

## Osteoarticular complications of brucellosis

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### Abstract

Two hundred and sixty three patients with a diagnosis of brucellosis between January 1984 and December 1987 were studied prospectively. Sixty five patients (25%) developed osteoarticular complications. These patients had a more prolonged course than those with no complications. Spondylitis in 38 (58%) and sacroiliitis in 29 (45%) were the most prevalent. There were no significant laboratory, serological, or bacteriological differences between patients with and without osteoarticular complications. At diagnosis 47 patients (72%) showed radiographic abnormalities, commonly in axial sites but rarely in peripheral sites. Radionuclide bone scan was positive with no radiographic abnormalities in 17 (26%) of cases. Fifty seven patients received medical treatment alone, 51 (89%) being cured with a single course of treatment. Treatment failed or there was a relapse in six patients (11%), of whom five had spondylitis. Eight of the 65 patients (12%), all of whom had spondylitis and paravertebral or epidural abscesses, also required surgical treatment.

Human brucellosis is a common disease in many areas, with more than 500 000 new cases each year.<sup>1</sup> In Europe this zoonosis is still endemic in many Mediterranean countries and is a severe public health problem.<sup>2</sup>

Brucellosis typically presents with a febrile syndrome with no apparent focus, accompanied by chills, profuse sweating, and malaise.<sup>3-4</sup> The disease often results in complications, of which the most common affect the locomotive apparatus.<sup>5-8</sup> Osteoarticular complications are important owing to their high prevalence and also the associated functional sequelae.<sup>9-10</sup> Nevertheless, there are important discrepancies in the criteria used for the diagnosis of osteoarticular complications of brucellosis, their prevalence, usual sites, therapeutic schedules, and prognoses.<sup>11-14</sup> These discrepancies, together with a lack of prospective studies of such complications, led us to undertake this study.

### Patients and methods

Between January 1984 and December 1987 263 patients with brucellosis (190 men, average age 34 (SD 15) years, range 14-73 and 73 women, average age 35 (15) years, range 14-71) were treated in the infectious diseases unit of the Hospital Regional 'Carlos Haya' in Málaga. Diagnosis was established by one of the following criteria: (a) isolation of *Brucella* species in

blood or other body fluids or tissue samples; (b) a clinical picture compatible with brucellosis in the presence of seroconversion or the demonstration of raised titres of specific antibodies by seroagglutination, indirect immunofluorescence, or Coombs' antibrucella test.

All patients were studied prospectively according to a previously designed protocol, which included the following: haemogram, differential leucocyte count, erythrocyte sedimentation rate, routine urine analysis and sediment, glucose, blood urea nitrogen, creatinine, bilirubin, serum alanine aminotransferase, serum aspartate aminotransferase, alkaline phosphatase,  $\gamma$ -glutamyltransferase, protein electrophoresis, rose bengal test, seroagglutination test, and indirect immunofluorescence test. Measurement of non-agglutinating antibodies by the Coombs' test was only carried out when the previous serological tests were negative or inconclusive.

All specimens were cultured in the diphasic medium of Ruiz-Castañeda (Materiales y Reactivos SA, Madrid, Spain), processed by the usual bacteriological techniques, and incubated for at least 21 days.<sup>15</sup> Seroagglutination, rose bengal, indirect immunofluorescence, and Coombs' test were all carried out as previously described.<sup>16-19</sup> A suspension of *B abortus* 99 Weybridge strain (Biomerieux, Charbonnières les Bains, France) was used as antigen for all serological tests. Fluorescein labelled human antiglobulin conjugates, polyvalent and monospecific anti-IgG, IgM, and IgA (Behring-Werke, Marburg, Western Germany) were used for the indirect immunofluorescence test.

A radiographic study of the chest, dorso-lumbar spine, and both sacroiliac joints in prone position, as well as any other clinically affected site, was made in every patient. A radionuclide bone scan with technetium-99m methylene diphosphonate (555 MBq) was performed in cases of inflammatory osteoarticular pain with no radiographically apparent lesion. Osteoarticular complications were considered to be those showing obvious inflammatory signs (heat, redness, swelling, pain, or functional disability) in any peripheral joint, or unrelieved pain at rest in any deep joint with radiographic or gammagraphic evidence, or both, of abnormality.

