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Like "North Americans," "Europeans," or "Others:" Where do Turkish children with juvenile idiopathic arthritis stand in the new classification system?

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To the Editor,

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood and is defined as a form of chronic arthritis with unknown origin. There have been several classification criteria systems and the most commonly used International League of Associations for Rheumatology (ILAR) defines JIA as chronic arthritis (persists at least 6 weeks) of unknown origin that begins before 16 years of age. ILAR classification system comprises seven subtypes of JIA; systemic arthritis, oligoarthritis (persistent and extended), polyarthritis rheumatoid factor (RF) positive, polyarthritis RF negative, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. Each subtype has inclusion and exclusion criteria [1]. This classification system was updated in 2001 and has been used for many years all over the world by pediatric rheumatologists. There have been some critics about this classification system. The major critics were that ILAR criteria have never been validated in children, the joint count to call oligoarticular (≤4 joints) and polyarticular (>5 joints) arthritis was arbitrarily chosen, each subtype has strict exclusion criteria, especially the presence of psoriasis or a history of psoriasis in the patient or first-degree relative, and antinuclear antibody (ANA)-positive patients seem to share similar features, such as young age at onset, female predominance, and high risk of chronic anterior uveitis, irrespective of the number of joints involved or presence of psoriasis [2–4]. Recently proposed JIA classification criteria by Pediatric Rheumatology International Trials Organization (PRINTO) define JIA as a group of inflammatory disorders that begin before the 18th birthday and persist at least 6 weeks and all other known pathologies must be excluded. This new classification divides JIA into six subtypes; systemic JIA, RF-positive JIA, enthesitis/spondylitis-related JIA, early-onset ANA-positive JIA, other JIA, and unclassified JIA [5]. The differences in the classification are as follows; the age limit was raised to 18, arthritis was not a mandatory criterion in systemic JIA, and the addition of sacroiliitis on imaging and anti-cyclic citrullinated peptide antibody positivity to the related subtypes. The major difference between the two criteria sets was the recent one has a new subtype called early-onset (≤6 years) ANA-positive (presence of two positive ANA tests with a titer ≥1/160, tested by immunofluorescence, at least 3 months apart) JIA. The limit of ANA titer was chosen to exclude spurious positivity of ANA that may be observed in healthy children and also in the other JIA disorders. The authors of the new classification criteria have clearly stated that these were not the final domains of the criteria set and the data of at least 1000 new-onset JIA will be collected prospectively and analyzed to create the final version of the system.

It is well-known that JIA subtypes differ from country to country. While oligoarticular JIA is the most common subtype by far in the European and North American children, Turkish children seem to have nearly equal frequency of oligoarticular JIA and enthesitis-related arthritis. Furthermore, some previous studies have shown that the rate of ANA positivity was lower in Turkish children with JIA [6–11].

This study was performed to see the distribution of JIA subtypes by ILAR and PRINTO classification criteria sets. The files of 192 children diagnosed with JIA in between January 2018 and January 2020 were reviewed. The files of 32 children with missing laboratory or clinical parameters that are used to classify were excluded from the study. The study was approved by the local ethics committee (date: October 14, 2019, number: 19/03/01) and was conducted according to the tenets of the Declaration of Helsinki.

The cohort consisted of 160 children (78 girls and 82 boys) with JIA. The distribution of subtypes for both classification systems is given in Table 1. It was seen that "other JIA" subtype was the most frequent one (74 children, 46.3%) in the new classification and the new entry

Table 1. The distribution of JIA subtypes for both classification systems

ILAR classification	n=160 (%)	PRINTO classification	n=160 (%)
Oligoarticular arthritis	40.6	Other JIA	46.3
Enthesitis-related arthritis	30.0	Enthesitis/spondylitis-related JIA	28.8
RF-negative polyarticular arthritis	11.3	Early-onset ANA-positive JIA	11.9
Systemic arthritis	6.3	Systemic JIA	7.5
Undifferentiated arthritis	5.0	RF-positive JIA	5.5
RF-positive polyarticular arthritis	3.8	Unclassified JIA	0
Psoriatic arthritis	3.0		

ILAR: International League of Associations for Rheumatology; PRINTO: Pediatric Rheumatology International Trials Organization; JIA: Juvenile idiopathic arthritis; RF: Rheumatoid factor; ANA: Antinuclear antibody.

