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Original article

Enteropathic arthritis in Brazil: data from the Brazilian registry of spondyloarthritis

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ABSTRACT

Inflammatory bowel diseases (Crohn's disease and ulcerative rectocolitis) have extraintestinal manifestations 25% of the patients, with the most common one being the enteropathic arthritis.

Methods: Prospective, observational, multicenter study with patients from 29 reference centers participating in the Brazilian Registry of Spondyloarthritis (RBE), which incorporates the RESPONDIA (Ibero-American Registry of Spondyloarthritis) group. Demographic and clinical data were collected from 1472 patients and standardized questionnaires for the assessment of axial mobility, quality of life, enthesitic involvement, disease activity and functional capacity were applied. Laboratory and radiographic examinations were performed. The aim of this study is to compare the clinical, epidemiological, genetic, imaging, treatment and prognosis characteristics of patients with enteropathic arthritis with other types of spondyloarthritis in a large Brazilian cohort.

Results: A total of 3.2% of patients were classified as having enteroarthritis, 2.5% had spondylitis and 0.7%, arthritis (peripheral predominance). The subgroup of individuals with enteroarthritis had a higher prevalence in women ($P < 0.001$), lower incidence of inflammatory axial pain ($P < 0.001$) and enthesitis ($P = 0.004$). HLA-B27 was less frequent in the group with enteroarthritis ($P = 0.001$), even when considering only those with the pure axial form. There was a lower prevalence of radiographic sacroiliitis ($P = 0.009$) and lower radiographic score (BASRI) ($P = 0.006$) when compared to patients with other types of spondyloarthritis. They also used more corticosteroids ($P < 0.001$) and sulfasalazine ($P < 0.001$) and less non-steroidal anti-inflammatory drugs ($P < 0.001$) and methotrexate ($P = 0.001$).

Conclusion: There were differences between patients with enteroarthritis and other types of spondyloarthritis, especially higher prevalence of females, lower frequency of HLA-B27, associated with less severe axial involvement.

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Artrite enteropática no Brasil: dados do registro brasileiro de espondiloartrites

RESUMO

As doenças inflamatórias intestinais (doença de Crohn e retocolite ulcerativa) apresentam manifestações extraintestinais em um quarto dos pacientes, sendo a mais comum a artrite enteropática.

Métodos: Estudo prospectivo, observacional e multicêntrico, realizado com pacientes de 29 centros de referência participantes do Registro Brasileiro de Espondiloartrites (RBE), que se incorpora ao grupo RESPONDIA (Registro Ibero-americano de Espondiloartrites). Dados demográficos e clínicos de 1472 pacientes foram colhidos, e aplicaram-se questionários padronizados de avaliação de mobilidade axial, de qualidade de vida, de envolvimento entesítico, de atividade de doença e de capacidade funcional. Exames laboratoriais e radiográficos foram realizados. Objetivamos, neste presente artigo, comparar as características clínicas, epidemiológicas, genéticas, imagenológicas, de tratamento e prognóstico de enteroartríticos com os outros espondiloartríticos nesta grande coorte brasileira.

Resultados: Foram classificados como enteroartrite 3,2% dos pacientes, sendo que 2,5% tinham espondilite e 0,7%, artrite (predomínio periférico). O subgrupo de indivíduos com enteroartrite apresentava maior prevalência de mulheres ($P < 0,001$), menor incidência de dor axial inflamatória ($P < 0,001$) e de entesite ($P = 0,004$). O HLA-B27 foi menos frequente no grupo de enteroartríticos ($P = 0,001$), mesmo se considerado apenas aqueles com a forma axial pura. Houve menor prevalência de sacroiliíte radiológica ($P = 0,009$) e também menor escore radiográfico (BASRI) ($P = 0,006$) quando comparado aos pacientes com as demais espondiloartrites. Também fizeram mais uso de corticosteroides ($P < 0,001$) e sulfasalazina ($P < 0,001$) e menor uso de anti-inflamatórios não hormonais ($P < 0,001$) e metotrexato ($P = 0,001$).