All patients were examined monthly by one of the authors for a period of six months or more.

Failure of treatment was defined as the persistence of initial signs and symptoms after completion of the first month's treatment, and relapse as the reappearance of these signs and symptoms after treatment was completed.

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Statistical analysis of data was carried out using the statistical package for the social sciences (SPSS),  $\chi^2$  test for qualitative variables, and Student's *t* test and Snedecor's *F* test for quantitative variables.

### Results

Of the 263 patients, 174 (66%) had no complications during the course of their disease. Eight of the other 89 patients (9%) developed more than one complication. Osteoarticular complications were the most commonly noted, developing in 65 patients (25%) (49 men (75%), 16 women (25%)), whereas the group with no complications comprised 122 men (70%) and 52 women (30%). The average age of patients with osteoarticular complications was 37 (SD 15) years compared with 33 (15) years for patients with no complications. Within the group with osteoarticular complications, those with spondylitis had a significantly higher average age (44 (12) years) than the other patients (28 (11) years) ( $p < 0.0005$ ). The average duration of the clinical picture from the onset of symptoms to diagnosis in patients with osteoarticular complications was 57 days in comparison with 27 days in patients without complications ( $p < 0.001$ ). There were no significant differences in job, urban or rural origin, means of contagion, or previous history of the disease between the groups. Table 1 shows the clinical features of both groups.

Eighty five sites were affected in the group with osteoarticular complications. Spondylitis was the most common (38/65 cases, 58%), followed by sacroiliitis (29/65 cases, 45%), monoarthritis (eight cases, 10.1%), and oligoarthritis and soft tissue rheumatism (two cases each, 3%). In 14 of 65 patients (22%) more than one site was affected (table 2). Of the 14 patients affected at multiple sites, eight (57%) developed concomitant spondylitis and sacroiliitis and three (21%) developed spondylitis affecting more than one rachidian segment.

At diagnosis 47 (72%) patients had radiographic abnormalities, usually central and rarely in peripheral sites (table 3). Radiographic studies were not performed on a patient with sacroiliitis in her fifth month of pregnancy, though residual radiographic lesions in the affected joint were shown after delivery.

Radionuclide bone scan was performed on 37 (57%) of the 65 patients with osteoarticular complications; all were positive. The scan was positive in all patients showing radiographic abnormalities, but it was also positive in 17

Table 2 Sites of osteoarticular complications in 65 patients

Site	Number (%) of patients
Spondylitis	38 (58)
Lumbar	30 (46)
Dorsal	4 (6)
Dorsolumbar hinge	2 (3)
Cervical	2 (3)
Sacroiliitis	29 (45)
Right	14 (22)
Left	12 (18)
Bilateral	3 (5)
Monoarthritis	8 (12)
Ankle	4 (6)
Hip	2 (3)
Knee	1 (2)
Sternoclavicular joint	1 (2)
Oligoarthritis	2 (3)
Olecranal bursitis	2 (3)
Multiples sites	14 (22)

Table 3 Radiographic abnormalities

Site/type of lesion	Number (%) of patients
Spondylitis (n=38)	
Disk involvement	28 (74)
Anterosuperior epiphysitis	21 (55)
Vertebral body destruction	14 (37)
Interapophysial involvement	7 (18)
Soft tissue abscess	8 (21)
Paravertebral	5 (13)
Epidural	3 (8)
Sacroiliitis (n=29)	
Poorly defined joint	20 (69)
Joint space narrowing	11 (38)
Subchondral erosion	8 (28)
Ankylosis	1 (3)
Ankle (n=4)	
Soft tissue swelling	1 (25)
Olecranal bursitis (n=2)	1 (50)

patients (26%) with no radiographic abnormalities.

There were no significant haematological or biochemical differences between patients with and without osteoarticular complications.

