Limitations in the Classification of Childhood-onset Rheumatoid Arthritis

Emily G. Ferrell, Lori A. Ponder, Lauren S. Minor, Sheila T. Angeles-Han, Christine W. Kennedy, Kelly A. Rouster-Stevens, Mina Rohani-Pichavant, Larry B. Vogler, and Sampath Prahalad

ABSTRACT. ***Objective.*** Rheumatoid factor-positive polyarthritis (RF+ poly) is the juvenile idiopathic arthritis (JIA) category that resembles adult seropositive rheumatoid arthritis (RA). We studied children with RF+ and/or anticyclic citrullinated peptide antibody (anti-CCP)+ JIA to determine what proportion of those children meet International League of Associations for Rheumatology (ILAR) criteria for RF+ poly JIA and to assess for significant differences between children who meet RF+ poly criteria and those who are classified in other categories.

Methods. Charts of children with JIA who were RF+ and/or anti-CCP+ were reviewed. Children with RF+ poly JIA were compared to children in other categories. Statistical analysis was performed using chi-square, Fisher's exact test, and the Student's t-test.

Results. Of 56 children with RF+ and/or anti-CCP+ JIA, 34 (61%) met ILAR criteria for RF+ poly JIA. Twelve children had RF–/anti-CCP+ JIA with low anti-CCP titers. When these 12 children were excluded, there were few significant differences between children who met criteria for RF+ poly and those who were classified in other categories. The American College of Rheumatology/European League Against Rheumatism criteria for RA identified more RF+ children than did the ILAR RF+ poly classification (100% vs 77%).

Conclusion. A number of children with RF+ arthritis were excluded from the RF+ poly JIA classification, though many demographic features and disease measures were similar to those of children who met criteria for RF+ poly JIA. We propose prioritization of RF/anti-CCP positivity over specific exclusions, along with inclusion of anti-CCP, in future revisions of the JIA classification criteria, to improve the sensitivity of diagnosing childhood-onset RA. (J Rheumatol First Release Feb 1 2014; doi:10.3899/jrheum.130563)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS RHEUMATOID FACTOR SEROLOGIC MARKERS
CYCLIC CITRULLINATED PEPTIDE RHEUMATOID ARTHRITIS

From the Department of Pediatrics, and the Department of Human Genetics, Emory University School of Medicine; Children's Healthcare of Atlanta, Atlanta, Georgia, USA.

Supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR-060893), the Arthritis Foundation, and the Marcus Foundation Inc.

E.G. Ferrell, MD, Emory University School of Medicine, current affiliation, Resident Physician, Seattle Children's Hospital, Seattle, Washington, USA; L.A. Ponder, BA, Children's Healthcare of Atlanta; L.S. Minor, MD, Resident Physician, Emory University School of Medicine; S.T. Angeles-Han, MD, MS, Assistant Professor, Department of Pediatrics, Emory University School of Medicine; C.W. Kennedy, NP, Department of Pediatrics, Emory University School of Medicine; K.A. Rouster-Stevens, MD, PharmD, Assistant Professor, Department of Pediatrics, Emory University School of Medicine; M. Rohani-Pichavant, MS, MBA, Department of Pediatrics, Emory University School of Medicine; L.B. Vogler, MD, Associate Professor, Department of Pediatrics, Emory University School of Medicine; S. Prahalad, MD, MSc, Marcus Professor and Chief of Division of Rheumatology, Department of Pediatrics and Department of Human Genetics, Emory University School of Medicine.

Address correspondence to Dr. S. Prahalad, Associate Professor of Pediatrics and Human Genetics, Emory University School of Medicine, 1760 Haygood Drive, W. 423, Atlanta, Georgia 30322, USA.
E-mail: sprahal@emory.edu

Accepted for publication November 12, 2013.

Juvenile idiopathic arthritis (JIA) refers to a heterogeneous group of chronic arthritides in children. The International League of Associations for Rheumatology (ILAR) criteria classify JIA accordingly: (1) systemic arthritis, (2) oligoarthritis (persistent and extended), (3) rheumatoid factor (RF)-positive polyarthritis, (4) RF-negative polyarthritis, (5) enthesitis-related arthritis (ERA), (6) psoriatic arthritis, and (7) undifferentiated arthritis[1].

