Evolução da Brucelose: Estudo de 12 Anos de Internamentos num Hospital Distrital

Trends in Human Brucellosis: A 12-year Study of Admissions in a District Hospital

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Resumo

Introdução: A brucelose humana tem uma variada apresentação clínica com uma importante carga socioeconómica. A elevada suspeita clínica e a interpretação adequada dos testes laboratoriais são essenciais para o diagnóstico. O objetivo deste estudo foi rever os internamentos atribuíveis à brucelose num hospital público de uma região endémica em Portugal.

Métodos: Estudo observacional retrospectivo de admissões hospitalares com o diagnóstico de alta de brucelose, entre 2000 e 2012 com análise das características epidemiológicas, clínicas, laboratoriais e terapêuticas.

Resultados: Foram incluídos 36 pacientes. A percentagem do sexo masculino foi de 69,4%, a idade média foi de 52,9 anos e 72,2% apresentaram exposição a um fator de risco para brucelose. Encontramos 14 internamentos em 2000 e zero internamentos em 2012. Os sintomas mais frequentes foram: febre (72%), mialgia (58,3%) e astenia (47,2%). O teste rosa bengala foi positivo para a maioria dos doentes (91,7%). Em contrapartida, apenas um paciente apresentou exame de cultura positivo para brucelose. A apresentação da doença foi essencialmente aguda (75%) e focalizada (69%). Na presença de doença focalizada, o envolvimento osteoarticular foi o mais frequente (37%). Na análise univariada, os pacientes que recaíram (16,6%) não apresentaram associação significativa com nenhuma das características epidemiológicas, clínicas, laboratoriais ou terapêuticas ($p > 0,05$). O regime de antibióticos mais frequentemente prescrito foi rifampicina mais doxiciclina (55,5%).

Conclusão: No nosso estudo, os internamentos hospitalares devido à brucelose diminuíram dramaticamente entre 2000 e 2012, o que mostra uma evolução no controle da doença. As formas agudas e focalizadas de doença foram as manifestações mais frequentes desta zoonose que ainda é um desafio para os clínicos.

Palavras-chave: Brucelose/diagnóstico; Brucelose/epidemiologia; Brucelose/tratamento.

Abstract

Introduction: *Human brucellosis can present various clinical forms and potentially lead to an important social-economic burden. High level of clinical suspicion and appropriate laboratory testing interpretation are essential for the diagnosis. The aim of this study was to review the admissions attributable to brucellosis in a public hospital of an endemic region of Portugal.*

Methods: *Retrospective observational study of consecutive hospital admissions with a discharge diagnosis of brucellosis between 2000 and 2012, by the analysis of epidemiological, clinical, laboratory and therapeutic features.*

Results: *A total of 36 patients were included. The percentage of male patients was 69.4%, with mean age of 52.9 years old and 72.2% presented a risk factor exposure for brucellosis. We found 14 admissions in 2000 and zero admissions in 2012. The most reported frequent symptoms were fever (72%), myalgia (58.3%) and asthenia (47.2%). The rose bengal test was positive for the majority of the tested patients (91.7%). On the other hand, only one patient had a positive culture for brucellosis. The disease was essentially acute (75%) and focalized (69%). When focalized, osteoarticular involvement was the most frequent presentation (37%). In univariate analysis, patients who relapsed (16.6%) showed no significant association with any of the epidemiologic, clinical, laboratory or therapeutic features ($p > 0.05$). Antibiotic regimen most often prescribed was rifampicin plus doxycycline (55.5%).*

Conclusion: *In our study, hospital admissions due to brucellosis dropped dramatically between 2000 and 2012, which shows an optimistic sign of disease control. Acute and focalized forms of the disease were the most frequent manifestations of this zoonosis that is still a challenge for clinicians.*

Keywords: *Brucellosis/diagnosis; Brucellosis/epidemiology; Brucellosis/therapy.*

Introduction

Brucellosis is a zoonotic disease caused by facultative intracellular Gram negative *coccobacillus* of the *genus brucella*. There are eleven species but only five cause disease in humans (*Brucella abortus, Brucella suis, Brucella melitensis, Brucella ovis* and *Brucella canis*).[1-4]

