ORIGINAL ARTICLES

Application of the new PRINTO classification criteria for juvenile idiopathic arthritis in a sample of Portuguese patients

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ABSTRACT

Background: The International League of Associations for Rheumatology (ILAR) classification system for juvenile idiopathic arthritis (JIA) does not depict homogenous subgroups of disease. As to unify our language with the adult rheumatic diseases, the Pediatric Rheumatology International Trials Organization (PRINTO) is attempting to revise these criteria.
Objective: To reclassify a JIA sample according to the new provisional PRINTO subsets: systemic JIA (sJIA), RF-positive JIA (RF-JIA), early-onset ANA-positive JIA (eoANA-JIA), enthesitis/spondylitis-related JIA (ESR-JIA), "other JIA" and "unclassified JIA".
Methods: Retrospective study including JIA patients followed in a Pediatric Rheumatology Unit at a university hospital. Medical records were reviewed, and patients were reclassified as per the provisional PRINTO criteria.
Results: Of a total of 104 patients, 41 (39.4%) were reclassified as "other JIA", 36 (34.6%) as eoANA-JIA, 15 (14.4%) as ESR-JIA, 8 (7.7%) as sJIA and 4 (3.8%) as RF-JIA. More than 90% of the oligoarticular JIA were reclassified into either eoANA-JIA or "other JIA". Only one negative RF polyarticular JIA converted to RF-JIA due to the presence of a positive anti-citrulinated peptide antibody (ACPA). The psoriatic arthritis (PsA) subgroup disappeared into eoANA-JIA (25%), ESR-JIA (25%) or "other JIA" (50%). There were significant differences in age of onset, but not on the gender ratio or uveitis presence. Antinuclear antibody was more frequent in females (p=0.035) and younger patients (p<0.001).
Conclusion: The number of affected joints and PsA features elapsed in favour of laboratory RF, ACPA and ANA traits. PsA and oligoarticular JIA were abolished. The "other JIA" entity is heterogenous and prevalent, claiming reformulation.

Keywords: Juvenile idiopathic arthritis; Classification; Rheumatoid factor; Antinuclear antibody; PRINTO; ILAR.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) includes pathophysiologically distinct inflammatory conditions, which amount different clinical aspects, treatments and prognosis. Its nomenclature "juvenile idiopathic arthritis" encompasses all forms of arthritis that start before the age of 16 years, are chronic in their evolution (persisting more than 6 weeks) and have no specific underlying cause[1]. The term JIA was first proposed in Santiago, 1994 by the International League of Associations for Rheumatology (ILAR)[2]. Later on, it was revised in Durban, 1997 and Edmonton, 2001[3-4]. Previously to this naming, both the American College of Rheumatology (ACR)[5-6] and the European League against Rheumatism (EULAR)[7] had offered classification criteria for juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA), respectively. As such, with two distinct terminologies, ILAR aimed to create universal groups for this spectrum of diseases. However, it stands to remember that this ILAR classification was incomplete, in a way that was based mostly on experts' opinion and less on factual evidence[8]. Thus, throughout scientific evolution, many discrepancies have been underlined. A particular set of features (antinuclear antibody [ANA] positivity, younger age at disease onset, female sex, asymmetric arthritis and higher chronic uveitis risk) seemed to depict an unique group[9]. Moreover, rheumatoid factor (RF)-negative polyarthritis and psoriatic

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arthritis (PsA) are suggested to be poorly characterized and to be heterogenous disease entities[10]. Lastly, the affected number of joints and psoriasis presence are doubting markers of grouping[11]. Following these pressing aspects, the ILAR classification system was formally proposed to be revised[12]. Therefore, in 2015, the Pediatric Rheumatology International Trials Organization (PRINTO) classification criteria for JIA were born and formally presented in the 23rd European Paediatric Rheumatology Congress (2016) at Genoa, Italy. In this new criteria exploit, RF and ANA became decisive, and the number of affected joints and presence of psoriasis were excluded. Hence, previous concepts of oligoarthritis, polyarthritis and psoriatic arthritis were abolished and replaced by RF and ANA-driven entities. In adult rheumatoid arthritis (RA), RF and anti-citrullinated protein/peptide antibody (ACPA) are important to its classification[13], with ACPA being a strong predictor for RA[14]. In the pediatric population, ACPA seems to be associated with RF-positive polyarthritis and more erosive disease[15].