Blood cultures were taken in 177 patients. One hundred and forty nine (84%) samples were taken under ideal conditions (no antibiotic treatment in the previous 48 hours, two or more samples cultured in a Ruiz-Castañeda medium, and incubation prolonged for a period of three weeks or longer) from 35 patients with osteoarticular complications and 114 without complications. Of these 149 samples, 108 (72%) were positive, 87/114 (76%) in the group with no complications and 21/35 (60%) in the group with osteoarticular complications. Only 44% of patients with spondylitis had positive blood cultures compared with 76% with other sites affected ( $p < 0.01$ ). The organism—*B meliitensis* (95.2% biotype 1, 4.8% biotype 2)—was isolated from the affected tissue in four patients with spondylitis, two with paravertebral abscess, and two with epidural abscess.

The serological response of patients with osteoarticular complications was similar to that of the group without complications (table 4).

Fifty seven patients (88%) received medical treatment alone—doxycycline 100 mg twice a day by mouth for two months plus streptomycin 1 g daily intramuscularly for three weeks in 47 cases, and doxycycline at similar doses plus rifampicin 15 mg/kg daily by mouth for two months for the remaining 10 patients. Fifty one patients (89%) receiving medical treatment were cured by a single course of treatment, the

Table 1 Number (%) of patients with clinical manifestations

Manifestation	Patients with osteoarticular complications (n=65)	Patients without complications (n=174)	Significance (p value)
Fever	61 (94)	173 (99)	<0.05
Chills	53 (82)	151 (87)	NS
Sweating	54 (83)	151 (87)	NS
Constitutional symptoms	45 (69)	122 (70)	NS
Myalgia	31 (48)	70 (40)	NS
Lymphadenopathy	4 (6)	21 (12)	NS
Hepatomegaly	17 (26)	60 (34)	NS
Splenomegaly	7 (11)	43 (25)	<0.05

Table 4 Bacteriological and serological data

	Patients with osteoarticular complications*	Patients without complications*	Significance
Blood cultures	21/35 (60)	87/114 (76)	NS
Rose bengal (positive)	57/60 (95)	148/161 (92)	NS
Seroagglutination >1/160	40/65 (62)	112/170 (66)	NS
IFI† >1/100	36/60 (60)	79/137 (58)	NS

\*Number of positive cases/total (%).  
†IFI=indirect immunofluorescence.

remaining six (11%) requiring more than one course owing to therapeutic failure in five cases and relapse in one. Eight patients (12%) received both medical and surgical treatment, all having spondylitis with paravertebral or epidural abscesses. One patient with an epidural abscess at the cervical level and secondary tetraplegia died after two operations from nosocomial pneumonia. Another patient with cervical spondylitis and spinal compression developed severe neurological sequelae. The remaining six patients were cured with scarcely any functional disability.

### Discussion

Kennedy was the first to describe osteoarticular disease in brucellosis in 1904, almost 20 years after the discovery of the causative organism by Sir David Bruce.<sup>20</sup> Osteoarticular disease is without doubt the most common complication of brucellosis. Its prevalence is uncertain, however, varying from one study to another. Buchanan *et al* reported no osteoarticular disease in his series of 166 patients,<sup>21</sup> Ganado and Craig reported a prevalence of 11% in a large series of 6301 patients,<sup>5</sup> Mousa *et al* reported a prevalence of 37.4% in 452 cases,<sup>22</sup> and Rivero-Puente *et al* a prevalence of 72.5% in 222 cases.<sup>7</sup> According to some authors, the high osteotropism and aggressiveness of *B melitensis* account for these differences.<sup>1 10 13</sup> This suggestion is not supported, however, by studies such as that of Pfischner *et al*, who found only three cases of osteoarticular complications in 228 patients from whom *B melitensis* was isolated.<sup>23</sup> We consider that the differences are due largely to the lack of prospective studies and to the diversity of criteria used for diagnosis of osteoarticular complications. In our series 65/263 (25%) of patients developed osteoarticular complications, a similar figure to that reported by Ariza *et al*.<sup>24</sup>

The ratio of men to women (3:1) is similar in patients both with and without osteoarticular complications, exemplifying the typical epidemiological trend in our community.<sup>25</sup>

In our study the age of patients with spondylitis was significantly higher than that of patients with other osteoarticular complications. Similar results have been reported by other authors.<sup>11 22 24 26-28</sup>

