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Uveitis in patients with oligoarticular juvenile idiopathic arthritis and juvenile spondyloarthritis/enthesitis related arthritis: is there any difference?

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Dear Editor,

Juvenile idiopathic arthritis (JIA) is the most common systemic disease causing uveitis in childhood and adolescence. Uveitis is the most frequent extra-articular manifestation of JIA and has an estimated prevalence ranging from 11 to 30% (1). Subtypes of JIA seem to have a different risk of uveitis development. Oligoarticular JIA (oJIA), especially in the presence of antinuclear antibodies (ANA), seems to have the greater risk, followed by juvenile spondyloarthritis/enthesitis related arthritis (jSpA-ERA) (2).

To compare the demographic and laboratory characteristics and clinical outcomes of uveitis in oJIA and jSpA-ERA patients, we conducted a retrospective single-center study of children with oJIA and jSpA-ERA that fulfilled the International League of Associations for Rheumatology (ILAR) classification and were followed in a rheumatology department of a tertiary hospital in the north of Portugal. Children with other subtypes of JIA were excluded. Sociodemographic, clinical, and treatment data were collected from the Portuguese Rheumatic Diseases Register (Reuma.pt) and medical records. Age at onset of uveitis, disease duration, acute-phase reactant proteins at diagnosis, and characteristics of uveitis including complications, and medical and surgical treatments were collected. Statistic was performed with independent samples t-test, Mann-Whitney U test, chi-square test, and Fisher's exact test. Statistical significance was set at a $p<0.05$.

A total of 75 children with oJIA (57 females, 76.0%) and 23 children with jSpA-ERA (6 females, 26.1%) were included. Thirty-five of the 98 children developed uveitis (35.7%), 28 children had oJIA (80.0%) and the remaining 7 children had jSpA-ERA (20.0%). The diagnosis of JIA was made at a younger age in oJIA patients than in jSpA-ERA patients (5.6±4.7 *vs* 14.3±2.1 years, p=0.005). Likewise, uveitis appeared at a younger age in patients with oJIA than in patients with jSpA-ERA (8.4±5.9 years *vs* 17.8±7.2 years, p=0.001) and approximately 3 years after the JIA diagnosis in both groups. In addition, the uveitis in the majority of oJIA patients was asymptomatic and the diagnosis was made during eye screening (n=21, 75.0%), as opposed to jSpA-ERA patients, in which the uveitis was symptomatic in the majority of patients (n=6, 85.7%, p=0.003). Concerning uveitis characteristics, anterior uveitis was the most frequent type in the 2 groups (and the only one in jSpA-ERA patients). In oJIA patients, panuveitis occurred in 8 patients (28.6%). Patients with jSpA-ERA had more frequently unilateral alternating

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uveitis (n=4), followed by unilateral uveitis (same eye, n=3). No one developed simultaneous bilateral uveitis. In oJIA patients, uveitis was more frequently unilateral (same eye, n=7), followed by bilateral involvement (n=9, 32.1%) and unilateral alternating (n=6, 21.4%). Complications of uveitis were more frequent in the oJIA

Table I - Sociodemographic, clinical, and treatment characteristics of patients with uveitis.