Children with RF+ polyarthritis are 5% to 10% of all patients with JIA. Children in this category closely resemble adults with seropositive rheumatoid arthritis (RA): they tend to demonstrate the characteristic biomarkers of RA, are older at symptom onset, and have symmetric polyarthritis that is more likely to persist into and cause functional disability in adulthood[2,3,4,5,6]. Consequently, most children with RF+ polyarthritis are treated more aggressively than children in other categories.

In addition to having a positive RF, seropositive RA is characterized by the presence of antibodies to citrullinated peptide antigens, such as antibodies to cyclic citrullinated

peptide (CCP). These antibodies can be present years before clinical symptoms of RA appear, and they are associated with development of more severe RA[7]. Between 5% and 10% of children with JIA appear to have an early onset form of RA characterized by the presence of RF and/or anti-CCP antibodies. These children are serologically identical to adults with RA and can be considered to have childhood-onset RA.

Not all children with childhood-onset RA are identified by the ILAR classification for RF+ polyarthritis because anti-CCP is not part of the diagnostic criteria. Likewise, children can be excluded from this category secondary to (1) lack of 2 positive RF tests at least 3 months apart; (2) fewer than 5 active joints in the first 6 months of symptoms; (3) first-degree family history of ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease (IBD), Reiter's syndrome, or acute anterior uveitis; (4) psoriasis in a first-degree relative; and (5) being an HLA-B27+ male with onset of arthritis after age 6. In contrast, the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for diagnosing adult RA do not contain the exclusions seen in the ILAR classification scheme[8]. Further, unlike the ILAR criteria, they take anti-CCP antibodies into account. Thus, a child who has high titers of anti-CCP antibodies but negative RF tests could be definitively classified as having RA secondary to their anti-CCP status, but could be placed in any of the current ILAR classes except RF+ polyarthritis, which requires 2 positive RF tests.

The presence of anti-CCP has been linked to more severe joint disease, yet it is not routinely tested in all pediatric patients[9,10,11,12]. It is unknown whether there is a difference between children with positive anti-CCP antibodies who meet criteria for RF+ polyarthritis and those who are otherwise classified. It is also unclear whether children with childhood-onset RA have a uniform phenotype, or whether the children who are classified as RF+ polyarthritis have a distinct form of JIA compared to children who are RF+ but meet exclusion criteria, such as having oligoarthritis.

The objectives of our study were to investigate children with JIA who were RF+ and/or anti-CCP+ to determine what proportion meet ILAR criteria for RF+ polyarticular JIA and to assess for significant differences between children who meet criteria for RF+ polyarticular JIA and those who fall into other JIA categories.

MATERIALS AND METHODS

We included 62 children with JIA who had at least 1 positive anti-CCP test and/or at least 2 positive RF tests. All subjects were seen at the Pediatric Rheumatology Clinics at Emory Children's Center and enrolled in the South Eastern Registry of Childhood Arthritis Study. Our study was approved by the Institutional Review Board at Emory University, Atlanta, Georgia, USA, and all subjects gave informed consent.

Paper clinical charts, research questionnaires, and RF and anti-CCP laboratory results were reviewed for each patient, and the following data were collected: age at symptom onset, age at diagnosis, sex, ethnicity, race, radiograph results, use of systemic steroids, disease-modifying antirheumatic drugs (DMARD), and biologic agents, and laboratory values [RF, anti-CCP, antinuclear antibody (ANA), erythrocyte sedimentation rate, C-reactive protein (CRP)]. A JIA category was assigned to each child by the investigators based on the child's available data by using the ILAR classification criteria[1]. ILAR criteria for RF+ polyarticular JIA require 2 or more positive tests for RF at least 3 months apart during the first 6 months of disease; however, only 16 out of 45 children with more than 1 positive RF test met this strict requirement, so for the purposes of our study, a child was considered to be RF+ if he or she had at least 2 positive RF tests at least 3 months apart. Each child was also assigned a score of 0–10 using the 2010 ACR/EULAR criteria for diagnosis of RA, with a score of ≥ 6 classified as RA[8]. These criteria assign an individual score based on the number and size of joints involved, absence or degree of elevation of RF and/or anti-CCP, normal or elevated levels of acute-phase reactants, and duration of symptoms (Table 1).