Palavras-chave:

Artrite enteropática

Doença de Crohn

Retocolite ulcerativa

Estudos de registro

Conclusão: Foram encontradas diferenças entre as enteroartrites e as demais espondiloartrites, principalmente maior prevalência do sexo feminino, menor frequência do HLA-B27, associados a uma menor gravidade do acometimento axial.

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Introduction

Inflammatory bowel disease (IBD) is the term currently used to designate two diseases considered idiopathic to date: Crohn's disease (CD) and ulcerative rectocolitis (URC). Although grouped together, the two can be differentiated by defined clinical, endoscopic, histological, and etiopathogenic characteristics.

Both diseases affect men and women equally and have a peak incidence in the second and third decades of life; the prevalence of each is estimated at 25-250 per 100,000 individuals, with a slight predominance of URC. Their main symptoms are diarrhea, abdominal pain, and gastrointestinal bleeding, in addition to systemic symptoms such as fever, weight loss, and fatigue. They often have an intermittent course, alternating periods of exacerbation and remission.

CD is characterized by transmural (granulomatous in only approximately 30%) and discontinuous inflammation of the digestive tract, and it affects mainly the distal small intestine (ileum), but with potential to reach any other segment, from the mouth to the anus. Due to its tendency to cause fibrosis, it can lead to stenosis and obstruction, and because of the possibility of micro-perforations, fistulas may appear.

URC, in turn, is characterized by a superficial and continuous involvement of the colonic mucosa, almost invariably involving the rectum and sometimes extending proximally. It is usually classified (regarding the severity and extent of involvement) as mild when only the rectum or rectosigmoid are affected (proctitis or proctosigmoiditis); as moderate, when the descending colon is also affected (left colitis); and as severe, when it reaches the cecum (pancolitis).

Other extraintestinal manifestations can be associated to IBD in approximately 25% of patients; the most common are those caused by joint (axial or peripheral), eye (uveitis and episcleritis), skin (erythema nodosum and pyoderma gangrenosum), and biliary tract (sclerosing cholangitis) involvement. These symptoms may precede, coexist with, or follow the intestinal manifestations.¹⁻⁴

Enteroarthritis is the most common extraintestinal manifestation of IBD, whose prevalence varies from 14% to 44%.⁵⁻⁸ It has two main patterns of clinical expression: the peripheral and axial forms. The first can be divided into two subgroups: type I, which is often self-limited, oligoarticular (< five joints involved), accompanies outbreaks of intestinal inflammatory activity, and is not associated with the presence of HLA-B27; and type II, polyarticular, usually follows an independent course from the intestinal disease. The latter rarely becomes chronic. The axial form can include sacroiliitis and/or spondylitis unrelated to the bowel disease activity, and may even precede its onset by years.⁹⁻¹² This is associated with the presence of HLA-B27 in 50% to 75% of cases – a similar frequency,

although lower, than that found in idiopathic spondylitis.¹³⁻¹⁵ There is often some overlapping between these forms, and periarticular involvement is possible, whether of the entheses, tendons, or the periosteum.^{5,16-18}

CARD15 gene polymorphisms have been associated with an increased risk of developing CD, and are considered predictors of both chronic inflammatory bowel disease in patients with spondyloarthritis and sacroiliitis in those with CD. This gene encodes an intracellular protein expressed in several cell types, which act as receptor for components of bacterial cell wall, and is involved in the activation of nuclear factor kappa β (NF- κ B) and apoptosis.^{8,19,20}

In this article, the main characteristics of the sample of enteropathic arthritis of the Brazilian Registry of Spondyloarthritis (Registro Brasileiro de Espondiloartrites – RBE) are discussed.

Methods

This was a prospective, observational, multicenter study, conducted with patients from 29 reference centers participating in the RBE. All patients met the criteria of the European Spondyloarthropathy Study Group (ESSG).²¹ Data were collected from June 2006 to December 2009. The RBE is a member of the Ibero-American Registry of Spondyloarthritis (RESPONDIA) group, which consists of nine Latin American countries (Argentina, Brazil, Costa Rica, Chile, Ecuador, Mexico, Peru, Uruguay, and Venezuela) and the two countries of the Iberian Peninsula (Spain and Portugal).

