

Brucellar Spondylodiscitis: Case Series of the Last 25 Years



Espondilodiscite Brucélica: Casuística dos Últimos 25 Anos

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ABSTRACT

Introduction: Brucellosis is an endemic zoonosis in Portugal. Brucellar spondylodiscitis is one of the most frequent focal manifestations which may cause severe sequelae despite appropriate therapy.

Material and Methods: Retrospective study of patients with diagnosis of brucellar spondylodiscitis admitted to the Infectious Diseases Department of Centro Hospitalar e Universitário de Coimbra, over a 25-year period (1988-2012).

Results: We identified 54 patients, 55.6% male, mean age of 54.8 years. In 81.5% an epidemiological context was identified, mostly contact with sheep and goats. The duration of symptoms prior to diagnosis was 5.5 months. The most common signs and symptoms were pain (98.1%), fever (46.3%) and neurological deficits (25.9%). Spinal magnetic resonance imaging was the most used imaging method (77.8%) showing abscesses in 29.6% of patients. Lumbar location predominated (77.7%). Diagnosis was attained in 47 patients (87.0%): positive blood cultures (3 patients), positive serology (32 patients) or by both methods (12 patients). Combined regimens of doxycycline and rifampicin (64.8%), or streptomycin (24.1%) were most used, for an average duration of 4.4 months. A patient was referred for surgery for abscess drainage. Evolution was mostly favorable (92.6%), no deaths occurring.

Discussion: Research of the epidemiologic context turned out to be a major key leading to the diagnosis. Treatment of osteoarticular brucellosis is still controversial.

Conclusions: Brucellar spondylodiscitis should be considered in the differential diagnosis of patients with low back pain, even in the absence of fever, particularly in regions where the disease is endemic. Antibiotic regimen, its' duration and the need for surgery should be individualized to achieve a better prognosis. Cases have declined over the years, a fact related to better control of animal endemic.

Keywords: Brucella; Brucellosis; Discitis; Osteomyelitis; Portugal.

RESUMO

Introdução: A brucelose é uma zoonose endémica em Portugal, sendo a espondilodiscite brucélica uma das manifestações focais mais frequentes. Pode provocar sequelas graves, apesar da terapêutica dirigida.

Material e Métodos: Estudo retrospectivo dos processos dos doentes com espondilodiscite brucélica, internados no Serviço de Doenças Infecciosas do Centro Hospitalar e Universitário de Coimbra, num período de 25 anos (1988-2012).

Resultados: Foram identificados 54 doentes, 55,6% do sexo masculino, com idade média de 54,8 anos. Em 81,5% identificou-se contexto epidemiológico, maioritariamente contacto com gado ovino e caprino. A duração da sintomatologia prévia ao diagnóstico foi de 5,5 meses. Os sinais e sintomas mais frequentes foram: dor (98,1%), febre (46,3%) e défices neurológicos (25,9%). A ressonância magnética nuclear da coluna foi o exame imagiológico mais usado (77,8%) evidenciando abcessos em 29,6% dos doentes. A localização lombar predominou (77,7%). O diagnóstico etiológico foi confirmado em 47 doentes (87,0%): microbiologicamente (3 doentes), serologicamente (32 doentes) ou por ambos (12 doentes). As associações de doxiciclina com rifampicina (64,8%), ou estreptomicina (24,1%) foram as mais utilizadas, com duração média de 4,4 meses de tratamento. Um doente teve indicação cirúrgica para drenar abscesso. A evolução foi maioritariamente favorável (92,6%), sem óbitos.

Discussão: A investigação de contexto epidemiológico revelou ser uma peça importante na suspeita do diagnóstico. O tratamento da brucelose osteoarticular ainda é controverso.

Conclusões: A espondilodiscite brucélica deve ser considerada no diagnóstico diferencial dos doentes com lombalgia, mesmo na ausência de febre, particularmente em regiões onde a doença é endémica. O esquema antibiótico, sua duração e a necessidade de cirurgia deverão ser individualizados, com vista a um melhor prognóstico. O número de casos tem diminuído ao longo dos anos, facto relacionado com melhor controlo da endemia animal.

Palavras-chave: Brucella; Brucelose; Discite; Osteomielite; Portugal.