Six children were excluded from analysis for the following reasons: 4 had symptom onset after age 16, thereby excluding them from the diagnosis of JIA; and 2 had insufficient records for classification. Of note, this study included a set of 3 sisters, all of whom were RF+/anti-CCP+ (2 had RF+ polyarticular JIA, 1 had undifferentiated JIA). We used standard reference ranges for anti-CCP antibody. Immunoglobulin G anti-CCP antibody titers were classified as negative < 20 EU; weak positive 20–39 EU; moderate/strong positive 40–59 EU; strong positive > 59 EU.

The children with RF+ polyarticular JIA were compared to the children who were RF+ and/or CCP+ who met criteria for other ILAR categories. Nominal variables were compared using chi-square or Fisher's exact test, and continuous variables were compared using Student's t test. Subgroup analysis was performed after excluding children who were RF–/anti-CCP+. P values < 0.05 were considered statistically significant.

Table 1. The 2010 ACR/EULAR criteria for diagnosis of rheumatoid arthritis (RA). A score ≥ 6 meets criteria for RA. Adapted from Aletaha D, *et al*. Arthritis Rheum 2010;62:2569–81.

Criteria	Score
Joint involvement	
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without large joints)	2
4–10 small joints (with or without large joints)	3
> 10 joints (at least 1 small joint)	5
Serology (≥ 1 test result needed for classification)*	
Negative RF and negative anti-CCP	0
Low-positive RF or low-positive anti-CCP	2
High-positive RF or high-positive anti-CCP	3
Acute-phase reactants (at least 1 test result needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

* Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN by ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are > 3 times the ULN for the laboratory and assay. Where RF information is only available as a positive or negative, a positive result should be scored as low-positive for RF. ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

RESULTS

Of the 56 children included in the study, 40 (71%) were RF+/anti-CCP+, 4 (7%) were RF+/anti-CCP–, and 12 (21%) were RF–/anti-CCP+. Children with RF+/anti-CCP+ JIA had higher anti-CCP titers than children who were RF–/anti-CCP+ (214 vs 29, $p < 0.001$) and had higher RF titers than children who were RF+/anti-CCP– (245 vs 107, $p = 0.09$). Of the 40 children with RF+/CCP+ JIA, 19 (48%) had been tested more than once for anti-CCP. Of the 12 children with RF–/CCP+ JIA, 6 (50%) had been tested more than once for anti-CCP; of those, 2 (33%) of the subsequent tests were negative. All children with at least 1 positive anti-CCP test were included in the analyses.

Only 34 of the 56 children (61%) met ILAR criteria for RF+ polyarticular JIA. Of those who did not meet criteria for RF+ polyarthritis, 6 (27%) had RF-negative polyarthritis, 2 (9%) had extended oligoarticular JIA, 4 (18%) had persistent oligoarticular JIA, and 10 (45%) had undifferentiated JIA. All children with undifferentiated JIA were RF+/anti-CCP+. Seven of the children (70%) classified as having undifferentiated JIA had presentations consistent with oligoarthritis (involvement of fewer than 5 joints in the first 6 mos), but were excluded from the oligoarthritis category because they had 2 positive RF tests. The other 3 children did not meet criteria for RF+ polyarthritis because 1 had a father with psoriasis, 1 was an HLA-B27+ male with symptom onset after age 6, and 1 had acute iritis.

Comparison of children who met ILAR criteria for RF+ polyarticular JIA to those who did not revealed that children with RF+ polyarticular JIA were significantly older at symptom onset and diagnosis and more likely to meet ACR/EULAR criteria for RA (Table 2). They also had significantly higher titers of anti-CCP antibodies and were more likely to have an elevated CRP within 3 months of diagnosis and a history of treatment with biologic agents. All other variables were not significantly different between the 2 groups.

