Effect of age at disease onset in the clinical profile of spondyloarthritis: a study of 1424 Brazilian patients

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Abstract

Objectives

To analyse demographic and clinical variables in patients with disease onset before and after 40, 45 and 50 years in a large series of Brazilian SpA patients.

Methods

A common protocol of investigation was prospectively applied to 1424 SpA patients in 29 centres distributed through the main geographical regions in Brazil. The mean age at disease onset was 28.56±12.34 years, with 259 patients (18.2%) referring disease onset after 40 years, 151 (10.6%) after 45 years and 81 (5.8%) after 50 years. Clinical and demographic variables and disease indices (BASDAI, BASFI, BASRI, MASES, ASQoL) were investigated. Ankylosing spondylitis was the most frequent disease (66.3%), followed by psoriatic arthritis (18%), undifferentiated SpA (6.7%), reactive arthritis (5.5%), and enteropathic arthritis (3.5%).

Results

Comparing the groups according to age of disease onset, those patients with later onset presented statistical association with female gender, peripheral arthritis, dactylitis, nail involvement and psoriasis, as well as negative statistical association with inflammatory low back pain, alternating buttock pain, radiographic sacroiliitis, hip involvement, positive familial history, HLA-B27 and uveitis. BASDAI, BASFI and quality of life, as well as physicians and patient's global assessment, were similar in all the groups. Radiographic indices showed worse results in the younger age groups.

Conclusion

There are two different clinical patterns in SpA defined by age at disease onset: one with predominance of axial symptoms in the group with disease onset ≤40 years and another favouring the peripheral manifestations in those with later disease onset.

Key words
spondyloarthritis, ankylosing spondylitis, age at onset, outcome

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Introduction

The spondyloarthritides (SpA) encompass a group of diseases including ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA), inflammatory bowel disease (IBD) related arthritis and undifferentiated SpA (uSpA) (1). This wide clinical spectrum is the result of the combination of different features such as inflammatory spinal involvement, peripheral arthritis, enthesitis, dactylitis, uveitis, aortic incompetence and the presence of HLA-B27 (2).

SpA usually affects males in the second and third decades of life, but later-onset of disease has also been reported (1, 2). In the elderly all subtypes of SpA are present and some of the characteristics of these diseases are peculiar to this age group. The recognition of a different SpA pattern with older age at onset helps not only in the correct diagnosis of this group of diseases but also allows one to choose the best possible treatment, as many of the used drugs may suffer the age effect on their metabolism and pharmacokinetics.

Most studies on clinical findings in patients with late-onset SpA have a small number of patients reflecting the frequency of distribution of the age at disease onset (3-13). Caplanne *et al*., comparing 8 patients with late-onset uSpA with 32 patients with normal age at onset, noted that the first referred more cervical pain, anterior chest wall involvement and peripheral arthritis (6). Others described a higher proportion of shoulder involvement (12), marked elevation of laboratory parameters of inflammation (1) and a lower proportion of hip involvement (1, 13). The observed differences in the disease phenotype according to the age at onset may be caused by distinct susceptibility factors (1). According to Brophy *et al*. SpA patients at a younger age may have a higher number of susceptibility factors than individuals with late-onset. This may affect the clinical expression of the disease but not its outcome (13).

A German survey in 1614 AS patients showed that the first symptoms occurred before the age of 15 years in 4%, between 15 and 40 years in 90% and after the age of 40 in the remaining 6% (14). The same distribution of age at disease onset was noted in SpA associated with psoriasis or IBD. A study analysing patients seen during the period 1935–1989 in Rochester, Minnesota, showed an incidence of AS of $2.2x10^5$/ year after 55 years of age compared with $7.3x10^5$/year for all ages (15). Due to the increased life expectancy, it is likely that the number of patients diagnosed with late-onset SpA may also have increased.

Although juvenile-onset SpA starts before 16-years of age and elderly-onset SpA can occur after 65 years, there is no clear definition of "conventional" or "late" onset in SpA. The Calin (16) and ASAS (17) criteria for inflammatory back pain include "age at onset <40 years" in the set of criteria, and so does the recent classification criteria for axial SpA whose patients should be at "age at onset below 45 years" (18).

In the present report we analysed demographic and clinical characteristics of SpA patients with disease onset after 40, 45 and 50 years in a large cohort of Brazilian patients from a nationwide Registry.

