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Original article

Epidemiologic profile of juvenile-onset compared to adult-onset spondyloarthritis in a large Brazilian cohort

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ABSTRACT

Objective: To analyze the clinical and epidemiologic characteristics of juvenile-onset spondyloarthritis (SpA) (< 16 years) and compare them with a group of adult-onset (\geq 16 years) SpA patients.

Patients and methods: Prospective, observational and multicentric cohort with 1,424 patients with the diagnosis of SpA according to the European Spondyloarthropathy Study Group (ESSG) submitted to a common protocol of investigation and recruited in 29 reference centers participants of the Brazilian Registry of Spondyloarthritis (RBE – Registro Brasileiro de Espondiloartrites). Patients were divided in two groups: age at onset < 16 years (JOSpA group) and age at onset \geq 16 years (AOSpA group).

Results: Among the 1,424 patients, 235 presented disease onset before 16 years (16.5%). The clinical and epidemiologic variables associated with JOSpA were male gender ($p < 0.001$), lower limb arthritis ($p = 0.001$), enthesitis ($p = 0.008$), anterior uveitis ($p = 0.041$) and positive HLA-B27 ($p = 0.017$), associated with lower scores of disease activity (Bath Ankylosing Spondylitis Disease Activity Index – BASDAI; $p = 0.007$) and functionality (Bath Ankylosing Spondylitis Functional Index – BASFI; $p = 0.036$). Cutaneous psoriasis ($p < 0.001$), inflammatory bowel disease ($p = 0.023$), dactylitis ($p = 0.024$) and nail involvement ($p = 0.004$) were more frequent in patients with adult-onset SpA.

Conclusions: Patients with JOSpA in this large Brazilian cohort were characterized predominantly by male gender, peripheral involvement (arthritis and enthesitis), positive HLA-B27 and lower disease scores.

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Perfil epidemiológico da espondiloartrite de início juvenil comparada com a espondiloartrite de início na vida adulta em uma grande coorte brasileira

RESUMO

Objetivo: Analisar as características clínicas e epidemiológicas da espondiloartrite (EspA) de início juvenil (< 16 anos) e compará-las com um grupo de pacientes com EspA de início na vida adulta (\geq 16 anos).

Pacientes e métodos: Coorte prospectiva, observacional e multicêntrica com 1.424 pacientes com diagnóstico de EspA de acordo com o *European Spondyloarthropathy Study Group* (ESSG) submetidos a um protocolo comum de investigação e recrutados em 29 centros de referência participantes do Registro Brasileiro de Espondiloartrites (RBE). Os pacientes foram divididos em dois grupos: idade no início < 16 anos (grupo EspAij) e idade no início \geq 16 anos.

Resultados: Entre os 1.424 pacientes, 235 manifestaram o início da doença antes dos 16 anos (16,5%). As variáveis clínicas e epidemiológicas associadas com a EspAij foram: gênero masculino ($p < 0,001$), artrite em membro inferior ($p = 0,001$), entesite ($p = 0,008$), uveíte anterior ($p = 0,041$) e HLA-B27 positivo ($p = 0,017$), em associação com escores mais baixos de atividade da doença (*Bath Ankylosing Spondylitis Disease Activity Index* – BASDAI; $p = 0,007$) e de capacidade funcional (*Bath Ankylosing Spondylitis Functional Index* – BASFI; $p = 0,036$). A psoríase cutânea ($p < 0,001$), a doença intestinal inflamatória ($p = 0,023$), a dactilite ($p = 0,024$) e o envolvimento ungueal ($p = 0,004$) foram mais frequentes em pacientes com EspA de início na vida adulta.

Palavras-chave:

Espondiloartrite de início juvenil

População brasileira

Epidemiologia

Artrite crônica na infância

Artrite relacionada à entesite

Conclusões: Nessa grande coorte brasileira, os pacientes com EspAij se caracterizavam predominantemente pelo gênero masculino, envolvimento periférico (artrite e entesite), HLA-B27 positivo e escores de doença mais baixos.