In this study, a standard protocol was applied to the 1,472 patients. The diagnosis of enteroarthritis was considered when a patient had peripheral or axial inflammatory joint involvement associated with CD or URC, diagnosed by a physician and confirmed by radiographic or endoscopic examination.

Demographic and clinical data were collected, and the following questionnaires, previously translated and validated for Brazilian Portuguese, were applied: Bath Ankylosing Spondylitis Metrologic Index (BASMI), to assess spinal mobility;²² Ankylosing Spondylitis Quality of Life (ASQoL), to assess quality of life;²³ Maastricht Ankylosing Spondylitis enthesitis score (MASES), to assess enthesitic involvement;²⁴ Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), to assess disease activity;²⁵ and Bath Ankylosing Spondylitis Functional Index (BASFI) to assess functional capacity.²⁶

Laboratory test results (HLA-B27, erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) were also recorded, as well as radiographs of the cervical and lumbosacral spine and the sacroiliac and coxofemoral joints. Radiological damage was evaluated using the Bath Ankylosing Spondylitis Radiologic Index (BASRI).²⁷

Statistical analysis

Pearson's chi-squared test was used to analyze the association between enteroarthritis and categorical variables, and Student's t-test was used to compare means of numerical variables between patients with enteroarthritis and other types of spondyloarthritis. An alpha of 5% was used in all tests: those with $P < 0.05$ were considered to be statistically significant.

Results

Of a total of 1,472 patients, 65.4% (N = 963) were classified as having ankylosing spondylitis (AS), 18.4% (N = 271) as psoriatic arthritis (PA), 6.7% (N = 98) as undifferentiated spondyloarthritis (USpA), 3.3% (N = 49) as reactive arthritis (ReA), and 3.2% (N = 48) as enteropathic arthritis (EA), with 2.5% (N = 7) of spondylitis associated with IBD and 0.7% (N = 11) of arthritis associated with IBD. Also, 2.9% were classified as having juvenile spondyloarthritis (JSpA) (Fig. 1).

Regarding the clinical forms identified among individuals with enteroarthritis, it was observed that the overlapping (mixed form, with both axial and peripheral involvement) was the most common phenotype with 52.5%, followed by the pure axial with 27.5%; isolated peripheral form, with 17.5%; and enthesitic form, without axial or peripheral joint involvement, with 2.5% (Fig. 2).

When comparing the clinical characteristics (Table 1) of the enteroarthritis group and of other types of spondyloarthritis, a statistically significant difference was observed regarding the higher frequency of females ($P < 0.001$) and the lower frequency of inflammatory axial pain ($P < 0.001$) and of enthesitis ($P = 0.004$) in patients with enteropathic arthritis.

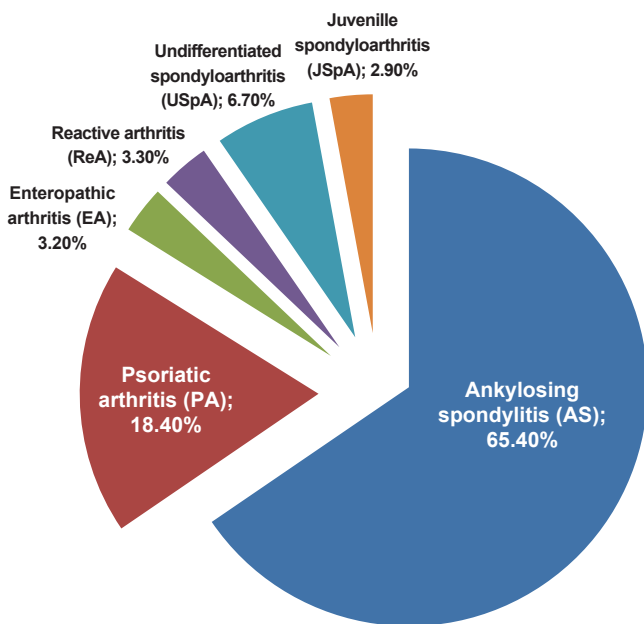


Fig. 1 – Brazilian Registry of Spondyloarthritis - diagnostic distribution.