Methods

This is a prospective, observational and multicentric cohort of consecutive SpA patients recruited from 29 referral centres participating in the Brazilian Registry on Spondyloarthritis (RBE: Registro Brasileiro de Espondiloartrites). All these SpA patients, from all of the five major geographic areas in Brazil, were classified according to the European Spondyloarthropathy Study Group (ESSG) criteria (19). The data were collected from June 2006 to December 2009. The Brazilian Registry of Spondyloartrhritis is a part of the RESPONDIA (Registro de Espondiloartrites de Ibero-America - Iberoamerican Registry of Spondyloarthritis), constituted by nine Latin-American countries (Argentina, Brazil, Costa Rica, Chile, Ecuador, México, Peru, Uruguay and Venezuela) and the two Iberian Peninsula countries (Spain and Portugal).

In this study, a protocol of investigation was applied to 1424 SpA patients. The diagnosis of AS was considered if the patients fulfilled the New York modified

criteria (20), and as psoriatic arthritis in case they fulfilled Moll and Wright criteria (21); 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 (22), 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).

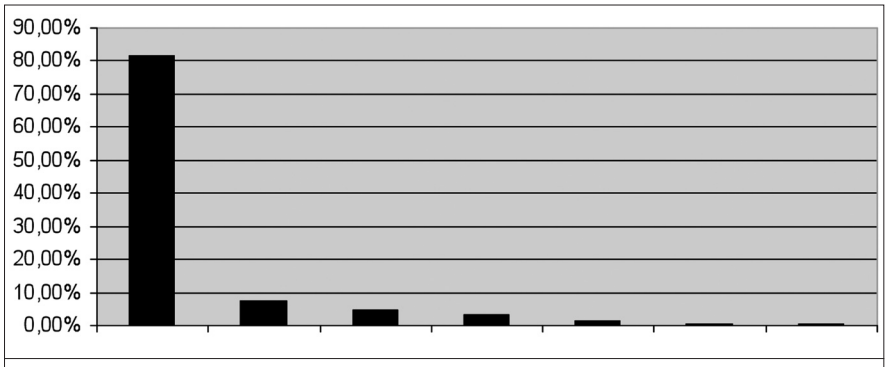
Since there is no clear definition of "conventional" or "late" onset in SpA, a sensibility test was performed in this cohort. The data was divided in three different ways: first, those younger and those older than 40 years; second, those younger and those older than 45 years; and third, those younger and those older than 50 years.

Demographic and clinical data were collected including time of disease duration, tender and swollen joint count, visual analogue scale for pain according to patient (VAS for pain) and disease activity according to patient and physician (patient and physician VAS for activity, respectively). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were also registered. The BASMI (Bath Ankylosing Spondylitis Metrology Index) (23) was used for the evaluation of the spine mobility. The presence of pain at enthesitis sites was evaluated by MASES (Maastricht Ankylosing Spondylitis Enthesitis Score) (24); the MASES scores varied from 0 to 13. Disease activity and functional status were evaluated according to BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) (25) and BASFI (Bath Ankylosing Spondylitis Functional Index) (26), respectively. Quality of life data were recorded through ASQoL (Ankylosing Spondylitis Quality of Life) questionnaires (27), varying from 0 to 18. All questionnaires used were previously translated, cross-translated, validated and culturally adapted to the Portuguese language (28). Radiological evaluation was performed by BASRI (Bath Ankylosing Spondylitis Radiology Index), including BASRI-spine (lumbar and cervical spine, and sacroiliac joints) and BASRI-total (BASRI-spine and BASRI-hips) (29). Cervical spine involvement was determined by means of the goniometric measurement of cervical rotation (defined as lower than 20°, 20–70° and higher than 70°). Shoulder involvement was evaluated by the presence of pain and/or limitation of motion. Hip involvement was also assessed by clinical (presence of pain and/or limitation) and radiological evaluations (classified as normal, suspicious, mild, moderate or severe) regarding BASRI-hips.

Peripheral arthritis was considered when present or past synovitis was diagnosed by a doctor (in the 66 joints count). Enthesitis was considered when the patients reported spontaneous pain or tenderness on examination at entheseal sites (according to the Maastricht Ankylosing Spondylitis Score). Dactylitis was considered when present or past dactylitis was diagnosed by a doctor.