"early-onset ANA-positive JIA" group included only 19 (11.9%) children. Eighteen (27.6%) patients from oligoarticular arthritis and 1 (5.5%) patient from RF-negative polyarticular arthritis subtype were transferred to early-onset ANA-positive JIA, but none of the psoriatic arthritis patients was able to fulfill criteria to be included in the new subtype. We evaluated the reasons why patients were grouped under the other JIA but not the early-onset ANA-positive JIA in 67 patients with oligoarticular arthritis, RF-negative polyarticular arthritis, and psoriatic arthritis subtypes. In 40 (58.9%) patients, both ANA were negative and the age at onset was over 6 years, in 21 (31.3%) patients, the age at onset was ≤6 years but ANA was negative, and in 6 (8.9%) patients, ANA was positive but the age at onset was >6 years. Furthermore, in 10 patients, ANA was positive but the titer was 1/100 which did not meet the ≥1/160 criteria in the new classification criteria.

Two patients with systemic arthritis phenotype that was grouped under undifferentiated arthritis according to ILAR criteria, due to lack of arthritis, were easily switched to systemic JIA in the new classification. Furthermore, three patients in the undifferentiated arthritis group with oligoarticular phenotype but with persistent RF positivity were switched to RF-positive JIA. Two old boys with peripheral arthritis and HLA-B27 positivity but without sacroiliitis or enthesitis were changed to other JIA in the new classification.

In conclusion, under the light of this study and previous reports on Turkish JIA patients, the most common JIA subtype in Turkish children will probably be "other JIA" in the newly proposed JIA classification criteria. Pediatric rheumatologists do not take into account positive ANA to call the child as having JIA if the child does not have arthritis. Moreover, this new subtype "early-onset ANA-positive JIA" is the only subtype that has already exclusions such as having systemic JIA, RF-positive JIA, and enthesitis/spondylitis-related JIA. We think that lowering the ANA threshold may be beneficial for children to be grouped where they belong. Furthermore, a new entry "double-negative (i.e., ANA negative and RF negative) JIA," irrespective of age onset, and joint count may be an option instead of calling them "other JIA."

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A case of human leukocyte antigen B27 positive reactive arthritis associated with severe acute respiratory syndrome coronavirus 2 infection

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To the Editor,

Reactive arthritis (ReA) is a form of seronegative spondyloarthritis associated with human leukocyte antigen B27 (HLA-B27) positivity that causes asymmetric, oligoarticular arthritis 1–6 weeks after an infection with a causative pathogen [1]. Associations with both bacterial and viral infections have been reported. Herein, we describe a case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-related ReA.

A 37-year-old male patient presented to our clinic with severe swelling and pain in both wrists, knees, and ankles for approximately 3 weeks and hospitalized for diagnostic evaluation and treatment. Patient history was unremarkable for any rheumatic disease or other medical conditions except for having watery diarrhea for a week and a dry cough for 2 days before the onset of arthritis. Physical examination revealed arthritis in bilateral knees, wrists, ankles, elbows, and metatarsophalangeal joints. In laboratory evaluation, blood count, liver and kidney function tests, urinalysis, coagulation parameters, ferritin, uric acid, and procalcitonin levels were found to be normal. Erythrocyte sedimentation rate and C-reactive protein (CRP) levels were elevated (63 mm/h, 117 mg/L, respectively). Arthrocentesis of the right knee revealed 617 leukocytes/mm^3, with negative gram staining and bacterial cultures. Tests for antinuclear antibodies, rheumatoid factor, anti-streptolysin O antibodies, anti-cyclic citrullinated peptide antibodies, anti-extractable nuclear antibodies, and antineutrophil cytoplasmic antibodies were all negative as well as serological and agglutination tests for infectious agents consisting hepatitis B and C, human immunodeficiency virus, Epstein–Barr virus, herpes simplex type 1 and 2, parvovirus B19, rubella, cytomegalovirus, toxoplasma, brucellosis, syphilis, and gonorrhea. Direct radiography of ankles, knees, pelvis, and feet showed no erosive changes or enthesophytes. Ultrasonographic evaluation of both knees revealed synovial effusion and synovial hypertrophy bilaterally. Chest computed tomography was found to be normal. No vegetation was observed in echocardiography. There was no growth in blood, stool, and urine cultures. No parasites were observed in the stool microscopy. Combined nasopharyngeal and throat swab sampling for real-time reverse transcription-polymerase chain reaction (PCR) confirmed that the patient was positive for SARS-CoV-2. A diagnosis of ReA secondary SARS-CoV-2 was then considered. Hydroxychloroquine 2 mg × 200 mg and methylprednisolone 16 mg daily were initiated as treatment. After 3 days, arthritis regressed, CRP levels dropped to normal limits, and the patient was discharged with methylprednisolone 8 mg after two consecutive negative COVID-19 PCR tests. In the 1st-