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Human brucellosis is the most important zoonosis worldwide, with more than 500 000 new cases reported each year.[5-8] In humans, this disease is also called Maltese fever, Bang's disease, undulant fever or Mediterranean fever.[3,8,9] In some endemic regions like the Mediterranean basin and South America major progress has been achieved over the past years, mostly because of effective veterinary sanitary measures, evolving socioeconomic factors and improvements in notification methods. However, new endemic foci have emerged (central Asia and near East) and the disease remains endemic in many regions of the world.[5]

In Portugal, human brucellosis is known as an uncommon disease. After an incidence peak in the 1980's and 1990's, reaching as high as 1576 notified cases for the year 1989, incidence has been decreasing for the past 20 years, with few exceptions corresponding to local outbreaks.[10] Less than 100 new cases are now reported each year.[11]

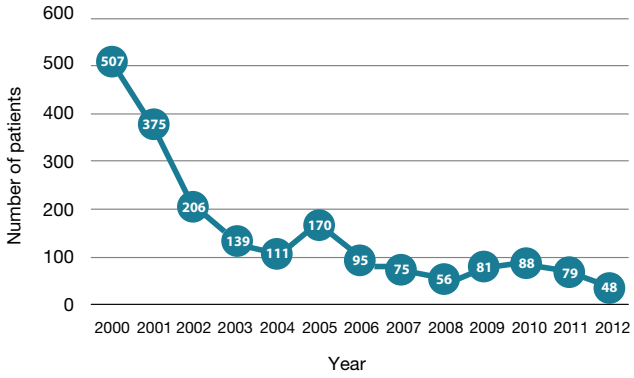

Figura 1: Reported cases of brucellosis in Portugal.[10]

Brucellosis remains a diagnostic challenge to clinicians because of several factors. This is mainly due to: nonspecific symptoms that can simulate a myriad of other diseases, incubation period that may differ according to virulence of the organism and also an important rate of non-culture proven disease.[12-14] Therefore, a high level of suspicion is important for establishing diagnosis.

Transmission of brucellosis to humans occurs mainly through ingestion of infected, unpasteurized animal-milk products, but also through contact with infected animals through damage skin, mucosa and airways.[1,2,3,7,9,15]

Clinical presentation is widely variable, it can be acute or chronic; focalized or not, depending on the stage of the disease and the organs involved. When focalized, brucellosis most frequently compromises osteoarticular, gastrointestinal, genitourinary, hepatobiliary, cardiovascular and central nervous systems.[12,16]

Medical history, physical examination, appropriate laboratory testing and its interpretation are essential for the diagnosis. Although the hallmark of diagnosis is the isolation of *Brucella spp.* in enriched culture, in most cases it is unsuccessful (especially in chronic cases), and it takes time to obtain the results. The best practical laboratory approach is through the serological tests available (rose bengal test, the serum agglutination test (SAT), antiglobulin or Coombs test, microagglutination test (MAT), enzymelinked immunosorbent assay (ELISA) and indirect fluorescent antibody test (IFA) for IgM and IgG assessment, a fluorescence polarization assay, a variety of indirect ELISA, and the immunocapture Brucellacapt test.[3,7,16-21]

The main objective of the therapy for brucellosis is, besides reducing morbidity and mortality, also reducing the chance of relapse.[16] Treatment is usually made with antibiotic association; the advised schemas are rifampicin or doxycycline plus streptomycin for a minimum duration of six weeks. For a second line of therapy, an aminoglycoside (gentamicin) can replace the rifampicin for the initial week of the association therapy (doxycycline six weeks plus gentamicin two weeks). Other regimens have been tested (example: fluoroquinolone or sulfamethoxazole trimethoprim) but proved to be less efficient.[7,22,23]

Methods

We conducted a retrospective observational study through identification of adult hospital admissions between 1 January 2000 and 31 December 2012 with a discharge diagnosis of brucellosis (International Classification of Diseases, Ninth Revision, Clinical Modification. Codes 023.0 to 023.9). Study conducted in a public district hospital with basic, intermediate and differentiated medical services and with a total number of admissions in 2012 of 9980. For each identified episode, the following variables were analyzed: age, sex, date of admission, length of stay, risk exposure, previous history of brucellosis, clinical symptoms and presentation, focal involvement, laboratory findings, therapeutic regimens, co-morbidities and mortality. Descriptive Statistical analysis performed using IBM SPSS v20®.