INTRODUCTION

Spondylodiscitis is an infection of the intervertebral disc and adjacent vertebrae, which usually occurs through haematogenous spread. Worldwide, *Staphylococcus aureus* is the most commonly involved bacteria¹ although in endemic areas for brucellosis the latter should be considered in the differential diagnosis.^{2,3} Brucellosis is the most common zoonosis worldwide,

with more than 500,000 new cases each year.⁴ The Mediterranean basin is considered an endemic area, although the number of cases of notified human brucellosis has been decreasing in Portugal.^{5,6} The transmission route of this disease is mainly related to non-pasteurized milk and dairy products ingestion or to direct contact with infected animals. Diagnosis is based

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on isolation of *Brucella spp.* mainly from blood cultures. Nevertheless, due to its relatively slow growth together with a variable isolation rate (depending on the duration of the infection and on the used method), serologic methods are mostly used. Brucellosis may affect any organ or system and osteoarticular involvement is most common, particularly of the spine.⁷ Brucellar spondylodiscitis (BS) is one of the most severe signs of this infection, with potentially severe outcomes despite optimized therapy.⁸ The most efficient antibiotic regimen and the most adequate duration of treatment are still not clearly defined, although some studies describe additional benefit from a doxycycline/streptomycin association.⁷

Our study aimed to determine the epidemiological, clinical and therapeutic characteristics of patients with a diagnosis of BS followed at our Department, comparing our results with data available in the literature. As few national clinical series regarding this pathology have been described, we felt this characterization was an important contribution to the Portuguese reality.

MATERIAL AND METHODS

A retrospective analysis of the clinical records of patients with a BS diagnosis admitted to the Infectiology Department at the *Centro Hospitalar e Universitário de Coimbra (CHUC)* between the 1st January 1988 and the 31st December 2012 was carried out.

The diagnosis of spondylodiscitis was established based on suggestive clinical symptoms (spinal pain and/or *de novo* neurological deficit related with medullary or radicular compression, with or without fever) in association to spondylodiscitis-defining imaging.

Brucellosis as an etiological diagnosis was considered as confirmed in the presence of *Brucella spp.* identified by blood culture and/or demonstration of specific antibody titres above a significance level (1/160)

obtained by agglutination. The diagnosis was considered as presumptive when based on epidemiological, serological and imaging suggestive data, in association to a positive response to antibiotic directed therapy.

The following variables were analysed: age, gender, epidemiological history, predominant signs and symptoms, duration of symptoms, hospital stay (in the patients with multiple admissions, the sum of these was considered), year of diagnosis, imaging (magnetic resonance imaging (MRI) and/or CT-scan), affected spinal level, presence of abscesses, microbiological and serological data, therapy and disease progression. The analysis of simple spinal X-rays were excluded from the study, as these were commonly absent in the patient's clinical records.

The clinical evolution was described as favourable when pain and/or neurological deficits improved with therapy and poor in patients whose clinical picture remained unchanged or had worsened.

RESULTS

Fifty-four patients with BS were identified over these 25 years, corresponding on average to 2.2 patients each year (Fig. 1).

Most patients (55.6%) were male, with a mean age of 54.8 at the time of diagnosis. An epidemiological factor was identified in 44 (81.5%) patients, mostly due to contact with sheep and/or goats (Table 1).

The period of time between the beginning of the symptoms and the diagnosis of spondylodiscitis was determined in 39 patients, with an average 5.5 ± 7.4 months [1 week - three years] and a median of three months. Major symptoms referred by patients at the time of admission were local pain, fever and neurological deficits (Table 1). The mean hospital stay was 29 ± 17.3 days [1 - 69].

