially assigned by the attending rheumatologists and were reviewed by ReACCh principal investigators. However, because criteria signs and symptoms were not always identified owing to their absence at the time of study visits, the JIA category assigned by the attending rheumatologist was accepted in most apparently equivocal cases. For our present study, the first selection step was a diagnosis of UJIA or JPsA in the ReACCh dataset. Criteria data at the enrollment and 6-month study visits were reviewed and diagnoses were validated based only on the recorded information by 2 pediatric rheumatologists (RP and MC), with discrepancies resolved by consensus. Children

From the Division of Pediatric Rheumatology, Department of Pediatrics, BC Children's Hospital, Vancouver, British Columbia, Canada.

Data used in this research were collected in the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) study, funded by the Canadian Institutes of Health Research.

M.O. Chan, MBBS, MHPE, FRCPC, Assistant Professor, Division of Pediatric Rheumatology, Department of Pediatrics, University of Alberta; R.E. Petty, CM, MD, PhD, FRCPC, FAAP, Professor Emeritus, Division of Pediatric Rheumatology, Department of Pediatrics, BC Children's Hospital; J. Guzman, MD, MSc, FRCPC, Clinical Associate Professor, Division of Pediatric Rheumatology, Department of Pediatrics, BC Children's Hospital.

Address correspondence to Dr. M.O. Chan, Edmonton Clinic Health Academy, 3-505, 11405 87 Ave. NW, Edmonton, Alberta T6G 1C9, Canada. E-mail: mercedes.chan@ualberta.ca

Accepted for publication January 6, 2016.

with a validated diagnosis of UJIA or JPsA were included in the analysis. Individual criteria classifying UJIA and JPsA patients were further analyzed. These children were then re-classified after disregarding the criterion of having an FRP.

RESULTS

There were 144 patients classified as having UJIA and 99 as having JPsA in the ReACCh-Out database. After review and discussion of all available data pertinent to ILAR criteria at the enrollment and 6-month visits, it was agreed to include 162 subjects. Patients were excluded because data available at enrollment and 6-month visits were insufficient to validate their classification as UJIA (n = 59) or JPsA (n = 22).

Eighty-five patients (51 females) had a validated classification of UJIA (Table 1). Reasons for classifying patients as UJIA were an FRP (57/85, 67%); RF positivity (18/85, 21%, 17 had only 1 positive test); HLA-B27 positivity in a male with onset of arthritis after the 6th birthday (4/85, 5%); HLA-B27–related conditions in a first-degree relative (4/85, 5%); and fulfilling criteria for 2 categories (2/85, 2%). If the exclusion criterion of an FRP were disregarded, 57 children would be reclassified as follows: 25 oligoarticular JIA, 13 polyarticular RF-negative JIA, 5 polyarticular RF-positive JIA, 12 enthesitis-related arthritis (ERA), and 2 systemic JIA.

Seventy-seven patients had a validated classification of JPsA, of whom 32/77 (42%) had an FRP. When this history was disregarded, 66/77 (86%) still fulfilled criteria for JPsA. Of the remaining 11 patients, 8 could be classified as polyarticular RF-negative (5 females, median age 2.6 yrs), and 3 as oligoarticular (all females, median age 10.5 yrs; Table 2). Eight of these 11 patients had dactylitis and 3 had nail pits. None had both dactylitis and nail pits.

DISCUSSION

Our study confirms the observation that an FRP is the most common reason for classifying children as having UJIA. Disregarding this exclusion criterion allowed 67% of patients with UJIA to be classified in defined categories of JIA. Our study did not confirm our previous findings suggesting that classification of JPsA would not be affected by disregarding FRP as an inclusion criterion. In 11 of 77 (14%) of our patients with JPsA, an FRP was critical to that classification. Removing FRP as an inclusion criterion would result in some children currently classified as JPsA being reclassified as oligoarticular or polyarticular RF-negative JIA, although many had dactylitis, an uncommon feature for these 2 groups. The median age of onset (2.6 yrs) of the patients reclassified as polyarticular RF-negative is also younger than usual for that JIA category. This suggests there is value in preserving the inclusion criterion of an FRP in classifying JPsA[4].

Skepticism remains as to whether an FH of psoriasis, unless diagnosed by a medical professional, is reliably reported, and has been a point of debate[4,10,11]. Removing FRP as an exclusion criterion may allow for more appropriate classification of children who may otherwise have a typical course of oligo-, poly-, or systemic JIA[12].

Removing FRP as an inclusion criterion for JPsA posits whether arthritis combined with dactylitis or nail changes is significant enough for classification as JPsA[13], as in the CASPAR criteria[5,14]. Three of the 85 patients with UJIA met CASPAR criteria for PsA: 1 ERA patient with an FRP and 2 patients who fulfilled criteria for ERA and JPsA. The predictive value of dactylitis and nail pits for future development of full-blown JPsA is unknown, although in younger children these may be present before frank skin disease develops[15]. In the CASPAR criteria, they have equal weight as supporting features of PsA[5]. Psoriasis can precede or follow the onset of arthritis within 15 years[16]. It is also possible that the skin disease may be absent or delayed when being treated with antirheumatic drugs.

If one removes FRP as an exclusion criterion and maintains it as an inclusion criterion in JPsA, there would still be difficult cases to classify. For example, a child with 2 swollen joints, an FRP, and nail pits would fulfill criteria for both oligoJIA and JPsA and thus would be unclassified. A child with 2 swollen joints, dactylitis, and nail pits but no

Table 1. Reclassification of children with UJIA.