Among the 22 children classified in a category other than RF+ polyarticular JIA, there was a distinct population of 12 children who were RF–/anti-CCP+. Six (50%) had RF–polyarthritis, 2 (17%) had extended oligoarthritis, and 4 (33%) had persistent oligoarthritis. Of these 12 children, 11

Table 2. Characteristics of children included in the study with RF and/or anti-CCP positive JIA based on ILAR classification. All values are n (%) of those tested/reporting data for particular variables, except as indicated.

	RF+ poly JIA, n (%)	All Other Categories, n (%)	p
Total no.	34	22	
Age at symptom onset, yrs, mean ± SD	10.3 ± 3.4	7.7 ± 4.3	0.023
Age at diagnosis, yrs, mean ± SD	11.3 ± 3.3	8.3 ± 4.6	0.012
Demographic features			
Female sex	29 (85)	15 (68)	0.13
Hispanic ethnicity	8 (25)	1 (5)	0.07
African ancestry	11 (37)	7 (32)	0.72
RF value, mean (range)	259.4 (11–1741)	44.7 (0–369)	0.019
Anti-CCP value, mean (range)	185.0 (0– >448)	118.6 (0– >250)	0.022
ILAR category			
RF+ poly	34 (100)	0 (0)	
RF– poly	0 (0)	6 (27)	
Oligo extended	0 (0)	2 (9)	
Oligo persistent	0 (0)	4 (18)	
Undifferentiated	0 (0)	10 (45)	
Positive ANA	12 (38)	11 (52)	0.29
Meets ACR criteria for RA	34 (100)	16 (73)	**0.002**
Number of affected joints in first 6 mo, mean (range)	13 (5–30)	10 (2–48)	0.38
Treatment			
Use of systemic steroids	21 (62)	8 (36)	0.06
Use of DMARD	32 (94)	18 (82)	0.20
Use of biologic	21 (62)	7 (32)	**0.029**
Elevated ESR within 3 mos of diagnosis	24 (71)	13 (65)	0.67
Elevated CRP within 3 mos of diagnosis	18 (86)	4 (36)	**0.013**

p values in boldface are statistically significant. Most common upper limit of normal for RF = 13.9. Most common interpretation of anti-CCP values: < 20 negative; 20–39 weak positive; 40–59 moderate/strong positive; > 59 strong positive. DMARD: methotrexate (oral or subcutaneous), plaquenil, sulfasalazine. Biologics: etanercept, adalimumab, anakinra, abatacept, infliximab. ACR: American College of Rheumatology; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ILAR: International League of Associations for Rheumatology; ANA: antinuclear antibody; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug.

had low titers of anti-CCP antibodies, and only 1 had a high-titer anti-CCP (greater than 3 times the upper limit of normal). There were a number of significant differences when these 12 children with RF–/anti-CCP+ JIA were compared to the children with RF+ JIA (Table 3). They were younger at symptom onset and diagnosis, had significantly lower anti-CCP titers, were less likely to have been treated with a DMARD or biologic agent, and fewer met ACR/EULAR criteria for RA.

A subgroup analysis was performed after excluding these 12 children with RF–/anti-CCP+ JIA, and the remaining 44 children were analyzed (Table 4). Thirty-four (77%) met ILAR criteria for RF+ polyarticular JIA and the same 10 children (23%) from the initial analysis were classified as undifferentiated. Analysis of demographics and disease characteristics revealed that compared to children with undifferentiated JIA, those with RF+ polyarticular JIA had significantly lower anti-CCP titers and were more likely to have an elevated CRP within 3 months of diagnosis. All other demographic and disease activity data were not significantly different between the 2 groups. Of the 44 patients who were RF-positive, 39 (89%) had high-titer RF values (high titer was defined by IU values > 3 times the upper limit of normal for the testing laboratory).

A significant proportion of children who were RF+ and/or anti-CCP+ met 2010 ACR/EULAR criteria for RA yet were not defined by the RF+ polyarthritis category in the ILAR criteria. Of the 56 children in our study, 50 (89%) met ACR/EULAR criteria for RA, whereas only 34 (61%) met ILAR criteria for RF+ polyarthritis. Forty-four (100%) of the RF+ children met criteria for RA using the ACR/EULAR criteria, while only 34 (77%) met ILAR criteria for RF+ polyarticular JIA. Of the children with RF–/anti-CCP+ JIA, 6 (50%) met ACR/EULAR criteria for RA, while 0 (0%) met ILAR criteria for RF+ polyarticular JIA.