Regarding imaging, 42 patients (77.8%) underwent

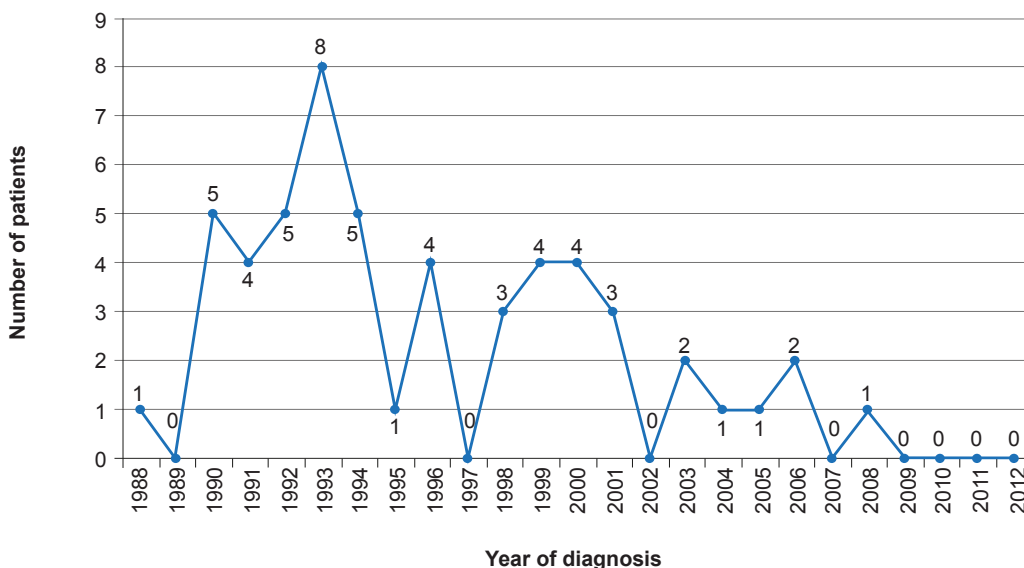


Figure 1 - Annual distribution of the patients with brucellar spondylodiscitis

MRI of the spine, 97.6% (41/42) of which presented with signs suggestive of spondylodiscitis. CT-scan of the spine was obtained in 32 (59.3%) patients, with suggestive signs in 81.3% (26/32). The presence of abscesses was identified in 16 (29.6%) patients in the following locations: paravertebral (eight patients), psoas (six patients) and epidural (five patients). The lesions' anatomical distribution is shown in Table 1, the lumbar segment being the most commonly affected.

The Rose Bengal test was positive in all patients. The aetiological diagnosis was confirmed in most of the patients (87.0%) as follows: a serological method in 32 patients, blood culture bacterial isolation in three

patients and with both tests in 12 patients (Table 1).

All patients were treated with double or triple antibiotic therapy (Table 2). The association of doxycycline with rifampicin (64.8%) or with streptomycin (24.1%) were mostly used. The mean treatment duration was 4.4 ± 2.3 months (1-12). One patient was submitted to surgery for paravertebral abscess drainage causing radicular compression.

A favourable outcome, with improvement or resolution of the symptoms, was found in 92.6% of the patients, while 3.7% of the patients had no clinical improvement upon therapy (one patient with disease localized to L2-L5 still complained of lower limb paraesthesia and another

Table 1 - BS patient's characteristics

	Result
Demographic	
Age. mean ± SD (min- max)	54.8 ± 14.2 (19 - 83)
Male, <i>n</i> (%)	30 (55.6)
Epidemiological characterization	
Contact with sheep/goats. <i>n</i> (%)	32 (59.3)
Non-pasteurized milk or dairy products ingestion. <i>n</i> (%)	17 (31.5)
Previous brucellosis history. <i>n</i> (%)	14 (25.9)
Symptoms at presentation	
Local pain. <i>n</i> (%)	53 (98.1)
Fever. <i>n</i> (%)	25 (46.3)
Neurological deficits. <i>n</i> (%)	13 (24.1)
Spinal segment	
Cervical. <i>n</i> (%)	3 (5.6)
Thoracic. <i>n</i> (%)	7 (13.0)
Thoracolumbar. <i>n</i> (%)	2 (3.7)
Lumbar. <i>n</i> (%)	31 (57.4)
Lumbosacral. <i>n</i> (%)	11 (20.3)
Serological and microbiological parameters	
Rose Bengal test. <i>n</i> (%)	54 (100.0)
Wright test. <i>n</i> (%)	
Negative	6 (11.1)
1/80	4 (7.4)
1/160	15 (27.8)
1/320	18 (33.3)
1/640	9 (16.7)
1/1280	2 (3.7)
Positive blood culture. <i>n</i> (%)	15 (27.8)

Table 2 - Therapeutic regimens

	Number of treatments (%)	Mean duration, in months (SD)
Doxycycline + Rifampicin	35 (64.8)	4.4 (2.3)
Doxycycline + Streptomycin	13 (24.1)	4.4 (1.4)
Doxycycline + Rifampicin + Streptomycin	3 (5.6)	3.5 (0.5)
Doxycycline + Gentamicin	2 (3.7)	5.0 (0)
Doxycycline + Rifampicin + Gentamicin	1 (1.8)	5.0 (0)

with an L5-S1 affection presented with a disabling mechanical type lumbar pain). The remaining 3.7% were transferred to another hospital and no patients died.