Statistical analysis

Categorical variables were compared by χ^2 and Fisher's exact test, and continuous variables were compared by ANOVA or Kruskal-Wallis test. A value of $p<0.05$ was considered significant, and $0.05>p>0.10$ was considered a statistical trend.



Age at onset	0-40	41-45	46-50	51-55	56-60	61-65	>65
%	81.8%	7.6%	4.8%	3.3%	1.6%	0.6%	0.3%
n	1165	108	69	47	22	9	4

Fig. 1. Distribution of age at disease onset.

Results

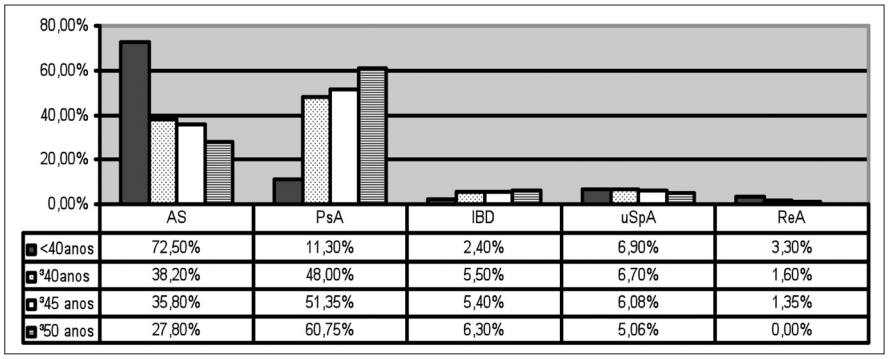
In the 1424 included patients, there were 66.3% with the diagnosis of AS, 18% psoriatic arthritis, 6.7% uSpA, 5.5% ReA, and 3.5% IBD. The mean age at first symptom was 28.56±12.34 years. Figure 1 shows that 259 patients (18.2%) presented disease onset after 40 years, 151 (10.6%) after 45 years and 81 (5.8%) after 50 years. Disease onset was rare after 55 years (2.5%), 60 years (0.9%) and 65 years (0.3%). Only four SpA patients had their disease onset after 65 years.

The distribution of the SpA clinical presentation according to age at disease onset is shown in Table I. The mixed (axial + peripheral arthritis + enthesitis) form was the most frequently observed clinical presentation, in a similar percentage in the three age cut-offs (40, 45 and 50 years). While the pure axial involvement decreased as the age cut-off increased, the pure periph-

Table I. Clinical variants according to age at onset in 1424 SpA patients.

	>40 years	>45 years	>50years
Mixed (axial+peripheral arthritis+ enthesitis)	43.6%	42.7%	42.0%
Axial	21.4%	21.4%	17.4%
Peripheral arthritis	27.4%	29.0%	36.2%
Enthesitis	7.6%	6.9%	4.3%

$p<0.001$ for all age cut-offs.



	AS	PsA	IBD	uSpA	ReA
<40anos	72,50%	11,30%	2,40%	6,90%	3,30%
≥40anos	38,20%	48,00%	5,50%	6,70%	1,60%
≥45 anos	35,80%	51,35%	5,40%	6,08%	1,35%
≥50 anos	27,80%	60,75%	6,30%	5,06%	0,00%

Fig. 2. Specific spondyloarthritis diagnosis according to age at onset.
AS: ankylosing spondylitis; PsA: psoriatic arthritis; IBD: inflammatory bowel disease; USpA: undifferentiated spondyloarthritis; ReA: reactive arthritis.

eral involvement increased as the age cut-off increased (p<0.001 for all age cut offs) (Table I). The distribution of specific SpA was similar to the clinical presentation: while the frequency of AS decreased as the age at disease onset increased, the frequency of PsA increased as the age at onset increased (Fig. 2).

Comparing the groups according to age of first symptoms, we found that patients whose diagnosis occurred at an older age presented a higher proportion of peripheral arthritis, dactylitis, nail involvement and psoriasis (Table II). The frequency of female patients increased as the groups got older (Table II). Positive familial history of SpA was significantly more frequent in the group with age at onset after 40 years (p=0.021). And the percentage of inflammatory low back pain, alternating buttock pain, radiographic sacroiliitis, hip involvement, HLA-B27 and uveitis significantly increased in the younger groups. A detailed comparison of epidemiological and clinical findings in these populations is shown in Table II.