Figure 1 displays our proposed classification. When applied to the children in our study, 40 (100%) of the children with RF+/CCP+ JIA were classified as having childhood-onset RA. Of the children with RF–/CCP+ JIA, 1 (8%) was classified as having childhood-onset RA, 6 (50%) were classified as having oligoarticular JIA, and 5 (42%)

Table 3. Comparison of children with RF+ JIA versus RF–/anti-CCP+ JIA. All values are n (%) of those tested/reporting data for particular variables, except as indicated.

	RF+, n (%)	RF–/anti-CCP+, n (%)	p
Total no.	44	12	
Age at symptom onset, yrs, mean ± SD	10.3 ± 3.3	5.7 ± 4.3	**0.004**
Age at diagnosis, yrs, mean ± SD	11.3 ± 3.2	6.0 ± 4.5	**0.002**
Demographic features			
Female	35 (80)	9 (75)	0.71
Hispanic ethnicity	9 (21)	0 (0)	0.18
African ancestry	14 (35)	4 (33)	1.00
Anti-CCP value, mean (range)	194.5 (0–> 448)	28.5 (0–81)	**< 0.0001**
RF value, mean (range)	222.3 (0–1741)	1.9 (0–14)	**< 0.0001**
ILAR category			
RF+ poly	34 (77)	0 (0)	
RF– poly	0 (0)	6 (50)	
Oligo extended	0 (0)	2 (17)	
Oligo persistent	0 (0)	4 (33)	
Undifferentiated	10 (23)	0 (0)	
Meets ACR criteria for RA	44 (100)	6 (50)	**< 0.001**
No. affected joints in first 6 mos, mean (range)	12 (2–30)	12 (1–48)	0.96
Treatment			
Use of systemic steroids	26 (59)	3 (25)	0.05
Use of DMARD	42 (95)	8 (67)	**0.01**
Use of biologic	27 (61)	1 (8)	**0.003**
Elevated ESR within 3 mos of diagnosis	30 (70)	7 (64)	0.72
Elevated CRP within 3 mos of diagnosis	20 (74)	2 (40)	0.29

p values in boldface are statistically significant. Most common upper limit of normal for RF = 13.9. Most common interpretation of anti-CCP values: < 20 negative; 20–39 weak positive; 40–59 moderate/strong positive; > 59 strong positive. DMARD: methotrexate (oral or subcutaneous), plaquenil, sulfasalazine. Biologics: etanercept, adalimumab, anakinra, abatacept, infliximab. ACR: American College of Rheumatology; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ILAR: International League of Associations for Rheumatology; ANA: antinuclear antibody; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug; JIA: juvenile idiopathic arthritis.

Table 4. Subgroup analysis of children with RF+ poly JIA compared to other categories. Data from children with RF-negative, anti-CCP positive JIA are excluded. All values are n (%) of those tested/reporting data for particular variables, except as indicated.

	RF+ poly JIA, n (%)	All other Categories, n (%)	p
Total number	34	10	
Age at symptom onset, yrs, mean ± SD	10.3 ± 3.4	10.2 ± 2.8	0.89
Age at diagnosis, yrs, mean ± SD	11.3 ± 3.3	11.1 ± 3.1	0.84
Demographic features			
Female	29 (85)	6 (60)	0.17
Hispanic ethnicity	8 (25)	1 (10)	0.32
African ancestry	11 (37)	3 (30)	1.00
Anti-CCP value, mean (range)	185.0 (24–> 448)	226.8 (> 60–> 250)	**0.04**
RF value, mean (range)	259.4 (11–> 448)	96.2 (0–346)	**0.004**
ILAR category			
RF+ poly	34 (100)	0	
RF– poly	0 (0)	0	
Oligo extended	0 (0)	0	
Oligo persistent	0 (0)	0	
Undifferentiated	0 (0)	10 (100)	
Meets ACR criteria for RA	34 (100)	10 (100)	1.00
Number of affected joints in first 6 mos, mean, (range)	13 (5–30)	8 (2–25)	0.14
Treatment			
Use of systemic steroids	21 (62)	5 (50)	0.51
Use of DMARD	32 (94)	10 (100)	1.00
Use of biologic	21 (62)	6 (60)	1.00
Elevated ESR within 3 mos of diagnosis	24 (71)	6 (67)	1.00
Elevated CRP within 3 mos of diagnosis	18 (86)	2 (33)	**0.02**