Patients with enteropathic arthritis showed lower mean disease duration (9.6 years vs. 14.1 years, $P = 0.005$), fewer inflamed joints (0.77 vs. 1.61, $P = 0.004$), as well as better rates of mobility in the lumbar spine (mean lateral lumbar flexion of 31.5 cm vs. 25.4 cm, $P = 0.03$; and Schober index of 6.2 cm

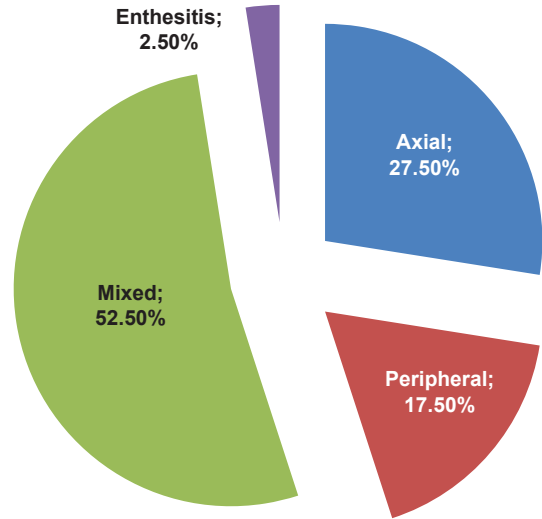


Fig. 2 – Brazilian Registry of Spondyloarthritis - clinical forms in enteropathic arthritis.

Table 1 – Comparison of demographic and clinical characteristics in patients with enteroarthritis and other types of spondyloarthritis.

	Brazilian Registry of Spondyloarthritis		
	Enteroarthritis	Spondyloarthritis	P
Male gender (N/%)	22/45.8%	1,067/73.2%	< 0.001
Age (mean in years)	45.9	42.6	0.100
Time of symptoms (mean in years)	9.6	14.1	0.005
Inflammatory axial pain ^a (N/%)	33/68.8%	1,286/88.3%	< 0.001
Alternating pain in buttocks (N/%)	23/47.9%	631/43.3%	0.500
Peripheral arthritis (N/%)	23/47.9%	863/59.2%	0.100
Number of inflamed joints (mean)	0.77	1.61	0.004
Enthesopathy ^b (N/%)	14/29.2%	732/50.2%	0.004
Psoriasis (N/%)	6/12.5%	265/18.2%	0.300
Anterior uveitis (N/%)	5/10.4%	296/20.3%	0.092
Positive family history ^c (N/%)	4/8.3%	245/16.8%	0.100
Lateral lumbar flexion (mean; cm)	31.5	25.4	0.030
Schober index (mean; cm)	6.2	4.8	0.051

^aLumbar, dorsal or cervical pain comprising at least four of the following criteria: insidious, onset before age 45, lasting more than three months, improvement with exercise, and morning stiffness.

^bPast or present spontaneous pain or at examination of the Achilles tendon insertion or plantar fascia.

^cPresence in first- or second-degree relatives with one of the following: ankylosing spondylitis, psoriasis, acute uveitis, reactive arthritis, and inflammatory bowel disease.

vs. 4.8 cm, $P = 0.051$). No statistical difference was observed between the prevalence of extra-articular manifestations, although there was a trend of lower incidence of ocular disease (anterior uveitis) in patients with enteroarthritis (10.4% vs. 20.3% in other types of spondyloarthritis, $P = 0.092$) (Table 1).

Positivity for HLA-B27 was also statistically significant, with a lower frequency in patients with enteroarthritis ($p = 0.001$). There was also a statistical difference in CRP measurements between the two groups, with lower values among those with enteropathic arthritis (5.48 mg/L vs. 10.29 mg/L, $P = 0.001$). Conversely, the latter showed a statistical trend to higher values of ESR (31.3 mm vs. 24.7 mm, $P = 0.08$).