In our study, we intended to reclassify a sample of JIA diagnosed patients, according to the new provisional PRINTO criteria subsets, which are currently undergoing prospective validation. Doing so, we also investigated how demographical, laboratorial, and clinical features affected this new classification.

MATERIALS AND METHODS

Patients

We conducted a longitudinal, retrospective, single-center study, including 104 JIA patients, followed at the Pediatric and Young Adult Rheumatology Unit of a third level hospital (university hospital of São João). Inclusion criteria were defined through the 2nd revision of ILAR classification for JIA, in Edmonton, 2001, which allowed for seven disease subtypes: systemic arthritis, oligoarthritis (persistent and extended type), RF-negative polyarthritis, RF-positive polyarthritis, psoriatic arthritis (PsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis. We excluded patients above 18 years old, and those with clinical features of another superimposed rheumatic disease. We registered sociodemographic data and proceeded to the reclassification accordingly to the PRINTO criteria to be validated. The new entities are: systemic JIA (sJIA), RF-positive JIA (RF-JIA), early-onset ANA-positive JIA (eoANA-JIA), enthesitis/spondylitis-related JIA (ESR-JIA), "other JIA" and "unclassified JIA". Systemic JIA remains a similar groups as it has a major systemic implication, but now without the need for arthritis; RF-JIA includes patients with positive RF and ACPA, independently of the affected number of joints; ESR-JIA resembles spondyloarthritis (SpA); eoANA-JIA comprises young (≤ 6 years) patients with positive ANA not included in the above groups; "other JIA" comprehends patients not included in the above groups; and "unclassified JIA" encloses patients with features of at least two other groups. A comparison of subsets and its migratory path between the ILAR and PRINTO classifications is shown in figure 1.

Data collection and laboratory definitions

We reviewed medical records for: sex, current age and at disease onset, disease evolution until diagnosis, presence of uveitis, enthesitis, psoriasis, family history of SpA, joint injections and remission status. Associated laboratory findings included RF, ANA, ACPA, and HLA-B27. Patients were considered ANA-positive if they had at least two positive results on indirect immunofluorescence assay at least 3 months apart; patients were considered RF-positive if they had at least two positive results at least 3 months apart. Patients were considered ACPA-positive if they had at least one positive test.

Statistical analysis

We used IBM SPSS statistics v25. Continuous variables were compared through t-test or Mann-Whitney U test, according to the normality categorization. Categorical variables were compared through chi-square or Fisher's exact test. All statistical tests were two-sided, and the significance level was defined as p-values < 0.05.

RESULTS

We included a total of 109 patients, but 5 were lost to follow-up and were therefore excluded. There remained 104 patients, 63.5% female, with a mean current age of 11.98 years (SD= 4.67) and at disease onset of 6.84 years (SD=4.44). Table I summarizes our reclassification from the ILAR to the PRINTO criteria viewpoint, and the characteristics of each new subtype. Forty-one patients (39.4%) were reclassified into "other JIA", 36 (34.6%) into eoANA-JIA, 15 (14.4%) into ESR-JIA, 8 (7.7%) into sJIA and 4 (3.8%) into RF-JIA. Adding to the previous 4 sJIA patients (as per the ILAR classification), 4 others were classified as having sJIA. The majority of the previously known oligoarticular JIA (95.7% of the persistent type and 90.9% of the extended type) were regrouped in eoANA-JIA or "other JIA". ESR-JIA combined patients previously classified as PsA, ERA and persistent oligoarticular JIA. Only one case of polyarticular JIA with negative RF was reclassified into FR-JIA due to the presence of ACPA; 66.9% were reclassified in "other JIA". Opposingly, RF-JIA gained