p values in boldface are statistically significant. Most common upper limit of normal for RF = 13.9. Most common interpretation of anti-CCP values: < 20 negative; 20–39 weak positive; 40–59 moderate/strong positive; > 59 strong positive. DMARD: methotrexate (oral or subcutaneous), plaquenil, sulfasalazine. Biologics: etanercept, adalimumab, anakinra, abatacept, infliximab. ACR: American College of Rheumatology; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ILAR: International League of Associations for Rheumatology; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug; JIA: juvenile idiopathic arthritis.

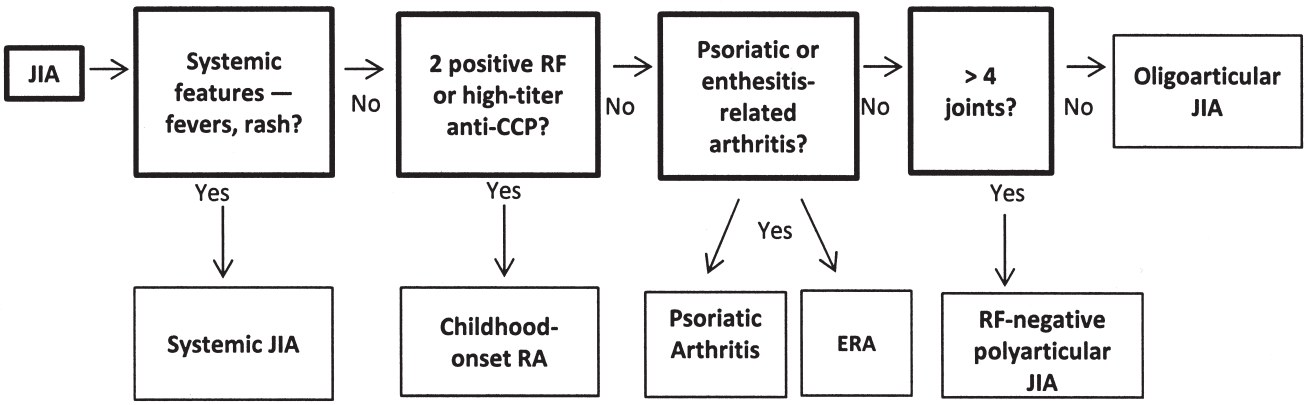

Figure 1. A proposed revision to the current International League of Associations for Rheumatology classification scheme. The proposal prioritizes positive serologies and phenotypic features over family history and joint count. According to standard reference ranges, anticyclic citrullinated peptide antibody (anti-CCP) titers are considered "strong positive" if they are > 59. Given the lack of data available about children with rheumatoid factor (RF)-negative juvenile idiopathic arthritis (JIA) with low anti-CCP titers, future analysis and revision will be necessary for accurate categorization of such children. In our proposed classification scheme, joint count is irrelevant other than to differentiate between oligoarticular JIA and polyarticular JIA. Thus, children with RF/CCP-positive arthritis will be identified as having childhood-onset rheumatoid arthritis (RA) irrespective of the number of joints, similar to the way in which the current classification scheme uses only the presence of arthritis and not the joint count for the classification of systemic JIA, enthesitis-related arthritis (ERA), and psoriatic JIA.

were classified as having RF-negative polyarticular JIA. All 4 of the children with RF+/CCP– JIA were classified as having childhood-onset RA. Thus, 45 (80%) of the 56 children were classified as having childhood-onset RA, compared to 34 (61%) by the current ILAR classification system.