We found that the most commonly affected sites were the rachis in 38/65 (58%) and sacroiliac joints in 29/65 (45%) of patients; peripheral joints were much less affected, as found by other authors.<sup>12 27</sup> Some studies found a predominance of peripheral disease, possibly because they included a significant

proportion of patients aged less than 14, in whom the high prevalence of peripheral arthritis is well known. Multiple sites were affected in 14/65 (22%) of patients in our series, with the association spondylitis-sacroiliitis being the most common (eight cases). Similar findings have been reported by other authors.<sup>11 24 27 31</sup> In the early 60s, Kelly *et al* reported a high percentage of osteomyelitis of long bones.<sup>12</sup> Our findings and those of many other studies suggest that this is an unusual site.<sup>14 22 24 29 31</sup> The involvement of sternoclavicular joints,<sup>32</sup> though unusual, has been reported more and more often over the past few years.<sup>22 29</sup>

Laboratory data are of very little value in the diagnosis of brucellosis in general and its osteoarticular complications in particular.<sup>11 12 21 23 25</sup> In our study we found no significant differences in any haematological or biochemical indices between either group.

Blood cultures reported in most studies have been of little diagnostic value,<sup>6-8 14 22 27 29</sup> which contrasts strongly with our data. We found positive blood cultures in 21/35 (60%) of the group with osteoarticular complications, which parallels figures reported by Ariza *et al*,<sup>24</sup> and in both cases these high percentages would seem to be the consequence of a high diagnostic suspicion. Nevertheless, our patients with spondylitis had a significantly lower percentage of positive blood cultures than patients with other sites affected.

To date we have found no study comparing the serological response of patients with and without osteoarticular complications. We found no significant differences either in the percentage of positive tests or in the average rose bengal titre, seroagglutination or indirect immunofluorescence test between either group.

It is well known that radiographic abnormalities develop later on in the course of brucellosis with osteoarticular complications, and that they are rare in peripheral arthritis.<sup>9-11 22 24</sup> In this study 47/65 (72%) of patients had radiographic abnormalities at diagnosis, a figure similar to that reported by Lifeso *et al*<sup>27</sup> and slightly higher than those of other studies, even though in these last studies



Spondylitis of the L4 vertebral body, and an extensive anterolateral low attenuation area compatible with an abscess.

there was a much higher percentage of peripheral arthritis.<sup>22 29 30</sup> Radiographic findings noted in spondylitis were similar to those found by other authors.<sup>22</sup> Involvement of the interapophysial joints, scarcely reported previously, seemed to be fairly common, however.

The presence of paravertebral or epidural abscesses, or both, is another unusual finding in many series.<sup>9 12 27 33 34</sup> The high percentage found by us (21%) and other authors (16.6–37.5%)<sup>24 26</sup> may perhaps be related to the accuracy of the diagnostic criteria and the use of computed tomography, a much more sensitive technique than the conventional radiographic studies for the diagnosis of this complication (figure).

The high percentage of patients with osteoarticular complications but without radiographic abnormalities prompted the use of radionuclide bone scan, a technique with a well known sensitivity in the early diagnosis of bone disease.<sup>35</sup> In this study 17 patients (26%) with normal radiographic studies had a positive radionuclide scan. Similar results have recently been reported.<sup>36 37</sup>

Treatment of brucellosis is still not completely satisfactory. The best results have been obtained by treatment with doxycycline and streptomycin for six and three weeks respectively, and continuing the doxycycline for up to two months in cases of osteoarticular and visceral complications.<sup>38–41</sup>

With this regimen 51/57 (89%) of our patients were cured with one single course of treatment, with no significant differences between the two schedules used. The six patients (11%) for whom treatment failed were mostly patients with spondylitis, as previously reported by other authors.<sup>24</sup>

The good response of sacroiliitis and peripheral arthritis to treatment is already known,<sup>11 25 28</sup> but the failure of treatment in patients with spondylitis suggests that it should be prolonged for more than two months in these cases.<sup>24</sup>

Surgical treatment, together with adequate medical treatment, should be reserved for those patients with large paravertebral abscesses, medular compression, or destructive spondylitis resulting in severe and persistent pain.<sup>9 24 26 27</sup>

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