The mean interval between the first symptom and the diagnosis of SpA was shorter in patients with disease onset after 40 years (3.04±0.34 years) compared to those with presentation before 40 years (7.29±0.34 years) (p<0.001). The time to diagnosis was also shorter in the patients with age at onset after 45 years (2.40±0.38 years *vs*. 7.03±0.27 years in those before 45 years [p<0.001]) and after 50 years (2.68±0.56 years *vs*. 6.80±0.26 years in those before 50 years [p=0.001]).

The physical examination of the SpA patients revealed that those with older age at onset presented higher number of painful and swollen joints (Table III). The mean MASES scores were similar in all the different groups. BASMI measurements presented better results in the older age groups (Table III), who also presented a significantly lower number of patients with axial disease.

Disease indices, as BASDAI, BASFI and ASQoL presented similar results in all the age groups (Table IV). ESR showed significant higher mean values in the group with age at onset >50 years, while there was a statistical trend between higher mean values of CRP and disease onset <40 years (Table IV). Radiographic indices showed worse results in the younger age groups (Table IV).

Discussion

With the recent proposition of the classification criteria for axial (18) and peripheral (30) SpA, the disease spectrum of the group has grown significantly.

Table II. Epidemiological and clinical profile of 1424 spa patients according to the age at onset.

	Age cut-off of 40 years			Age cut-off of 45 years			Age cut-off of 50 years		
	<40years n=1165	≥40 n=259	p-value	<45 years n=1273	≥45 years n=151	p-value	<50 years n=1434	≥50 years n=81	p-value
Female gender	24.1%	39.4%	**<0.001**	24.8%	43.5%	**0.001**	25.6%	46.2%	**<0.001**
Alternating buttock pain	34.7%	28.2%	**0.045**	44.9%	35.4%	**0.028**	34.4%	19.2%	**0.006**
Inflammatory low back pain	91.2%	76.8%	**<0.001**	90.5%	72.1%	**<0.001**	90.2%	61.5%	**0.001**
Radiographic sacroiliitis	81.9%	55.2%	**<0.001**	79.5%	57.8%	**<0.001**	78.9%	48.7%	**<0.001**
Cervical pain	30.1%	37.1%	**0.030**	30.5%	39.5%	**0.026**	31.1%	37.2%	0.259
Hip involvement	27.1%	18.9%	**0.006**	26.6%	17.7%	**0.019**	26.3%	15.4%	**0.032**
HLA B27 (#)	72.8%	49.5%	**<0.001**	71.2%	50.0%	**0.002**	70.5%	45.5%	**0.012**
Arthritis (lower limbs)	47.6%	57.5%	**0.004**	47.9%	61.2%	**0.002**	48.9%	56.4%	0.196
Arthritis (upper limbs)	19.1%	38.2 %	**<0.001**	19.9%	43.5%	**<0.001**	20.8%	48.7%	**<0.001**
Enthesitis	28.5%	23.9%	0.138	28.0%	25.2%	0.473	28.2%	19.2%	0.086
Dactylitis	7.7%	15.1%	**<0.001**	8.1%	6.3%	**0.001**	8.2%	21.8%	**0.001**
Uveitis	22.1%	12.0%	**<0.001**	20.1%	12.2%	**0.022**	19.9%	9.0%	**0.017**
Inflammatory bowel disease	4.2%	6.2%	0.169	4.3%	6.1%	0.319	4.4%	6.4%	0.405
Psoriasis	11.4%	46.7%	**<0.001**	14.2%	48.3%	**<0.001**	15.4%	59.0%	**<0.001**
Nail lesions	6.8%	23.6%	**<0.001**	8.0%	23.8%	**<0.001**	8.4%	30.8%	**<0.001**
Uretritis	4.8%	3.1%	0.227	4.6%	3.4%	0.495	4.7%	1.3%	0.158
Balanitis	3.8%	1.5%	0.072	3.5%	2.0%	0.343	3.4%	2.6%	0.682
Acne conglobata	1.5%	2.3%	0.383	1.7%	1.4%	0.743	1.6%	2.6%	0.538
Positive familial history	19.2%	13.1%	**0.021**	16.7%	15.0%	0.585	16.8%	11.5%	0.221
Cardiac involvement	2.9%	2.3%	0.383	3.0%	1.4%	0.260	2.8%	2.6%	0.890

(#) data available in 638 patients.