DISCUSSION

JIA is a collection of chronic arthropathies of childhood classified according to the ILAR criteria[1]. These criteria allow for the differentiation of JIA from other, usually transient, causes of arthritis in children, and divide children with JIA into categories based on the distinct features of their disease. Generally, children classified as having RF+ polyarthritis are thought to represent the development of RA during childhood. Undifferentiated JIA is the ILAR category that encompasses a heterogeneous group of children who are excluded from other categories because of laboratory tests, family history, or specific disease features.

In contrast to the ILAR criteria, the ACR/EULAR criteria for RA allow for diagnosis of RA with a minimum score based on size and number of joints involved, presence and level of RF and/or anti-CCP, acute-phase reactants, and duration of symptoms[8]. Unlike the ILAR criteria, there are no specific exclusions, and individuals are not assigned to a specific category. Given that JIA is a more heterogeneous disease, with different disease categories being associated with varied treatments and outcomes, the ILAR classification appropriately divides children with JIA into categories. Adult seropositive RA, on the other hand, is a more homogeneous disease regarding biomarkers and disease features, so the ACR/EULAR criteria are simpler.

The ILAR criteria accurately classify the majority of children with JIA; however, our study revealed that almost a fourth of the 44 RF+ children (who were positive for either RF or both RF and anti-CCP) did not meet ILAR criteria for RF+ polyarticular JIA and were classified as undifferentiated even though their demographics and disease characteristics were consistent with childhood-onset RA (Table 4). In contrast, all of these children met ACR/EULAR criteria for RA. Though these children were classified differently, they all had similar demographics and disease characteristics with few exceptions. To avoid children with the uniform phenotype of childhood-onset RA being classified as undifferentiated, we suggest that in future modifications of the classification scheme, the presence of serological markers (RF/anti-CCP) should carry more weight than the number of joints involved or family history, and to be accurately classified, all children with JIA should be tested for RF and anti-CCP. Currently, joint counts are irrelevant for diagnosis of systemic JIA, ERA, psoriatic arthritis, and undifferentiated JIA. Similarly, we believe that they should not be taken into account for children with positive RF or high-positive anti-CCP titers, because biomarkers are more prognostic than the number of joints.

This is not the first time that the classification scheme has been critiqued. In a 2003 editorial, Martini suggested that the number of joints involved and the presence of psoriasis serve as descriptors rather than main classification criteria, to better divide children into categories of homogeneous disease[13]. In 2012, Martini cited new findings in the field of JIA to call for further refinements in classification, including changing the name and criteria for systemic JIA to include more children, changing the name of enthesitis-related arthritis to better align with the related adult-onset disease, and grouping children with ANA-positive early onset arthritis together regardless of the number of joints involved or the presence of psoriasis[14].

A metaanalysis of 86 studies found that for the diagnosis of RA, the sensitivity and specificity of anti-CCP was 67% and 95%, respectively, and the sensitivity and specificity of RF was 69% and 85%, respectively[15]. Therefore, these tests are also valuable for the diagnosis of childhood-onset RA, and accurate classification of these children with childhood onset RA is necessary to ensure that they are managed appropriately, given the tendency toward more aggressive and chronic disease associated with positive RF and anti-CCP serologies.

Interestingly, this study revealed a subset of 12 children with JIA who were RF– but anti-CCP+. These children were phenotypically different from the RF+ children in our study and notably had low titers of anti-CCP (range 20–45, mean 29). This confirms findings from a previous study that identified 23 children who had RF–/anti-CCP+ JIA[16]. Consistent with our results, children from the prior study also had low titers of anti-CCP (range 21–75, mean 27). Anti-CCP antibodies are highly specific for adult RA, and have been found in the serum of many individuals several years before they develop RA[17]. The implication of an isolated positive anti-CCP in children with JIA is unclear. Longterm followup of these children is necessary to determine whether the positive anti-CCP status warrants more aggressive treatment. Until further studies are conducted, we propose that in children who are RF–, higher titers of anti-CCP should be necessary for the illness to be considered childhood-onset RA. However, because the anti-CCP antibodies are highly specific for RA in adults, it will be important to further study the implication of low anti-CCP titers in children with JIA.