Exclusion criteria contributing to classification of children with UJIA							
	First-degree relative with psoriasis, n = 57	B27+ male > 6 yrs + arthritis, n = 4	RF+ on 2 occasions, n = 1	RF+ on 1 occasion only, n = 17	First-degree relative with B27-related disease, n = 4	Systemic JIA, n = 0	Fulfills criteria for 2 categories, n = 2
Revised category if exclusion criterion excluded							
OligoJIA	25			9	2		
Poly RF–	13				2		
Poly RF+	5 (1RF+ × 2, 4RF+ × 1)						
ERA	12			5			
Systemic	2			1			
JPsA		4		1			
UJIA			1	1			2 (JPsA + ERA)

OligoJIA: oligoarticular juvenile idiopathic arthritis; poly RF–: polyarticular rheumatoid factor–negative JIA; poly RF+: polyarticular rheumatoid factor–positive juvenile idiopathic arthritis; ERA: enthesitis-related arthritis; JPsA: juvenile psoriatic arthritis; UJIA: undifferentiated JIA.

Table 2. Characteristics of patients with psoriatic juvenile idiopathic arthritis (JIA) who would be classified as polyarticular or oligoarticular JIA if the inclusion criterion of psoriasis in a first-degree relative was disregarded.

		Characteristic	
Age, yrs	Sex	At Diagnosis	At 6 Months
Polyarticular, n = 8			
1.6	F	No. active joints: 15 Dactylitis: 1	No active joints recorded Dactylitis: 5
0.8	F	No. active joints: 14 Dactylitis: 3	No. active joints: 1 Dactylitis: 1
2.6	F	No. active joints: 7 Dactylitis: 1	No. active joints:1 Dactylitis: not recorded
4.2	F	No. active joints: 14 Dactylitis: 3	No. active joints: 5 Dactylitis: not recorded
0.3	M	No. active joints: 15 Dactylitis: 2	No. active joints: 1 Dactylitis: not recorded
8.5	F	No. active joints: 10 Sacroiliitis Nail pits	Nothing recorded
2.8	M	No. active joints: 6 Nail pits	No. active joints: 2 Nail pits: not recorded
2.4	M	No. active joints: 5 Dactylitis: 1	Nothing recorded
Oligoarticular, n = 3			
11.1	F	No. active joints: 2 Dactylitis: 1	Nothing recorded
7.7	F	No. active joints: 3 Dactylitis: 1	Nothing recorded
10.5	F	No. active joints: 1 Sacroiliitis Nail pits	Nothing recorded

FRP would also be unclassified. Using a hierarchical system of classification as per Manners, *et al*[11] may help avoid these situations.

Removing FRP as an exclusion criterion may also result in some children initially categorized in a defined category of JIA being later reclassified as JPsA if they develop psoriasis. Evolution of disease is a reality in rheumatology. Nordal, *et al*[7] showed that 10.8% of patients with JIA in a Nordic cohort changed ILAR categories when followed for at least 7 years after disease onset. The reasons for change were emerging clinical findings such as onset of enthesitis, sacroiliitis, acute uveitis, or psoriasis, or new information about these conditions in a first-degree relative of the patient. The percentage of children with JPsA increased from 1.4% to 3.2%[7].

In our current study, 17 children were labeled as having UJIA because of a single positive RF test. ILAR criteria require 2 positive RF tests performed at least 3 months apart as an exclusion criterion in all subtypes of JIA with the exception of polyarticular RF-positive disease, where it is a major inclusion criterion[1]. Without a second confirmatory RF test, it is impossible to know whether the test was falsely positive, as can occur in cases of concurrent or preceding infection[17]. In contrast, a single negative RF test as per ILAR criteria is interpreted as a true negative.

From their inception, it was anticipated that ILAR criteria would be modified based on new evidence. Proposed revisions include algorithmic exercises[11], categorization based on ANA status[18], and age at disease onset[19]. Ideally, a revised classification should be shown to be substantially improved before it is adopted and should correlate with disease course, response to treatment, and biological homogeneity, e.g., cytokine profiles and genetic signatures[20]. Our study suggests that eliminating FRP as an exclusion criterion but keeping it as an inclusion criterion in JPsA will reduce the number of unclassified subjects and simplify use of the ILAR criteria. Whether this would improve the overall classification remains unclear.

APPENDIX

List of study collaborators. ReACCh-Out investigators: Jaime Guzman, Kiem Oen, Adam M. Huber, Karen Watanabe Duffy, Gilles Boire, Natalie Shiff, Roberta A. Berard, Deborah M. Levy, Elizabeth Stringer, Rosie Scuccimarri, Kimberly Morishita, Nicole Johnson, David A. Cabral, Alan M. Rosenberg, Maggie Larché, Paul Dancey, Ross E. Petty, Ronald M. Laxer, Earl D. Silverman, Paivi Miettunen, Anne-Laure Chetaille, Elie Haddad, Kristin Houghton, Lynn Spiegel, Stuart E. Turvey, Heinrike Schmeling, Bianca Lang, Janet Ellsworth, Suzanne E. Ramsey, Alessandra Bruns, Johannes Roth, Sarah Campillo, Susanne Benseler, Gaëlle Chédeville, Rayfel Schneider, Shirley M.L. Tse, Roxana Bolaria, Katherine Gross, Brian Feldman, Debbie Feldman, Bonnie Cameron, Roman Jurencak, Jean Dorval, Claire LeBlanc, Claire St. Cyr, Michele Gibbon, Rae S.M. Yeung, Ciarán M. Duffy, and Lori B. Tucker.

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