Table III. Physical findings in 1424 SpA patients according to age at onset.

	Age cut-off of 40 years			Age cut-off of 45 years			Age cut-off of 50 years		
	<40years n=1165	≥40 n=259	*p*-value	<45 years n=1273	≥45 years n=151	*p*-value	<50 years n=1434	≥50 years n=81	*p*-value
Occiput-to-wall (cm) (mean±SE)	5.78 ± 0.22	4.23 ± 0.33	**<0.001**	5.62 ± 0.21	4.40 ± 0.48	**0.022**	5.57 ± 0.20	4.34 ± 0.60	0.60
Chest expansion (cm) (mean±SE)	3.78 ± 0.22	3.16 ± 0.11	0.13	3.74 ± 0.20	3.08 ± 0.14	**0.009**	3.70 ± 0.19	3.15 ± 0.19	**0.046**
Schober test (cm) (mean±SE)	4.66 ± 0.17	5.56 ± 0.28	**0.008**	4.74 ± 0.16	5.55 ± 0.38	0.054	4.78 ± 0.15	5.54 ± 0.52	0.16
Lateral lumbar flexion (cm) (mean±SE)	24.06 ± 0.63	28.94 ± 1.41	**0.002**	24.33 ± 0.60	30.17 ± 1.93	**0.005**	24.48 ± 0.59	33.26 ± 2.86	**0.004**
Number of painful joints (mean±SE)	3.38 ± 0.21	5.41 ± 0.59	**0.001**	5.58 ± 0.21	5.34 ± 0.72	**0.021**	3.56 ± 0.20	7.20 ± 1.22	**0.004**
Number of swollen joints (mean±SE)	1.24 ± 0.11	2.74 ± 0.43	**0.001**	1.35 ± 0.12	2.86 ± 0.50	**0.004**	1.42 ± 0.12	3.01 ± 0.70	**0.031**
MASES score	2.12 ± 0.08	2.22 ± 0.19	0.647	2.13 ± 0.08	2.29 ± 0.27	0.580	2.14 ± 0.07	2.27 ± 0.35	0.72

Table IV. Comparison of inflammatory activity, functional and quality of life indices and degree of radiographic involvement in 1424 SpA patients according to age at onset.

	Age cut-off of 40 years			Age cut-off of 45 years			Age cut-off of 50 years		
	<40years n=1165	≥40 n=259	*p*-value	<45 years n=1273	≥45 years n=151	*p*-value	<50 years n=1434	≥50 years n=81	*p*-value
Physician global assessment (mean±SE)	3.84 ± 0.07	3.81 ± 0.17	0.8	3.82 ± 0.07	3.87 ± 0.22	0.85	3.83 ± 0.06	3.88 ± 0.34	0.87
Patient global assessment (mean±SE)	4.86 ± 0.08	5.00 ± 0.18	0.47	4.88 ± 0.08	4.84 ± 0.24	0.86	4.89 ± 0.05	4.63 ± 0.34	0.46
BASDAI (mean±SE)	4.15 ± 0.06	4.47 ± 0.15	0.061	4.18 ± 0.06	4.44 ± 0.20	0.21	4.21 ± 0.07	4.03 ± 0.26	0.509
BASFI (mean±SE)	4.58 ± 0.08	4.69 ± 0.17	0.551	4.58 ± 0.07	4.74 ± 0.23	0.52	4.62 ± 0.07	4.28 ± 0.32	0.313
ASQoL (mean±SE)	7.79 ± 0.16	7.81 ± 0.33	0.95	7.78 ± 0.15	7.90 ± 0.44	0.79	7.79 ± 0.13	7.77 ± 0.52	0.543
ESR (mm/h) (mean±SE)	24.74 ± 0.69	26.07 ± 1.42	0.40	24.59 ± 0.66	26.98 ± 1.90	0.23	24.51 ± 0.64	30.30 ± 2.70	**0.040**
CRP (mg/dl) (mean±SE)	10.31 ± 0.75	8.02 ± 0.97	0.06	10.15 ± 0.71	7.79 ± 1.15	0.08	10.00 ± 0.68	8.35 ± 1.39	0.291
BASRI-TOTAL mean±SE)	7.28 ± 0.15	6.31 ± 0.31	**0.006**	7.19 ± 0.14	6.53 ± 0.40	0.13	7.18 ± 0.14	6.07 ± 0.58	0.071
BASRI SPINE (mean±SE)	6.10 ± 0.11	5.35 ± 0.25	**0.008**	6.04 ± 0.11	5.43 ± 0.31	0.073	6.04 ± 0.11	4.89 ± 0.44	**0.015**
BASRI HIPS (mean±SE)	1.23 ± 0.04	0.96 ± 0.09	**0.01**	1.20 ± 0.09	1.05 ± 0.12	0.254	1.19 ± 0.08	1.12 ± 0.19	0.736