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Introduction

Most patients with SpA start disease in the adult age. Recognizing juvenile-onset SpA (JOSpA) can be a challenge, as many patients present the classic manifestations of the disease in the 3rd to 4th decades of life. Nevertheless, as SpA can start at a pediatric age, it is important the early diagnosis of the disease, contributing to avoid structural damage and the consequent functional incapacity in adult age.¹

Most patients with JOSpA can present an undifferentiated form of disease, characterized by the presence of peripheral arthritis, enthesitis and hip involvement, on the contrast of adult-onset patients, who present more frequently the axial complaints characteristic of SpA. As a consequence of this presentation, JOSpA can be confounded with other forms of juvenile arthritis.²

Nowadays, classification criteria for JOSpA are included in the International League Against Rheumatism (ILAR) criteria for juvenile idiopathic arthritis. Many cases of JOSpA can be considered as enthesitis-related arthritis (ERA) if they present arthritis and/or enthesitis associated with at least two of these variables: (1) presence or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain; (2) presence of HLA-B27 antigen; (3) onset of arthritis in a male over 6 years of age; (4) acute symptomatic anterior uveitis; (5) history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis or acute anterior uveitis in a first-degree relative. Exclusion criteria include psoriasis or history of psoriasis in the patient or in a first-degree relative; presence of positive rheumatoid factor in at least two occasions in a three month interval; or systemic juvenile idiopathic arthritis.³ Patients classified as enthesitis-related arthritis under the current ILAR classification criteria for juvenile idiopathic arthritis can in fact represent early cases of JOSpA.

Recently, the proposition of the classification criteria for the peripheral SpA can include many juvenile patients with undifferentiated arthritis or ERA in the group of SpA.⁴ The modern concept of peripheral SpA consider that patients with arthritis or enthesitis or dactylitis with at least one (anterior uveitis; psoriasis; Crohn's disease or ulcerative colitis; preceding infection; positive HLA-B27; sacroiliitis by imaging) or two (arthritis; enthesitis; dactylitis; inflammatory low back pain somehow; family history of SpA) characteristics should be considered as a SpA.

The main objectives of this article are to analyze the clinic and epidemiologic characteristics of patients with JOSpA in a large cohort of patients with SpA, and compare them with

those presented by patients with adult-onset SpA in the same cohort.

Methods

This is a prospective, observational and multicentric cohort of consecutive SpA patients recruited from 29 referral centers participants in the RBE (RBE -). All these SpA patients, from all the five major geographic areas in Brazil, were classified according to the ESSG,⁵ with the data collected from June 2006 to December 2009. The Brazilian Registry of Spondyloarthritis is part of the RESPONDIA group, constituted by nine Latin-American countries (Argentina, Brazil, Costa Rica, Chile, Ecuador, Mexico, Peru, Uruguay and Venezuela) and the two Iberian Peninsula countries (Spain and Portugal).

In this study, a common protocol of investigation was applied to 1,424 SpA patients. The diagnosis of ankylosing spondylitis was considered if the patients fulfilled the New York modified criteria,⁶ and as psoriatic arthritis in case they fulfilled Moll and Wright criteria;⁷ reactive arthritis was considered when asymmetric inflammatory oligoarthritis of lower limbs was present associated with enthesopathy and/or inflammatory low back pain following enteric or urogenital infections,⁸ and enteropathic arthritis when the patient presented inflammatory axial and/or peripheral joint involvement associated with confirmed inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis).

Patients were divided in two groups: JOSpA was considered when the patient started SpA symptoms < 16 years of age, and adult-onset SpA was considered when disease onset was \geq 16 years.

Demographic and clinical data were collected including time of disease duration, extra-articular manifestations, and treatment. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were also registered.

Disease activity and functional status were evaluated according to the BASDAI and the Bath Ankylosing Spondylitis Functional Index (BASFI),^{9,10} respectively. The presence of pain at entheses sites was evaluated by the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES);¹¹ the MASES scores varied from 0 to 13. Quality of life data has been recorded through Ankylosing Spondylitis Quality of Life (ASQoL) questionnaires.¹² All questionnaires used were previously translated, cross-translated, validated and culturally adapted to the Portuguese language.¹³