Results

Of the total 45 identified patients, we excluded four pediatric patients and five miscoded episodes. A total of 36 patients were eligible for the study, corresponding to a total of 41 admissions. The majority of patients was male (69.4%) and the mean age was 52.9 years (SD = 18.7).

Thirty five percent of the patients that have been analyzed had history of contact with farm animals (cows and sheep), 16.7% consumed unpasteurized milk products, 22.2% presented both previous risk factors and 16.7% had not had any contact with infected animals or products (four patients had missing information about risk exposure in their clinical records). Of the 26 patients in whom a risk exposure for brucellosis was identified (72.2% of total), 5 (19.2%) patients had a professional exposure (slaughterman or shepherd).

Hospital admissions decreased over the past years (13 admissions in 2000 to Ø admissions in 2012 (cf. Fig.2), but

admissions show seasonality with predominance during the months of Summer (cf. Fig. 3).

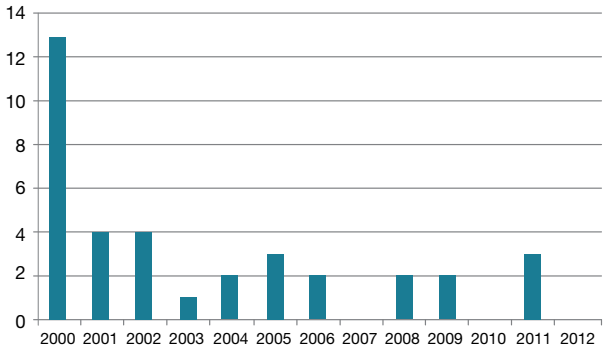

Figura 2: Annual distribution of hospital admissions attributable do human brucellosis in our study 2000-2012 (number of cases).

Length of stay in the hospital was 11.5 days (median with a range 58). The symptoms and physical findings are reported in Fig. 4. The most frequent symptoms were fever (72.2%), myalgia (58.3%) and asthenia (47.2%), and the most frequent findings observed on physical examination were fever (69.4%), hepato-splenomegaly (27.8%) and arthritis (8.3%). The following laboratory abnormalities were identified: raised CRP (97.2%), raised ESR (58.3%), abnormal liver enzymes (55.6%), anemia (50.0%), neutropenia (50.0%), leucopenia (33.3%), thrombocytopenia (11.1%).

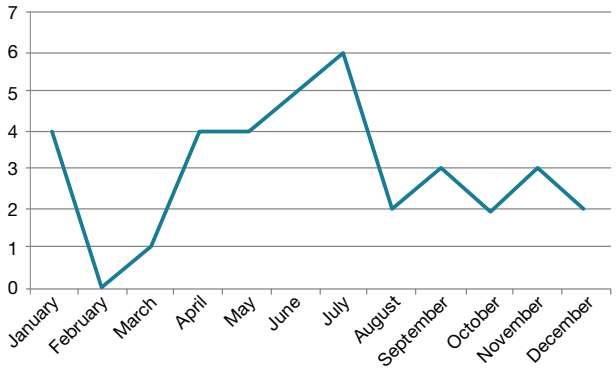

Figura 3: Monthly distribution of hospital admissions attributable to human brucellosis in our study (number of cases between the year 2000-2012).

Relapsing cases are defined according to World Health Organization (WHO) as presenting recurrence of typical signs and symptoms with or without culture proven disease, after antibiotic completion. In our series, we observed 16.6% of the patients were relapsers.