The prevalence of SpA in the general population can be similar to rheumatoid arthritis in some countries (31-33). SpA characteristics may be different when disease starts at an older age, since chronic inflammatory diseases in the elderly may have some specificity regarding their clinical presentation. Analysing the results of the present study, we can observe two different SpA groups, according to age at onset. First, the patients who start symptoms before 40 years present the classical symptoms related to the axial involvement such as inflammatory low back pain, alternating buttock pain and radiographic sacroiliitis, which is associated with higher frequency of HLA-B27, hip involvement and uveitis, and higher BASRI scores. Second, a group with disease onset >40 years shows a predominance of female patients with peripheral involvement and psoriasis, as well as nail involvement and dactylitis.

The predominance of peripheral involvement in older patients with SpA has already been noted (3, 6, 8). Studies analysing uSpA (6) and PsA (34) also verified the higher prevalence of peripheral arthritis in older patients. The latter authors also noted that early onset PsA showed higher rates of HLA-B27 positivity and isolated axial pattern (34), similar to that found in the present study.

In 1989, Dubost and Sauvezie described a form of late-onset uSpA characterised by oligoarthrits associated with pitting oedema of the extremities, systemic symptoms, and mild involvement of the axial skeleton (3). Although other series (5, 8) presented similar cases, in the present study there were no patients with this pitting oedema of the extremities. Other studies have analysed the differences among SpA and other rheumatic diseases, like rheumatoid arthritis (11, 35) and polymyalgia rheumatic (36).

With reference to extra-articular manifestations, uveitis and psoriasis were the most frequent findings in the present study. Uveitis was associated with disease onset before 40 years, while psoriasis was associated with the groups with later age at onset. The presence of inflammatory bowel disease and cardiac manifestations was uncommon in the cohort, and they presented no association with a specific age at onset. Other extra-articular manifestations (37) were observed in <2% of the patients, and were not described in the statistical analysis.

In the present analysis, we found discrepant results related to the inflammatory activity (ESR, CRP) between groups: ESR showed significant higher mean values in the group with age at onset >50 years, while there was a statistical trend between higher mean values of CRP and disease onset <40 years. Other studies (3, 6, 38) have

found marked elevation of inflammatory parameters in patients with late-onset SpA.

A more severe outcome has been noted in PsA of elderly-onset by some authors, showing higher prevalence of erosive arthritis (39), although these data are controversial (34). No influence of age at onset in disease outcome was observed by Brophy *et al*. (13) in patients with AS. In the present study we did not note differences in BASFI and quality of life (ASQoL) in the different groups.

AS was underrepresented in the older-onset group, as it is more frequent to start in the 2nd to 4th decades. A higher proportion of patients with PsA was observed in the group >40 years (Fig. 1) and the later-onset for this form of disease has also been noted by Rojas-Vargas who studied 150 patients with less than two years of disease duration (40). Despite the fact that late-onset SpA patients may have an atypical pattern, the time between first symptoms and diagnosis was shorter in this group of patients. This may be due to the higher prevalence of peripheral symptoms that are readily visible and could be considered more valuable in the physician's judgment.

In conclusion, SpA patients who present disease onset >40 years have an atypical clinical profile with predominance of peripheral arthritis, female gender, nail and psoriasis involvement as well as dactylitis. This atypical clinical profile may lead this group of diseases to be underdiagnosed at this age in favour of other inflammatory disorders, so rheumatologist should be alert to these variations in order to succeed in the diagnosis.

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