Regarding radiographic alterations, there was a lower prevalence of radiographic sacroiliitis, considering at least grade II bilateral or III unilateral (modified New York criteria)²⁸ in individuals from the enteroarthritis group (60.4% vs. 76.8% $P = 0.009$). BASRI scores were also lower, with a mean of 5.2 and 7.1 in enteroarthritis and other diseases ($P = 0.006$), respectively and of the BASRI coxofemoral-component (0.6 vs. 1.2; $P = 0.001$).

No statistical differences were observed between the two groups regarding professional activity, work disability, exercise habits, or ASQoL, BASDAI, BASFI, and MASES scores (Table 2).

As for the therapeutic regimens used (Table 3), a more frequent use of corticosteroids was observed (62.5% vs. 34.6%; $P < 0.001$) and less frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) (43.8% vs. 68.2%; $P < 0.001$). There was also a difference regarding the evaluation of NSAIDs efficacy by patients. In the enteroarthritis group, only 35.4% of the patients described NSAIDs as being effective (i.e., capable of effectively improving pain within 48 hours), compared with 69.3% of individuals with the other diseases ($P < 0.001$). There is a limitation on the scoring for this comparison, since different drug doses and regimens were grouped under the same category.

Among the disease-modifying antirheumatic drugs (DMARDs), there was also a statistical difference between the use of methotrexate (with lower use in enteroarthritis, 29.2%

vs. 52.6%, $P = 0.001$) and sulfasalazine (with greater use in this group, 79.2% vs. 43.2%, $P < 0.001$). Among the anticytokine agents, infliximab showed only a statistical trend in the frequency of use between the groups (use in the enteroarthritis group, 25%, and in other diseases, 15%, $P = 0.057$). There was no difference between the groups regarding the use of other anti-TNF agents, adalimumab, and etanercept; it is noteworthy that the latter drugs were introduced more recently in Brazil.

Discussion

The enteroarthritis, classified within the group of spondyloarthritis, have peculiar characteristics that differ in some aspects from idiopathic ankylosing spondylitis and other diseases in this group. In this study, a small predominance of the female gender was observed among patients with enteroarthritis, in contrast with other types of spondyloarthritis (where the male/female ratio approaches 3:1). The findings are consistent with the results of studies that found a balance^{5,6,9,29-31} or higher frequency in the female gender,³²⁻³⁴ although some authors found a male predominance even among patients with enteropathic arthritis.^{8,10,17,35-37}

These discrepancies may reflect population differences, but above all, they can be related to the fact that some of the aforementioned studies did not subdivide their patients into more specific groups, such as axial or peripheral involvement, or did not consider only patients with enteropathic arthritis, but also individuals with inflammatory bowel disease without joint involvement, which in practice greatly diminishes the validity of the comparison.

Regarding the clinical presentation, no significant differences were observed between the groups with enteropathic arthritis and other types of spondyloarthritis. In both groups, there was a predominance of mixed form in approximately

Table 2 – Comparison of laboratory tests, imaging studies and disease rates in patients with enteroarthritis and other types of spondyloarthritis.

	Brazilian Registry of Spondyloarthritis		
	Enteroarthritis	Spondyloarthritis	P
HLA-B27	10/38.5%	492/70.1%	0.001
CRP (mean; mg/L)	5.49	10.29	0.001
ESR (mean; mm)	31.3	24.7	0.080
BASDAI (mean)	4.62	4.18	0.246
BASFI (mean)	4.77	4.54	0.536
MASES (mean)	1.9	2.1	0.642
High-grade radiological sacroiliitis ^a	29/60.4%	1,119/76.8%	0.009
BASRI- column (mean)	4.8	5.9	0.055
BASRI- coxofemoral (mean)	0.6	1.2	0.001
BASRI-total (mean)	5.2	7.1	0.006

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
^aThe mere presence of sacroiliitis at plain radiography, graded as at least grade II bilateral or unilateral grade III.

Table 3 – Description of the medications used and their frequency in patients with enteroarthritis and other types of spondyloarthritis.