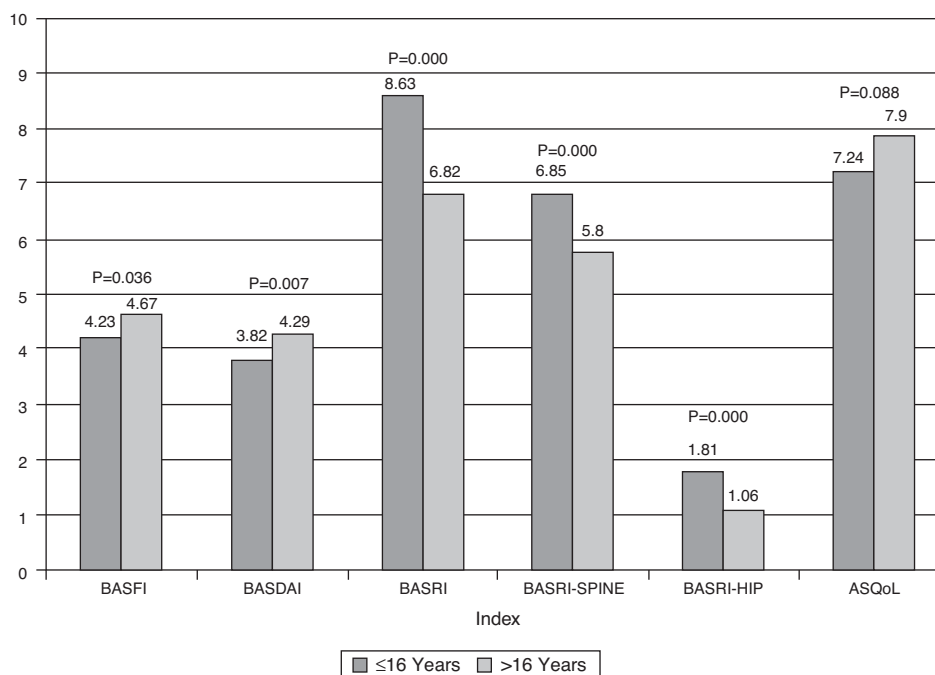


Figure 1 – Mean scores of the disease activity (BASDAI), functional (BASFI), and quality of life (ASQoL) indexes in the juvenile-onset SpA group (JOSpA) compared with the adult-onset SpA group (AOSpA).

ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

Statistical Analysis: Categorical variables were compared by ² and Fisher's exact test, and continuous variables were compared by ANOVA test. A value of $P < 0.05$ was considered significant, and $0.05 > P > 0.10$ was considered a statistical trend.

Results

Among the 1,424 SpA patients, 235 referred disease onset before 16 years (16.5%). At the moment, they were evaluated for the SpA protocol, just 3.0% of the patients were below 16 years. Patients considered as JOSpA presented significant delay in the diagnosis (10.02 ± 9.28 years vs. 5.84 ± 7.27 years; $P < 0.001$) compared to the adult-onset patients. At the moment of the clinical investigation, JOSpA patients were significantly younger (32.53 ± 11.78 years) than the adult-onset patients (44.51 ± 11.94 years) ($P < 0.001$).

The clinical and epidemiologic variables associated with JOSpA were male gender ($P < 0.001$), lower limb arthritis ($P = 0.001$), enthesitis ($P = 0.008$), and positive HLA-B27 ($P = 0.017$). Inflammatory back pain ($P = 0.006$), cervical pain ($P = 0.034$) and dactylitis ($P = 0.024$) were more frequent in patients with adult-onset SpA (Table 1). Ethnicity was similar in both age-onset groups.

When we studied the extra-articular manifestations, anterior uveitis ($P = 0.041$) was associated with JOSpA, while cutaneous psoriasis ($P < 0.001$), inflammatory bowel disease

($P = 0.023$), and nail involvement ($P = 0.004$) were associated to adult-onset SpA (Table 1).

The analysis of the physical examination showed that the mean number of painful joints (3.40 ± 6.99 vs. 3.83 ± 7.52 ; $P = 0.423$), mean number of swollen joints (1.19 ± 3.73 vs. 1.58 ± 4.62 ; $P = 0.183$), as well as the mean MASES scores (2.04 ± 2.89 vs. 2.17 ± 3.02 ; $P = 0.548$) were similar in the two groups.

Disease indices indicated that disease activity (BASDAI; $P = 0.007$) and functionality (BASFI; $P = 0.036$) were better in the JOSpA group, while ASQoL ($P = 0.088$) did not reach statistical significance (Fig. 1).

Discussion

The clinical characteristics of this cohort have shown concordance with the classic description of JOSpA:³ predominance of male gender, positive HLA-B27, and peripheral involvement characterized by lower limb arthritis and enthesitis. These characteristics also agree with the concept of the peripheral SpA.⁴

Most studies about JOSpA in fact analyze ankylosing spondylitis juvenile.¹⁴⁻¹⁹ In this study, we found a statistical predominance of the male gender in JOSpA. Other recent studies have found similar gender prevalence in their cohorts in Canada and China,^{14,15} while Gensler et al. in USA showed a trend to present more women in juvenile ankylosing spondylitis.¹⁶

Table 1 – Associations between clinic-epidemiologic variables and age at onset (before and after 16 years-old) in 1,424 patients.