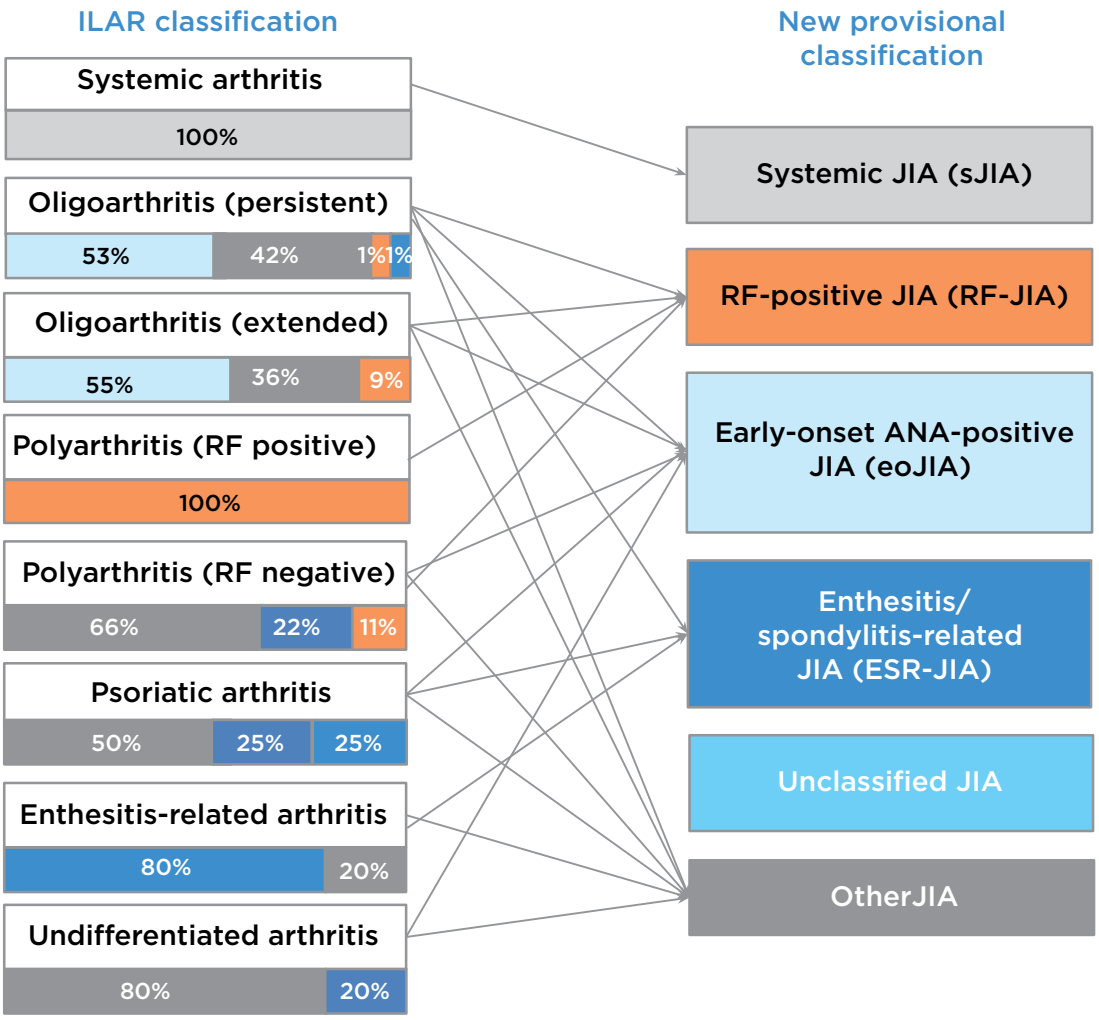

Figure 1. Flowchart of the reclassification's results.
ILAR: International League of Associations for Rheumatology; RF: Rheumatoid factor; ESR: enthesitis/spondylitis-related; JIA: Juvenile idiopathic arthritis; ANA: antinuclear antibody.

patients from other ILAR subtypes who had consistent ACPA positive antibodies. The former PsA entity redistributed its patients as follows: 25% to eoANA-JIA, 25% to ESR-JIA and 50% to "other JIA". Further, eoANA-JIA included patients from persistent (n=25) and extended (n=6) types of oligoarthritis, RF-negative polyarthritis (n=2), PsA (n=2) and undifferentiated JIA (n=1) from the ILAR classification. Twelve patients with positive ANA were excluded from the eoANA-JIA subtype because of their age of disease onset (> 6 years). Of the 15 ESR-JIA patients, 12 were previously classified as ERA, 2 as PsA and 1 as persistent oligoarticular JIA. There were no "unclassified JIA" patients. The "other JIA" group was the largest, having received patients from all ILAR subtypes, apart from sJIA and polyarticular JIA with positive RF.