DISCUSSION

Brucellosis was until recently one of the zoonosis with higher incidence in Portugal, included in the list of compulsory notifiable diseases. The evolution of notified cases shows a decrease in endemic prevalence, according to the *Direcção Geral de Saúde* data; from 1994 to 2008, the number of notified annual brucellosis cases has been consistently reduced, from 1,240 to 56 cases in this timeframe.^{5,6}

Brucellosis is a systemic infection, in which most organs and systems may be affected. The osteoarticular complications occur in 20-40% of the cases.⁷ Three relevant studies on brucellosis found 9.7 to 12.3% of spondylodiscitis.⁹⁻¹¹

Our study involved 54 patients with brucellar spondylodiscitis diagnosed over the last 25 years (1988-2012) at the Infectiology Department of a tertiary hospital from the central region of Portugal, following on the publication presenting the results of the first four years of this clinical series (1988-1991).¹² The distribution of the number of cases over this period of time was uneven, as most cases were diagnosed in the nineties with no BS cases in the last five years. These data are in line with the decrease of brucellosis prevalence that has already been described in the central region of Portugal.^{5,6} Regarding gender prevalence, we found a slight male predominance (55.6%), lower to what has been found in some clinical series,^{7,9,13} although similar to others.¹⁴ In line with current literature,^{9,15} patients with brucellosis developing BS tend to be older, aged 50-60, similar to our results (mean age 54.8 ± 14.2).

In this study, the epidemiological assessment has shown to be an important aspect when there is high clinical suspicion. Of note, only 18.5% of the patients did not present a suggestive context. Previous brucellosis diagnosis and treatment history were referred by approximately one quarter of the patients, suggesting that BS may arise during or after antibiotic therapy.

However, as we did not have any data regarding most of previous diagnosis and treatments (ranging from three months to ten years prior to the present episode), we were prevented from reliably interpret BS as a relapse or as re-infection. In addition, these patients maintained risk factors for this infection. Furthermore, due to the relative scarcity of recorded data and, with the same frequency, due to the fact that these were diagnosis and treatments carried out elsewhere, we decided not to focus on the assessment of other brucella affected organs coincidental with spondylodiscitis in the same individual. Although some clinical reports of neurobrucellosis ($n = 3$), peripheral polyarthritis ($n = 3$) and sacroiliitis ($n = 1$) were documented, the limitations previously alluded to did not allow for a correct definition of their occurrence in relation to BS as well as for a correct distinction between re-infection or post sub-optimal treatment relapses, explaining why these manifestations were not included in our study.

In BS patients, the most common symptoms are generally described as local pain (93-100%), fever (60-92%) and neurological deficits (19-31%).^{2,13,14,16} In our series, the clinical expression was similar to the previously referred studies, except fever, which was less common (46.3%). BS relatively non-specific clinical presentation may result in a delayed and more difficult diagnosis, with an increase in morbidity.¹³ Several studies describe time intervals between the beginning of the symptoms and the diagnosis between 1 and 103 weeks.^{2,9,13,17} An average of five months of symptoms prior to diagnosis has been found in our group of patients, with a maximum of three years in one patient with cervical pain of insidious onset.

MRI of the spine has a high sensitivity for spondylodiscitis early diagnosis, allowing for the assessment of surrounding soft-tissues and the presence of abscesses affecting these structures.^{11,18} All patients in our study were submitted to X-ray imaging of the spine and most diagnosis were obtained by MRI (Fig. 2). Although in this series all segments of the spine were found to be affected, lumbar lesions were the most common, in line with other clinical series.^{2,3,19}



Figure 2 – Fat-suppressed post-contrast T1 (B) and T2 (A) weighted sagittal view MRI of the spine of one patient from our study showing major L4-L5 intervertebral disc and adjacent vertebral endplates involvement. There are less severe changes in the L5-S1 disc, with pre-vertebral extension (*), contiguous epidural (+) and inter-spinal posterior soft tissues (-) components. There is signal intensification of the intervertebral discs in T2 (A), with a clear post-contrast enhancement of L4 and L5 discs and vertebral bodies (B). This image highlights the relatively dominant involvement of the vertebral bodies when comparing with the vertebral discs, a feature that may help to differentiate brucellar from other pyogenic spondylodiscitis, namely from tuberculosis, which is usually characterized by a clear vertebral deformity.

