

Brucellosis, an uncommon and frequently delayed diagnosis

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ABSTRACT

In the Netherlands, brucellosis is uncommon. Diagnosis is difficult and frequently delayed. We present three patients with back pain and/or arthralgia caused by brucellosis. We emphasise the importance of considering brucellosis in patients returning from a stay in a rural area of an endemic country, who present with osteoarticular symptoms and signs of chronic inflammation. Clues to the diagnosis come from a thorough medical history.

KEYWORDS

Brucellosis, spondylodiscitis, zoonotic infection

INTRODUCTION

Brucellosis is the most common zoonotic infection worldwide.^{1,2} It is endemic in the Mediterranean region, the Middle East, Latin America and parts of Asia and Africa, but the epidemiology is changing over the last decades due to socioeconomic changes, improved disease recognition and eradication programmes.^{2,3}

In the Netherlands brucellosis is uncommon.⁴ The presentation of an infection caused by *Brucella* species can be extremely variable and nonspecific and diagnosis is therefore difficult. Early recognition is important, as delay in treatment allows disease progression resulting in complications. The following cases illustrate the importance of considering brucellosis in patients with back pain or arthralgia together with signs of chronic inflammation, particularly when they have a history of travel to rural areas of countries where brucellosis is endemic.

CASE REPORTS

Patient A, a 72-year-old Turkish male, presented to the emergency department with severe lower back pain. Acute lumbago was diagnosed, nonsteroidal anti-inflammatory drugs were prescribed and the next day he was discharged. However, in the next two weeks, the pain increased and he was readmitted. His medical history, with the help of a translator, revealed that the pain had started several weeks before admission and was accompanied by fatigue, malaise and a weight loss of 12 kg without any fever. Three months earlier, the patient had stayed with relatives in Turkey where he consumed local meat. Physical examination revealed a systolic cardiac murmur. Local tenderness to gentle spinal percussion was elicited and neurological examination was unremarkable. The temperature was normal. Laboratory studies revealed an erythrocyte sedimentation rate (ESR) of 98 mm/h (0-20), a haemoglobin (Hb) concentration of 6.2 mmol/l (8.5-10), a normal white blood cell count (WBC) and a C-reactive protein level (CRP) of 57 mg/l (0-9). Lumbosacral spine radiographs showed joint space narrowing at L4-L5 and L5-S1. On the suspicion of spondylodiscitis, magnetic resonance imaging (MRI) was performed. It showed reactive changes at L4-L5 and L5-S1, consistent with severe discopathy. A cardiac ultrasound showed sclerosis of the aortic valve only. Both pairs of blood cultures grew *Brucella melitensis* after five days. The MRI scan was re-evaluated and early spondylodiscitis was considered. *Brucella* spondylodiscitis with bacteraemia was concluded and the patient was treated with rifampicin 600 mg/day and ciprofloxacin 750 mg twice daily orally for three months. After one week the pain had considerably decreased and after three weeks he was free of symptoms. ESR, CRP and Hb levels had improved. The patient has been well during a follow-up of seven months.

Patient B, a 28-year-old Indian male, residing in the Netherlands, presented with a three-month history of fever, progressive lower back pain and a weight loss of 12 kg. Eight months earlier, he had stayed with relatives in rural India. The patient had repeatedly visited his general practitioner with these symptoms and laboratory results showed signs of inflammation, but a diagnosis had not been made. On admission, there was local tenderness on percussion of the lumbosacral spine. Neurological examination showed a positive Lasègue's sign and a diminished Achilles tendon reflex on the left side. The temperature was 37.8°C. Laboratory results revealed an ESR of 79 mm/h, a CRP of 89 mg/l, an Hb concentration of 7.5 mmol/l and a normal WBC. MRI of the lumbosacral spine showed findings consistent with spondylodiscitis of L4-L5 with epidural and presacral abscess formation (figure 1). Because of the neurological dysfunction, lumbar spinal surgery was performed. During the procedure, pus was removed from the epidural space and sent for microbiological examination. After four days, cultures grew *Brucella melitensis*. At that time, a *Brucella* agglutination test on serum was positive at a titre of 1:320. Three pairs of blood cultures remained negative. The patient was successfully treated with ciprofloxacin 750 mg twice daily and doxycycline 100 mg twice daily orally for three

months. After three weeks, the pain had diminished and the ESR, CRP and Hb concentration had improved. During a follow-up of four years, there had been no signs of relapse.

Patient C, a 51-year-old Turkish female, living in the Netherlands, presented to the emergency department with dyspnoea, a productive cough and fever. She had a previous medical history of chronic obstructive pulmonary disease (COPD). On physical examination, the temperature was 37.9°C and the peripheral oxygen saturation was 98%. Auscultation revealed expiratory wheezing and no cardiac murmurs. Laboratory workup showed an Hb concentration of 7.2 mmol/l, a normal WBC and a CRP of 61 mg/l. The ESR was not determined. The chest X-ray showed no infiltrates. COPD exacerbation due to an upper respiratory tract infection was diagnosed. She was admitted and treated with corticosteroids and a bronchodilator. The day after, she developed high fever and blood cultures were taken. On the suspicion of pneumonia, antibiotics were started. After five days, six pairs of blood cultures grew *Brucella melitensis*. At that time, medical history revealed that she had been experiencing fatigue, malaise, back pain and arthralgia for several weeks before admission. Moreover, she had recently stayed in Turkey with relatives

Figure 1A. On T1-weighted images, decreased signal intensity of the vertebral bodies L5 and S1 is seen with hypointense masses in paraspinal soft tissues and in the epidural space



Figure 1B. Contrast-enhanced T1-weighted images show enhancement of the inferior endplate of L5 and the superior endplate of S1, the disc space at L5-S1 and the masses in paraspinal soft tissues and in the epidural space.



where she had consumed local cheese. Lumbosacral MRI was normal. The patient was treated for *Brucella* bacteraemia without a primary focus with rifampicin 600 mg/day and doxycycline 100 mg twice daily orally for six weeks. After one day, the fever had disappeared and she was discharged. During one year of follow-up, there were no signs of relapse.