Variables	Age at onset of symptoms				p ^a
	< 16 years n = 235	≥ 16 years %	n = 1189	%	
Gender					< 0.001
Male	202	86.0	839	70.6	
Female	33	14.0	350	29.4	
Ethnicity					0.621
White	121	51.5	686	57.7	
Non-white	114	48.5	503	42.3	
Inflammatory low back pain	142	60.4	827	69.6	0.006
Buttock pain	81	34.5	396	33.3	0.730
Cervical pain	60	25.5	387	32.5	0.034
Hip pain	71	30.2	294	24.7	0.078
Lower limb arthritis	140	59.6	563	47.4	0.001
Upper limb arthritis	47	20.0	274	23.0	0.307
Enthesitis	137	58.3	581	48.9	0.008
Dactylitis	17	7.2	147	12.4	0.024
HLA-B27 ^b	82	79.6	396	67.9	0.024
Anterior uveitis	59	25.1	229	19.3	0.041
Inflammatory bowel disease	4	1.7	61	5.1	0.021
Psoriasis	9	3.8	245	20.6	< 0.001
Nail involvement	11	4.7	129	10.8	0.004
Balanitis	11	4.7	37	3.1	0.223

^a Qui-square.

^b Calculated for 103 (< 16 years) and 583 patients (≥ 16 years).

JOSpA and adult-onset SpA, particularly ankylosing spondylitis, can differ in some clinical aspects, but there is no evidence that they could be considered as different diseases. The main differences are in the disease presentation. Different from what happens in the adult-onset patients, children and adolescents with JOSpA frequently start disease symptoms with peripheral complaints (lower limb arthritis and enthesitis), and will develop axial symptoms after five to 10 years of follow-up.¹⁴⁻²⁰ In the present study, the authors found a significant frequency of lower limb arthritis and enthesitis in JOSpA. This study also showed that there was a significant delay in the diagnosis of JOSpA compared to adult-onset SpA patients; we suppose that this delay is associated with the many times undifferentiated clinical presentation of SpA in children and teenagers.

Regarding extra-articular manifestations, the present study found that anterior uveitis was more frequent in the JOSpA group, while psoriasis, nail involvement and inflammatory bowel disease were more frequent in the adult-onset group. These findings are similar to the results observed in other cohorts.^{14,19,21} In a Turkish study, uveitis was observed in 11.6% of the patients with juvenile idiopathic arthritis and was related to the clinical form, associated with the oligoarticular (extended and persistent) and psoriatic forms.²¹

The frequency of positive HLA-B27 in the JOSpA group was significantly higher than that observed in the adult-onset SpA group. These results were similar to other studies including European and Asiatic populations,²¹⁻²³ and confirm that HLA-B27 should be done in all the patients suspected to have SpA,

according to its elevated positivity and association with more severe disease.²³

The severity of ankylosing spondylitis is frequently high in juvenile cases as there are many patients with juvenile ankylosing spondylitis who require hip arthroplasty. The results of functional incapacity in patients with JOSpA can be discordant. While Stone et al.²⁴ have found a worse functional capacity in juvenile ankylosing spondylitis patients, Gensler et al.¹⁶ showed similar results compared to adult-onset patients. In the present study, BASDAI and BASFI mean scores were significantly lower in the JOSpA patients, while ASQoL scores were similar in the two groups. These findings can suggest that the impact of SpA in the quality of life in the juvenile group is high, despite better disease activity and functional indices.

Despite the lower frequency of axial involvement in the JOSpA, studies have demonstrated 40% of functional incapacity after 10 to 15 years of disease duration is significantly associated with hip involvement.^{16,25} In another study with 326 JOSpA patients, mean BASFI was 5.1 ± 1.5 , significantly higher than the BASFI of the adult-onset SpA group (4.6 ± 0.4).²⁴ In a 3-year Norwegian prospective study analyzing the predictors of disability in JOSpA by the Children Health Assessment Questionnaire (CHAQ), the authors found that a high disability index and a poor well-being at baseline predicted reduced physical function after 3 years.²⁶ Compared to other subgroups of juvenile idiopathic arthritis, patients with juvenile ankylosing spondylitis referred more chronic pain and higher scores of CHAQ, associated to poorer quality of life.²⁷

Concluding, the present study, analyzing a large Brazilian cohort of patients with SpA, attended in university centers in all the main geographic regions in the country, showed that JOSpA was associated with male gender, HLA-B27 positivity, anterior uveitis and peripheral involvement. This characterization will help to understand the characteristics of the JOSpA patients and their needs in the long-term follow up.

Conflicts of interest

The authors declare no conflicts of interest.

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