	oJIA with uveitis (n=28)	jSpA-ERA with uveitis (n=7)	P-value
Sex, female, n (%)	20 (71.4)	1 (14.3)	**0.006**
ANA positivity, n (%)	18 (64.3)	1 (16.7)	**0.012**
HLA-B27 positivity, n (%)	3 (10.7)	4 (57.1)	**0.002**
Age at onset of uveitis, years, mean±SD	8.4±5.9	17.8±7.2	**0.001**
Age at diagnosis of JIA, years, mean±SD	5.6±4.7	14.3±2.1	**0.005**
Disease duration, years, mean±SD	12.8±7.4	5.7±1.5	0.114
Number of joints involved, median (Q1-Q3)	1.0 (1.0-2.0)	0.50 (0.0-1.75)	**0.011**
Actual treatment, n (%) Topical corticosteroids Systemic corticosteroids csDMARD Methotrexate Sulfasalazine bDMARD Adalimumab Etanercept Golimumab Infliximab	 10 (35.7) 6 (21.4) 18 (64.3) 18 (64.3) 0 (0) 12 (42.9) 10 (35.7) 1 (3.6) 0 (0) 1 (3.6)	 2 (28.6) 1 (14.3) 3 (42.9) 2 (28.6) 1 (14.3) 3 (42.9) 2 (28.6) 0 (0) 1 (14.3) 0 (0)	 1.0 1.0 0.401 0.112 0.200 1.0 1.0 1.0 0.200 1.0
Uveitis diagnostic approach, n (%) Screening Symptoms	 21 (75.0) 7 (25.0)	 1 (14.3) 6 (85.7)	 **0.003**
Uveitis classification, n (%) Anterior Panuveitis	 20 (71.4) 8 (28.6)	 7 (100) 0 (0)	 0.274
Laterality, n (%) Unilateral Unilateral alternating Bilateral	 13 (46.4) 6 (21.4) 9 (32.1)	 4 (57.1) 3 (42.9) 0 (0)	 0.092
Decreased visual acuity at the last follow-up visit, n (%)	14 (50.0)	1 (14.3)	0.143
Best corrected visual acuity at the last follow-up visit, median (IQR) Right eye Left eye	 10.0 (8.0-10.0)/10 9.0 (3.0-10.0)/10	 10 (9.5-10.0)/10 10 (9.5-10.0)/10	 0.353 0.117
Complications of uveitis, n (%) Vitritis Vitreous hemorrhage Synechiae Band keratopathy Cataracts Ocular hypertension Glaucoma Retinal detachment	15 (53.6) 3 (10.7) 2 (7.1) 6 (21.4) 8 (28.6) 12 (42.9) 8 (28.6) 2 (7.1) 2 (7.1)	1 (14.3) 0 (0) 0 (0) 1 (14.3) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)	0.062
Eye surgery, n (%)	12 (42.9)	0 (0)	**0.033**

ANA, antinuclear antibodies; HLA-B27, human leukocyte antigen-B27; bDMARD, biologic disease modifying antirheumatic drugs; csDMARD, conventional synthetic disease modifying antirheumatic drugs; JIA, juvenile idiopathic arthritis; oJIA, oligoarticular juvenile idiopathic arthritis; jSpA-ERA, juvenile spondyloarthritis/enthesitis related arthritis; SD, standard deviation; IQR, interquartile range.

group (n=15, 53.6%) than in jSpA-ERA (n=1, 14.3%, p=0.062). The most common complications in the oJIA group were cataracts (n=12, 42.9%), band keratopathy (n=8, 28.6%), ocular hypertension (n=8, 28.6%), and synechiae (n=6, 21.4%). Fourteen patients with oJIA (50.0%) and 1 patient with jSpA-ERA (14.3%) had permanently decreased visual acuity. Twelve patients with oJIA (42.9%) were submitted to eye surgery compared to none with jSpA-ERA. More detailed information is reported in Table I.

In our study, uveitis manifested in 35.7% of the included patients with oJIA and jSpA-ERA. Unilateral anterior uveitis was the most frequent type in the 2 groups. Furthermore, panuveitis and bilateral uveitis only occurred in oJIA patients. Uveitis in oJIA patients appeared at a younger age and was more frequently asymptomatic. oJIA-associated uveitis had poorer outcomes, such as worse visual acuity, complications, and eye surgery requirement. Also, females with oJIA had a higher risk to develop uveitis than females with jSpA-ERA.

Based on our study and previous literature, uveitis seems to have different characteristics depending on the JIA subtype, which leads us to think that possibly different immunologic mechanisms may be involved, which may reflect important biologic differences in the JIA subtypes. jSpA-ERA-associated uveitis has characteristics similar to those of uveitis in adult SpA, including a strong association with human leukocyte antigen-B27 and an increased risk of acute anterior unilateral symptomatic uveitis (3). Also, the risk of uveitis in oJIA patients is increased in those who are ANA positive raising the question as to whether ANAs are pathogenic or an epiphenomenon of JIA (4).

As uveitis-associated JIA can be clinically silent, a close collaboration between ophthalmologists and pediatric rheumatologists and a periodical ophthalmic examination in asymptomatic JIA patients are of crucial importance. This interdisciplinary approach guarantees an early diagnosis of uveitis, which will prevent permanent ocular damage and improve the long-term prognosis of these patients.

Further studies are needed to clarify the pathogenesis of uveitis in the JIA subtypes. This may lead to the identification of biomarkers, either genetic or immunological, that will enable the stratification of patients at a higher risk of uveitis development and help physicians to tailor therapeutic interventions.

Conflict of interest

The authors declare no potential conflict of interest.

Availability of data and materials

Data and materials are available by the authors.

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