As for the univariate analysis, we did not find a significant association between any of these subtypes and sex, even though numerically ESR had more male patients (53.3%) and eoANA-JIA, RF-JIA and "other JIA" had more females (75%, 75%, 63.5%, respectively). The median age at diagnosis was statistically different ($p>0.001$), being lower for sJIA (Md=3.5, IQR=6) and eoANA-JIA (Md=3, IQR=4), and higher for RF-JIA (Md=11.5, IQR=9.75) and ESR-JIA (Md=14, IQR=7). Systemic JIA associated with absence of relevant family history, ESR-JIA with positive SpA family history and "other JIA" with psoriasis family history ($p=0.029$). Patients with ERA-JIA presented more frequently the HLA-B27 allele ($p<0.001$). As expected, RF-JIA was associated with positivity for RF and ACPA ($p=0.007$); and eoANA-JIA with positive ANA ($p<0.001$). The presence and titer of RF was statistically associated with the presence and titer of ACPA ($p<0.001$). We found no

TABLE I. DEMOGRAPHIC AND PATIENT CHARACTERISTICS OF SUBTYPES IN PRINTO CLASSIFICATION.

Variables	New PRINTO criteria						Total	p-value
	sJIA	RF-JIA	eoANA-JIA	ESR-JIA	Other JIA	Unclassified JIA		
Patients – n	8	4	36	15	41	0	104	
ILAR Criteria – n (%)								
Systemic	4 (50)	0	0	0	0	0	4 (3.8)	
† Did not fulfill ILAR criteria	4 (50)	0	0	0	0	0	4 (3.8)	
Oligoarticular (Persistent)	0	1 (25.0)	25 (69.4)	1 (6.7)	20 (48.8)	0	47 (45.2)	
Oligoarticular (Extended)	0	1 (25.0)	6 (16.7)	0	4 (9.7)	0	11 (10.6)	
Polyarticular RF +	0	1 (25.0)	0	0	0	0	1 (0.9)	
Polyarticular RF –	0	1 (25.0)	2 (5.6)	0	6 (14.6)	0	9 (8.7)	
Psoriatic Arthritis	0	0	2 (5.6)	2 (13.3)	4 (9.8)	0	8 (7.7)	
Enthesitis-related	0	0	0	12 (80)	3 (7.3)	0	15 (14.4)	
Undifferentiated	0	0	1 (2.7)	0	4 (9.8)	0	5 (4.8)	
Female gender - n (%)	4 (50)	3 (75)	27 (75)	7 (46.7)	25 (61)	0	66 (63.5)	NS (0.284)
Age at disease onset in years, median (IQR)	3.5 (6)	11.5 (9.75)	3 (4)	14 (7)	7 (6.5)	0	6.5 (7)	**< 0.001**
Disease evolution by the time of diagnosis in months, median (IQR)	1 (1)	9 (-)	3 (3)	6 (8.5)	3 (11)	0	3 (7)	**0.002**
Familial history – n (%)								**0.029**
None	6 (100) *	2 (66.7)	14 (48.3)	7 (46.7)	10 (43.5)	0	39 (51.3)	* 2.5
Psoriasis	0	0	7 (24.1)	1 (6.7)	9 (39.1) *	0	17 (22.4)	* 2.3
Rheumatoid arthritis	0	0	3 (10.3)	0	2 (8.7)	0	5 (6.6)	
Spondyloarthritis	0	0	2 (6.9)	7 (46.7) *	1 (4.3)	0	10 (13.2)	* 4.3
Inflammatory bowel disease	0	1 (33.3) *	2 (6.9)	0	1 (4.3)	0	4 (5.3)	* 2.2
Other	0	0	1 (3.4)	0	0	0	1 (1.3)	
Uveitis – n (%)	0	1 (25)	10 (27.8)	3 (20)	4 (9.8)	0	18 (17.3)	NS (0.153)
Joint injection – n (%)	0 *	2 (50)	28 (77.8) *	2 (13.3) *	20 (48.8)	0	52 (50)	**< 0.001** *- 2.9, 4.1, -3.1
Remission – n (%)	8 (100)	4 (100)	32 (88.9)	9 (64.3)	31 (79.5)	0	84 (83.2)	NS (0.174)
HLA-B27 present – n (%)	0	0	0	5 (35.7) *	0	0	5 (5.8)	**<0.001** * 5.8
Rheumatoid Factor – n (%)								**0.007**
Negative	6 (100)	1 (25) *	28 (93.3)	14 (100%)	32 (94.1)	0	81 (92.0)	* -5.1
[10-30[	0	1 (25)	2 (6.7)	0	2 (5.9)		5 (5.7)	
[30-100[	0	1 (25) *	0	0	0		1 (1.1)	* 4.6
≥ 100	0	1 (25) *	0	0	0		1 (1.1)	* 4.6
ACPA – n (%)								**< 0.001**
Negative	6 (100)	0 *	31 (100)	14 (100)	36 (100)	0	87 (95.6)	* -9.7
[10-30[	0	1 (25) *	0	0	0		1 (1.1)	* 4.7
[30-100[	0	1 (25) *	0	0	0		1 (1.1)	* 4.7
≥ 100	0	2 (50) *	0	0	0		2 (2.2)	* 4.7
Positive ANA – n (%)	0 *	0 *	35 (100) *	0 *	12 (36.4) *	0	48 (51.1)	**<0.001** * -2.6, -2.1, 7.4, -4.2, -2.1