Antibiotic regimen most often prescribed was rifampicin plus doxycycline (55.5%). Other regimens prescribed were: doxycycline + rifampicin + streptomycin (11.1%), doxycycline + streptomycin (8.3%), sulfamethoxazole trimethoprim (2.8%), doxycycline (2.8%), doxycycline + gentamicin (2.8%), doxycycline + streptomycin + metronidazole (2.8%), doxycycline + rifampicin + gentamicin (28%), sulfamethoxazole

Table 1: *Brucella* cases: symptoms and findings on physical examination

Symptoms	Nº of cases	% of cases	Findings on physical examination	Nº of cases	% of cases
Fever	26	72.2	Fever (Temp > 38ºC)	25	69.4
Myalgia	21	58.3	Hepatomegaly	5	13.9
Asthenia	17	47.2	Splenomegaly	5	13.9
Anorexia	14	38.9	Arthritis	3	8.3
Back pain	14	38.9	Abnormal breath sounds	3	8.3
Headache	12	33.3	Exanthema	3	8.3
Weight loss	14	30.6	Orchitis	2	5.6
Sweating	10	27.8	Meningeal signs	1	2.8
Polyarthralgia	8	22.2	Neurological focal signs	1	2.8
Arthralgia	5	13.9	Heart murmur	0	0
Abdominal pain	5	13.9	Jaundice	0	0
Other symptoms	24	66.7	Other findings	10	27.7

trimethoprim + gentamicin (2.8%), sulfamethoxazole trimethoprim + rifampicin (2.8%), levofloxacin (2.8%). The duration of the treatment was variable: six weeks to 2 month (36.1%), 2-3 month (13.9%), 3-4 month (11.1%), 4-5 month (5.6%), more than 6 months (8.3%). A minority of patients presented co-morbidities (41.7% of the total) and one patient had a background of immunosuppression due to pharmacological treatment.

All the patients had a favorable clinical outcome at discharge (0% mortality).

Discussion

In this study we demonstrate that hospital admissions due to brucellosis dropped dramatically between 2000 and 2012, which is an optimistic sign of disease control. This probably reflects improvements in the recognition and notification of the disease, the eradication programs in animals and also local socioeconomic development. However, complete eradication is difficult even in developed industrialized countries, where residual cases and/or outbreaks are reported every year, and the maintenance of epidemiological vigilance is crucial in surveilling disease.

Our findings are consistent with other series, however there are differences to be highlighted.

Buzgan T *et al* from Turkey described in their series focalized forms in 36.1% of cases, while we observed 69%.[25] The same authors described a percentage of 25.3% of osteoarticular involvement, which is lower than our series (37%) and the Greek series by Andriopoulos P *et al* (42%).[26]

Osteoarticular involvement is the most frequent focal complication of brucellosis. Sacroiliac joints are the most common site involved in younger patients whereas spondylitis and peripheral arthritis usually occur in older patients.[13]

As for relapse, globally described at a rate of about 10%,[17] it is higher in our series (16.6%). Andriopoulos P *et al* presented a 3% rate of relapse, while Pappas G *et al* observed 4% and Buzgan T *et al* observed 4.7%. Relapse cases found in our study are surprisingly high. We compared this group of patients with non-relapsers, but found no significant differences, as in contrast to Ariza J *et al* that found in their study an association with characteristics of the initial infection that included duration of less than 10 days, male sex, bacteremia and thrombocytopenia.[27] Typically, high rates of relapse are associated with antibiotic monotherapy,[7] and 8.4% of our patients were in fact treated with only one antibiotic, despite that 72.1% of the patients underwent the recommended first line therapy.

Another important difference is the low rate of culture proven disease in our study (2.8%). This is a dramatically difference if we compare to other studies where there is a description of 15% – 70% positive cultures.[7,9,28,29]

A complete and exhaustive clinical history with the inclusion of epidemiological information remains the golden standard for suspicion of human brucellosis. Our results show 72.2% of the patients had a least one risk factor (professional exposure or unpasteurized dairy products consumption).

The major challenge for the clinical diagnose is the recognition of varied, atypical and insidious forms.[29] The patient can refer multiple symptoms and present with a variety of signals in the emergency department. From fever to testicular pain, every symptom can translate an infection with *Brucella spp*. The most common symptom and sign was fever, the most nonspecific sign or symptom of all. If we compare the reported symptoms and signs with other studies, it is similar. In terms of laboratory findings, the rise of CRP was the most common.

There are no clinical findings or laboratory findings that may increase the clinical suspicion. That is also part of the challenge in the diagnosis of brucellosis.