DISCUSSION

Brucellosis is a zoonotic infection caused by small gram-negative coccobacilli of the genus *Brucella*. Four species are known to cause human disease, each having their own specific animal host: *B. melitensis* (goat, sheep, camel), *B. suis* (pig), *B. abortus* (cattle), and *B. canis* (dog).² Transmission occurs through cuts and abrasions of the skin, via the conjunctiva, by inhalation of infected aerosols or by consumption of contaminated food (unpasteurised dairy products, raw meat).² Brucellosis can be occupational, e.g. in veterinarians, farmers and laboratory workers.² In our cases, brucellosis was probably caused by ingestion of contaminated food.

Brucellosis is a systemic infection with a wide clinical spectrum and symptoms are often nonspecific. The most common symptom is fever and brucellosis is a well-documented cause of fever of unknown origin. Other prominent symptoms are sweats, fatigue, malaise, anorexia, arthralgia and weight loss. Because brucellosis is rare in the Netherlands, it is often not recognised. Our three cases demonstrate the importance of taking a thorough patient history, including questions about recent travel to countries of origin in non-native patients. Due to incomplete medical history taking, there was a delay in making the diagnosis in all three patients. The combination of increasing lumbar pain and/or arthralgia and signs of chronic inflammation together with their visit of an endemic country and the consumption of potentially contaminated food should have raised the suspicion of brucellosis with or without accompanying spondylodiscitis.

Although virtually any organ system can be affected, osteoarticular involvement is the most frequent complication of brucellosis.² Other, less frequent complications are epididymo-orchitis, meningitis and endocarditis.⁵⁻⁷ Two out of our three cases had proven osteoarticular involvement. Patient C had arthralgia only. Physical examination is usually normal and even fever can be absent, which is illustrated by patients A and B. Laboratory results are nondiagnostic as well. WBCs are usually normal to low and pancytopenia can occur. ESR and CRP are usually elevated. Subtle elevation of liver enzymes frequently occurs.² Radiological examination can be helpful in identifying focal disease. MRI is the most suitable modality for early detection of abnormalities.⁸⁻¹⁰

Even with MRI, however, the diagnosis of discitis may be difficult, which is demonstrated in case A.

Confirmation of brucellosis requires isolation of the organism from blood or tissue. The sensitivity of blood culture ranges from 15 to 80%, due to differences in laboratory techniques.² Using conventional culture methods, *Brucella* bacteria tend to grow slowly and cultures generally become positive after several weeks. Culture in a biphasic medium, lysis concentration and automated culture systems, such as BACTEC™, have been recommended to improve the recovery of *Brucella* spp. However, these methods are not routinely used in all laboratories. Therefore, when brucellosis is suspected, the clinician should communicate with the medical microbiologist to hold cultures for several weeks, to perform blind subcultures, or to use specific culture methods to prevent false-negative results. Additionally, knowledge of a potential *Brucella* infection may prevent airborne spread and subsequent contamination of laboratory personnel.^{2,11} Awaiting the results of blood cultures, serological testing can be done. The serum agglutination test is the most commonly used. Titres above 1:160 in the presence of a compatible clinical picture are considered diagnostic. In patient B, serology would have been diagnostic in the absence of positive blood cultures. The treatment of brucellosis has been extensively studied. The antibiotic regimens proposed by the World Health Organisation (WHO) in 1986 are still considered the gold standard. They consist of doxycycline 100 mg twice daily orally for six weeks with either rifampicin 600-900 mg/day orally for six weeks or streptomycin 1 g/day intramuscularly for two to three weeks.¹² Several alternative regimens have been proposed. Replacing streptomycin by gentamicin is considered equally effective.^{13,14} Quinolones have been frequently studied but their role is still controversial. Clinical studies were small and major differences in design hamper comparison.¹⁵ Overall, there seems to be a lack of evidence supporting the inclusion of quinolones in the initial therapeutic regimen.¹⁶ A recent report on spinal brucellosis shows equal efficacy of quinolones and rifampicin compared with the classical doxycycline and streptomycin combination. However, the higher costs make this regimen unattractive as first-choice therapy in developing countries.¹⁷ Finally, triple therapy adding an aminoglycoside or cotrimoxazole to the standard regimen has been associated with a lower relapse rate, but is not routinely used yet.^{18,19} Prolonged treatment seems to be advisable when complications such as spondylodiscitis occur.^{18,20} Patient A and B, who had osteoarticular complications, received prolonged treatment combining rifampicin and ciprofloxacin without signs of relapse. Patient C, who suffered from systemic brucellosis, was treated with doxycycline and rifampicin during the standard recommended period of six weeks.

CONCLUSION

Although brucellosis is rare in the Netherlands, it is important to consider the diagnosis when patients returning from native endemic countries present with a clinical picture of arthralgia or back pain and chronic inflammation. A thorough medical history is of paramount importance, because it provides clues to the diagnosis.

ACKNOWLEDGEMENT

We would like to acknowledge J.G.M. Koeleman, medical microbiologist in the Sint Franciscus Gasthuis Rotterdam, for providing us with information about the third case.

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