Paravertebral and epidural abscesses may arise associated with BS¹⁴, having been identified in 29.6% of our patients.

Brucellosis final diagnosis requires an isolation of the bacteria in blood, bone marrow, other tissues or biological fluids. However, the probability of isolating the bacteria in a blood culture depends on the infection stage and on the culture technique used, with 80-90% identification in the acute and 30-70% in the chronic phases. In the patients where *Brucella* isolation is not possible, diagnosis is based on serological methods, an indirect evidence of infection.²⁰ However, in previously treated patients, serological titres may be low¹² and in patients with localized disease, some studies describe a low sensitivity¹³ – therefore this should not lead to diagnostic exclusion, when a high suspicion of infection remains, as it happened with some of our patients.²¹ In our study, the percentage of positive cultures was lower than that previously described, which may be explained, in some cases, by the laboratory unawareness of suspected brucellosis, not allowing for an optimization of the methodology used for the bacterial culture and, in other cases, due to previous use of antibiotic therapy. *Brucella* species was not identified in the isolations that

were performed as this methodology is not followed by our laboratory, apart from the fact that this result would not change therapy. Therefore, high specific antibody titres (Wright test $\geq 1:160$), associated with a compatible clinical, imaging and usually epidemiological presentation were the usual diagnostic method used, the Rose Bengal test having been used as a quick screening procedure in every suspected case.

Optimal osteoarticular brucellosis treatment is still controversial. Issues such as the best antibiotic regimen, duration of therapy and the role of surgery remain to be solved.²² Most studies suggest a better response with doxycycline/aminoglycoside (streptomycin and gentamicin) vs. doxycycline/rifampicin combination^{9,13,23} which nevertheless offers the advantage of allowing for oral administration.²⁴ According to a meta-analysis assessing eight relevant studies, the results are related to treatment duration and not to the type of regimen used.²⁵ Patients with osteoarticular localized disease benefit from longer treatment. A prospective study on BS revealed that longer than six months therapy was efficacious, presenting 100% success rates, with no serious relapses, sequelae or mortality.²² In this study, doxycycline/rifampicin or streptomycin regimens were

the more frequently used, the latter being most utilized over the last years of this study. The triple antibiotic regimen was an option in only 7.4% of the patients. Treatment duration was variable, on average 4.4 months, according to the clinical response.

Surgery is a rare option for BS treatment, indicated in the case of neurological deficit progression or persistence, spinal instability and absence of response to medical therapy.²⁶

Although paravertebral and/or epidural abscesses were identified in 29.6% of patients and a neurological impairment was found in 24.1%, only one patient was submitted to surgery due to neurological impairment related to a paravertebral abscess.

In our group of patients, in line with other studies^{2,14} most patients had a favourable outcome and there was no mortality.

Our study presented some limitations due to its retrospective nature, considering the information may be unreliable due to data insufficiency. Patient's follow-up was not standardized and as such we were unable to evaluate long-term relapse and sequelae.

CONCLUSIONS

This study describes our experience in BS patient's approach, reflecting the difficulties and delays in a disease with a non-specific clinical presentation. In areas where brucellosis is an endemic pathology, BS should be considered in the differential diagnosis of patients with back pain, even in the absence of fever,

especially when there is a history of contact with sheep or goats, or with non-pasteurized milk or dairy products ingestion. Spinal MRI is the imaging method with best sensitivity for studying brucella osteoarticular localized disease, allowing for an earlier and better assessment of local structures. Antibiotics, their duration and the need for adjuvant surgery should be individualized in order to improve the outcome, which has occurred in most of our patients. Although our study does not allow for definite conclusions, due to heterogeneity in treatment choice and duration, we recommend that the best regimen to treat osteoarticular brucellosis is the association of doxycycline with one aminoglycoside for at least six months, keeping the doxycycline/rifampicin regimen for the patients who cannot follow the first regimen due to toxicity or logistic unfeasibility. BS cases were not diagnosed in the last few years, a fact that we explain through improved control of this zoonosis.

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CONFLICTS OF INTEREST

There were no conflicts of interest in writing this manuscript.

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