* Adjusted residues values – positive association if > 1.96 and negative if < -1.96

Abbreviations: NS – non-statistically significant; IQR – interquartile range; PRINTO - Pediatric Rheumatology International Trials Organization; sJIA -systemic juvenile idiopathic arthritis; RF-JIA - Rheumatoid factor-positive juvenile idiopathic arthritis; eoANA-JIA - early-onset antinuclear antibody-positive juvenile idiopathic arthritis; ESR-JIA - enthesitis/spondylitis-related juvenile idiopathic arthritis; JIA - juvenile idiopathic arthritis; ILAR - International League of Associations for Rheumatology; RF - rheumatoid factor; HLA-B27 - human leukocyte antigen B27; ACPA - anti-citrulinated peptide antibody; ANA - antinuclear antigen.

association between the subtypes of disease and uveitis, although eoANA-JIA had the most cases (10/18). Patients classified as eoANA-JIA, which comprised a high number of previously Oligoarticular JIA, were associated with local intra-articular corticosteroid treatments ($p<0.001$). Positive-ANA patients were more likely to be younger (Md=3, IQR=5; $p<0.001$) and female ($p=0.035$). Nonetheless, we found no statistical correlation between the presence of this antibody and uveitis.

DISCUSSION

This new PRINTO classification criteria for JIA is currently under validation on a large-scale prospective study by the The Paediatric Rheumatology European society (PReS). Its main differences are the inclusion of RF and ANA as main dictators of some subtypes in replacement of the number of affected joints, which had prevailed for a long time, derailing the oligoarticular/polyarticular binominal phenotyping. Also, PsA was abolished as well; and sJIA became a broader group as it no longer requests the presence of arthritis. We showed a slight sex tendency on the female side for eoANA-JIA and RF-JIA, opposed to one on the male side for ESR-JIA. This is a shy congruence to what previous studies have found[1]. The age of disease onset was lowest on eoANA-JIA. This subtype amounted more cases of uveitis, albeit not statistically significant so. ANA positivity, which gains relevance in these new criteria, occurred in 48/104 patients, rating 51.1%, a number slightly higher than those of previous studies[16]. Overall, in caucasians, ANA positivity has been reported in about 38-85% of oligoarticular, 30-50% of polyarticular and 0-17% of systemic JIA[17]. A previous study has stated an increased prevalence of this positivity in Europeans versus Asians[18]. Concerning our biggest subtype, "other JIA", it does not, by its definition, characterize a homogenous subgroup. However, most of the patients with oligoarticular and polyarticular forms of disease, without the presence of RF or ANA, will, in this new representation, most likely migrate to this "other JIA" form. This represents a meaningful blind spot; one that has been replicated in other studies[19], and that needs to be settled. Other works[20] have attempted to undermine this by applying the Assessment of SpondyloArthritis international Society (ASAS) criteria for SpA to the "other JIA" entity; however, care should be taken in this regard as arthritis in the presence of uveitis is significant for both peripheral SpA and eoANA-JIA. Furthermore, ASAS peripheral SpA criteria might be established in the presence of arthritis and HLA-B27, which, in the PRINTO criteria, might equal not only ESR-JIA but undefined/other JIA as well. Our study's rate of HLA-B27 presence was 5.8%, a number relatively smaller to those of previous studies[18], and belonged exclusively to the ESR-JIA patients. These ASAS/PRINTO discordances are to be considered. In this SpA topic, juvenile patients differ from adults by having less axial involvement, more frequent hip arthritis and enthesitis[21], and greater undifferentiated SpA. Classifying ERA seems to be more sensitive when applying the ASAS criteria for peripheral SpA, while ILAR and PRINTO are the most specific[22]. Also, ASAS axial SpA criteria may provide earlier detection of axial involvement. When looking from the other side, according to the ILAR classification, most juvenile SpA are either ERA-JIA or PsA, and the latter closely relates to both ERA-JIA and eoANA-JIA. In the adult population, however, PsA is not individually separated from SpA. These disparities complicate the transitioning follow-up of patients that go from pediatric to adult care. Eliminating PsA and rearranging the ERA-JIA subtype might ease the SpA stratification.