Overall, our proposed classification scheme identifies more children with disease consistent with childhood onset RA than does the current ILAR classification scheme. Further study of children with RF-negative JIA who have low titers of anti-CCP is necessary to determine the most appropriate category for these children.

Our study had limitations. Though this was a large sample size for the relatively rare phenotype of RF+ and/or anti-CCP+ JIA, the overall number of participants was small. Consequently, our study had lower power to detect

differences when the effect sizes were modest. Because it was a retrospective study, the timing and frequency of imaging was influenced by provider preference and hence was not uniform, therefore precluding analysis. Not all subjects had been tested twice for RF 3 months apart in the first 6 months as recommended by the ILAR criteria; however, all subjects considered to be RF+ had at least 2 tests 3 months apart during their disease. Despite these limitations, our study illuminates some issues with the current criteria and ways to improve them.

Further study is needed to determine the significance of low anti-CCP titers in younger children with JIA who are RF-negative. Future directions for research in this area also include investigation of the predisposing factors for development of RA early in life in children with childhood-onset RA.

ACKNOWLEDGMENT

We thank all the study participants.

REFERENCES

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
2. Cassidy JT, Levinson JE, Bass JC, Baum J, Brewer EJ Jr., Fink CW, et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. Arthritis Rheum 1986;29:274-81.
3. Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. J Rheumatol 2002;29:1989-99.
4. Foster HE, Marshall N, Myers A, Dunkley P, Griffiths ID. Outcome in adults with juvenile idiopathic arthritis: a quality of life study. Arthritis Rheum 2003;48:767-75.
5. van Rossum MA, Zwinderman AH, Boers M, Dijkmans BA, van Soesbergen RM, Fiselier TJ, et al. Radiologic features in juvenile idiopathic arthritis: a first step in the development of a standardized assessment method. Arthritis Rheum 2003;48:507-15.
6. Oen K, Duffy CM, Tse SM, Ramsey S, Ellsworth J, Chedeville G, et al. Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicenter inception cohort. Arthritis Care Res 2010;62:527-36.
7. van Venrooij WJ, van Beers JJ, Pruijn GJ. Anti-CCP antibodies: the past, the present and the future. Nat Rev Rheumatol 2011;7:391-8.
8. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid Arthritis Classification Criteria: An American College of Rheumatology/European League against Rheumatism Collaborative Initiative. Arthritis Rheum 2010;62:2569-81.
9. Omar A, Abo-Elyoun I, Hussein H, Nabih M, Atwa H, Gad S, et al. Anti-cyclic citrullinated peptide (anti-CCP) antibody in juvenile idiopathic arthritis (JIA): correlations with disease activity and severity of joint damage (a multicenter trial). Joint Bone Spine 2013;80:38-43.
10. Habib HM, Mosaad YM, Youssef HM. Anti-cyclic citrullinated peptide antibodies in patients with juvenile idiopathic arthritis. Immunol Invest 2008;37:849-57.
11. Ferucci ED, Majka DS, Parrish LA, Moroldo MB, Ryan M, Passo M, et al. Antibodies against cyclic citrullinated peptide are associated with HLA-DR4 in simplex and multiplex polyarticular-onset juvenile rheumatoid arthritis. Arthritis Rheum 2005;52:239-46.
12. Gilliam BE, Chauhan AK, Low JM, Moore TL. Measurement of biomarkers in juvenile idiopathic arthritis patients and their significant association with disease severity: a comparative study. Clin Exp Rheumatol 2008;26:492-7.
13. Martini A. Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous disease entities in juvenile idiopathic arthritis? J Rheumatol 2003;30:1900-3.
14. Martini A. It is time to rethink juvenile idiopathic arthritis classification and nomenclature. Ann Rheum Dis 2012;71:1437-9.
15. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007;146:797-808.
16. Tebo AE, Jaskowski T, Davis KW, Whiting A, Clifford B, Zeft A, et al. Profiling anti-cyclic citrullinated peptide antibodies in patients with juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2012;10:29.
17. Rantapää-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003;48:2741-9.