Bone marrow culture is considered the gold standard for the diagnosis of brucellosis: more sensitive especially in chronic disease and maintains the sensitivity after the start of antibiotic treatment but because it is an invasive procedure usually only takes place in the presence of hematological disorders.[27,28,30] In our study, the culture of bone marrow was done in one patient because he presented hematological disorders.

On the other hand, the screening test of excellence, the bengal rose has sensitivity > 90% although less specificity, for that reason requires a confirmation test with high specificity like MAT (not possible in our hospital), SAT or Brucellacapt (like in our hospital).[31-33] In the last decade, the Brucellacapt has shown similar sensitivity and specificity to the coombs tests for the diagnosis of human brucellosis, is more rapid and less difficult to carry out and could become a better marker of infection activity.[12,35] Since 2002, in our hospital, we started using Brucellacapt and progressively replaced the SAT as a confirmatory test in brucellosis.

The results described are similar to those described in literature. Serological tests are the simpler and faster methods for brucellosis identification. The ELISA test is not useful as a diagnosis test of brucellosis and was not executed as a diagnosis test.[31-33]

In our hospital, 74.9% of the patients underwent the recommended first line of antibiotherapy. We identified the follow monotherapy regimens: sulfamethoxazole trimethoprim (2.8%), doxycycline (2.8%). Monotherapy has generally been considered inadequate because of the high relapse rates except perhaps the monotherapy withdoxycycline.[31-35] In the other regimens prescribed in our hospital: doxycycline + rifampicin+ gentamicin and doxycycline + gentamicin. These regimens can be considered since the relapse rates were at least similar to the first line of therapy. However the duration of gentamicin treatment needs further randomized trials.[38-41] The inclusion of sulfamethoxazole trimethoprim (TMP-SMX) in several regimens in combination with doxycycline

Table 2: Osteoarticular involvement due to brucellosis found in our study (number of cases)

Osteoarticular involvement	Nº of cases	% of cases
Lumbosacral spondylodiscitis	3	31
Lumbosacral spondylodiscitis with psoas abscess	1	8,3
Lumbar spondylodiscitis	1	8,3
Sacroiliitis with osteomyelitis	1	8,3
Tenosynovitis (hip)	1	8,3
Peripheral arthritis (knee)	1	8,3
Costochondritis	1	8,3
Atypical findings or absence of early imaging signs	3	31

or rifampicin, especially in low income countries had good results.[35-39]

The regimens containing fluoroquinolones can be an acceptable alternative but never a first choice since the risk of acquire resistance to the antibiotherapy. There is no study with metronidazole in human brucellosis but it is sometimes prescribed in patients with abscess, further studies are needed.[35-40] Regardless the focus, the duration of antibiotic treatment should be six weeks.

Several limitations are present in our study. First, retrospectivity may introduce important information biases namely clinical records inaccuracy. Second, this study reflects only a part of the total brucellosis cases of our region, because it refers to the cases that needed hospitalization (presumably the most serious ones). All the cases in the emergency department that did not meet the criteria for hospitalization have not been included, and therefore broader conclusions about the panorama of this disease in this endemic region should comprise also the ambulatory cases.

Conclusion

In our study, hospital admissions due to brucellosis dropped dramatically between 2000 and 2012, which shows an optimistic sign of disease control. Acute and focalized forms of disease were the most frequent manifestations of this zoonosis that is still a challenge for clinicians.

Although hardly fatal, this disease is responsible for several incapacitating clinical conditions and it carries a significant Human brucellosis is unknown. Major challenges defying clinicians are unrecognition and underdiagnosing the disease, consequences of a varied, atypical and unspecified form of presentation (WHO/FAO/ONIG) and difficulties in isolation of *Brucella spp* because of microbiological conditionings.[7,41] Another major problem is the high under reporting rate (WHO/FAO/ONIG) both in animals and humans social-economic burden to rural areas.

Despite the achievements in the control of this disease in Portugal, we should never forget the possibility of brucellosis in the presence of a patient with fever and positive epidemiological data. ■

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Protection of Human and Animal Subjects: The authors declare that theprocedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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Protecção de Seres Humanos e Animais: Os autores declaram que não foram realizadas experiências em seres humanos ou animais

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