Within polyarticular disease, RF-positive polyarticular JIA is homologous to adult RF-positive RA[1]. Applying the RF only to polyarthritis, while rejecting the oligoarticular cases is another controversy. In this case, of a RF-positive oligoarthritis the patient would be classified as "undifferentiated arthritis" in the ILAR criteria. This artefact has been diminished in the PRINTO criteria, since the number of affected joints are neglected: for once, they may just indicate disease spread and not different diseases, and also subclinical synovitis (detectable only through imaging) subverts this countable notion. As such, both RF and ACPA are used as subset biomarkers, following RA's principles[13]. These autoantibodies are known to precede symptoms and to have prognostic power. Literature estimates a positive RF in about 2-12% of JIA patients[17]; we have, in our sample, a 7.9% positivity rate. As for ACPA, it is almost exclusive of RF-positive polyarthritis[17]; we have a 4.3% positivity rate, all of them concomitantly RF-positive.

Systemic JIA was a major flaw in the ILAR classification due to the requirement of chronic arthritis. Therefore, clinical practice mostly obviated this definition by understanding that this predominantly systemic disease might appear without this obligatory articular feature, as well as with a shorter duration of fever than the proposed two weeks. As such, removing articular symptoms as mandatory, and lessening the fever duration to periods of at least 3 consecutive days greatly broadened its diagnosing capacity. Adult-onset Still's disease, a pair of the sJIA, needs no arthritis for its diagnosis[12], a similitude embraced with the new provisional PRINTO criteria. Corroborating this better performance for this PRINTO subset of sJIA criteria, they have been recently shown to provide earlier recognition of sJIA comparing to ILAR, with greater sensitivity (80.5% vs 62.2%) but

comparable specificity (90.5% vs 91%)[23].

On Canada, using the ReACCh-Out (Research in Arthritis in Canadian Children, Emphasizing Outcomes) cohort, Lee et al[24] have found, in 1228 patients, that 63.3% of them belonged to the "other JIA", reinforcing that a large proportion of patients become unclassifiable with this system. The authors also stated that the PRINTO criteria did not align better with clinicobiologic subtypes or adult forms of arthritis compared to the older ILAR classification.

The limitations of our study embody its retrospective longitudinal design (albeit with a prospective data collection), the small population, and the single center inclusion. Reclassification amounted significant changes, based on laboratory findings, carving a similar road to the adult population. Rheumatoid factor-positive patients are now comparable to ACPA-positive patients, as in RA. Patients with positive ANA were frequent (51.1%), with an association with female sex and lower age of onset, but which did not reach statistical significance for uveitis despite a tendency.

CONCLUSION

The previous ILAR classification system did not categorize homogenous entities. It privileged the number of affected joints and PsA features, while the provisional PRINTO classification criteria acknowledge the RF and ANA positivity. The six new subtypes are: sJIA, RF-JIA, eoANA-JIA, ESR-JIA, "other JIA" and "unclassified JIA". The RF-JIA subtype lost the exclusivity of polyarticular pictures and gained the specificity of the RF and ACPA autoantibodies. Psoriatic arthritis and oligoarticular JIA have disappeared as entities. Systemic JIA, even though it is broader by excluding mandatory arthritis, remained unaltered in this sample. With this overall reclassification, we have not found an association between female gender and uveitis, or positive-ANA and uveitis. Nonetheless, the phenotypic features of disease maintained their association with serologic (RF, ANA and now ACPA) and genetic (HLA-B27) traits. The new "other JIA" subtype is too heterogenous and prevalent, demanding a reconfiguration. Larger studies with a prospective quality are needed to further prime this classification system.

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