	Brazilian Registry of Spondyloarthritis		
	Enteroarthritis	Spondyloarthritis	P
Use of NSAIDs (N/%)	21/43.8%	994/68.2%	< 0.001
Efficacy of NSAIDs ^a (N/%)	17/37.4%	1,009/69.3%	< 0.001
Corticosteroids (N/%)	30/62.5%	504/34.6%	< 0.001
Methotrexate (N/%)	14/29.2%	766/52.6%	0.001
Sulfasalazine (N/%)	38/79.2%	630/43.2%	< 0.001
Infliximab (N/%)	12/25.0%	218/15.0%	0.057
Etanercept (N/%)	1/2.1%	43/3.0%	0.725
Adalimumab (N/%)	- /0%	34/2.3%	0.284

NSAIDs, non-steroidal anti-inflammatory drugs.

^aThe medication was considered effective if it improved pain after 48 hours of its onset and/or resulted in rapid pain worsening after 48 hours of withdrawal, regardless of the subclass or dose regimen.

50% of patients, followed by axial and peripheral forms, and less frequently, the enthesitic form. These data are similar to those found in other studies.^{17,38,39}

A less severe axial involvement was observed in patients with enteroarthritis when compared to individuals with other types of spondyloarthritis, verified by the lower prevalence of inflammatory axial pain, better rates of mobility in the lumbosacral spine, lower frequency of radiographic sacroiliitis, and lower BASRI scores (lower radiographic damage). Nevertheless, no difference was observed between measures of functional capacity, disease activity and quality of life. However, this finding does not necessarily indicate a more "benign" nature of IBD-related spondylitis, as it may be due to the difference in time of evolution between the two groups in this sample (on average, patients with enteropathic arthritis had approximately four years and six months less time of symptoms than the others). Some authors have found a positive association between the duration of bowel disease and the likelihood of developing extraintestinal manifestations, reinforcing this hypothesis.^{9,10,40} A number of case series are consistent with the finding of lower radiographic grade in patients with IBD, even in symptomatic axial disease.^{29,41,42} In other studies, however, the radiographic classification of severity was similar between classical and enteropathic spondylitis.^{43,44}

When comparing the frequency of radiographic sacroiliitis among patients with enteropathic arthritis in the current sample (60%) with several other studies (20% to 61%),^{17,31,36,37,45} a high frequency of these alterations was confirmed, even without a clear clinical correlation, i.e., no history of pain in the buttocks or lumbar region, constituting what some authors call subclinical or asymptomatic sacroiliitis.^{6,7,40,41,46-49} Nevertheless, the comparison of these data is possibly flawed, given the great variation among the selected populations, imaging methods used, the criteria used, and the observers according to different studies - many of which were multicenter, including the present study.

This study also found a lower prevalence of HLA-B27 in individuals with enteroarthritis when compared to other types of spondyloarthritis (38.5% vs. 70.1%; $P = 0.001$), although this difference decreases when the subgroup with pure axial involvement (IBD-related spondylitis), in which the presence of this antigen reaches 47.6, is analyzed separately. Among those classified as having the pure peripheral form that were tested, none had it. The results are consistent with those of studies that found a higher prevalence of HLA-B27 in patients with IBD and axial form than in patients without the axial form (albeit at a lower frequency when compared to that found in idiopathic ankylosing spondylitis).^{10,17,35,40,48,50}

However, the population frequency of the allele should always be considered when interpreting data on the prevalence of genetic markers, which may explain discrepancies between different studies with different populations.^{35,51}

Regarding the medications, the lower frequency of use of NSAIDs and higher use of corticosteroids have also been observed in other studies,^{17,50} and probably reflect the fear of administering NSAIDs to patients with IBD at risk of exacerbation of bowel symptoms. This risk, however, has no consensus regarding its real magnitude.⁵²

In the present study, differences between patients with enteroarthritis and other spondyloarthritides were observed, es-

pecially higher prevalence in females, and lower frequency of HLA-B27, even in those with the pure axial form and associated with the lower degree of severity of axial involvement. These peculiarities should be taken into account when managing patients with IBD and musculoskeletal complaints.

Conflicts of interest

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Erratum

In the original article "Enteropathic arthritis in Brazil: data from the Brazilian registry of spondyloarthritis" (Rev Bras Reumatol 2013;53(6):452-459), where it reads:

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