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Brucellosis

Joseph V Zammit-Maempel

Professor Joseph V Zammit-Maempel was formerly Senior Physician and Head of Medicine at St Luke's Hospital, Malta. He has extensive clinical experience of brucellosis, and his chief research interests have included diabetes in Malta and its cardiovascular complications.

Aetiology and epidemiology

Brucellosis (also known as undulant fever, Mediterranean fever, Malta fever), is a specific disease of animals which is occasionally transmitted to man, by direct or indirect contact. It is caused by small, Gram-negative, non-spore-forming coccobacilli of the genus *Brucella*. There are three important pathogenic species.

- *Brucella melitensis*, the most virulent and invasive species, usually affects goats, and occasionally sheep; it is mainly transmitted to man through consumption of raw (unboiled, unpasteurized) milk, or milk products from infected animals.
- *Brucella abortus* is less virulent and is primarily a disease of cattle, in which it causes contagious abortion.
- *Brucella suis* is of intermediate virulence and chiefly affects pigs.

B. abortus and *B. suis* are usually transmitted to man by direct contact with raw meat or vaginal discharges from infected animals. Infection is most common in farmers, meat-handlers (e.g. abbatoir workers, butchers, meat-packers, tanners), and veterinary surgeons. Hence, brucellosis is considered an occupational disease.

Brucellosis is distributed worldwide and is endemic wherever cattle, pigs, goats and sheep are raised in large numbers. Transmission is usually from animals to man, and only in exceptional circumstances from man-to-man (e.g. unsuspected brucellosis in blood donors may lead to infection of recipients, or there may be contamination of food with urine); occasionally, brucellosis is acquired directly from contaminated laboratory material.

PRACTICE POINT

Brucellosis is usually transmitted from animals to man, and only in exceptional circumstances from man-to-man.

Pathology

The portal of entry for brucella organisms is usually the upper digestive tract (buccopharyngeal lymphoid tissue) or through cuts and abrasions in the skin, and seldom via the conjunctiva or the respiratory tract. The organisms reach the regional lymph nodes by lymphatic spread. There they multiply and eventually invade the bloodstream, causing bacteraemia. They are then taken up by macrophages, in which they may multiply, and subsequently localize in the endothelial cells of the bone marrow, lymph nodes, spleen and liver, and also in other structures, such as bone and meninges (intracellular parasitization). Once localized, they induce a characteristic (but nonspecific) cellular reaction, a granuloma, consisting of lymphocytes, plasma cells, endothelial cells and, usually, giant cells as in tuberculosis, syphilis or sarcoidosis.

The subsequent histopathology depends on the nature and extent of the immunological reaction of the host and the degree of hypersensitivity to brucella antigen. Often, after a variable period, the granulomas regress; but in other cases necrosis is extensive and a 'cold abscess' forms, from which an orange-yellow pseudopurulent material containing brucellae is eventually discharged. In other instances, proliferative changes occur with reticuloendothelial hyperplasia, hyperaemia, increased tissue infiltration, and diffuse granuloma formation. Thus, brucellae may remain latent for some time (weeks, months or even years), before eventually being destroyed or causing overt disease.

Clinical features

Several patterns of disease are recognized.

Acute brucellosis: after an incubation period, generally of 1–3 weeks, the onset is usually abrupt, and often associated with one or more of the symptoms and signs given in Figure 1.

In about 10% of cases (especially infections with *B. melitensis*), the patient is markedly toxic, with high continued fever and serious visceral complications (notably bronchopneumonia, toxic myocarditis and nephritis) and the mortality rate is high if specific therapy is not

Common manifestations of acute/subacute brucellosis

- Swinging pyrexia (up to 40°C–41°C), with rigors and drenching sweats
- Arthralgia/arthritis, usually monoarticular, in larger joints (hip, knee, shoulder, ankle, etc.), resolving in under 6 weeks
- Low back pain. Sciatica is common (from compression by numerous newly-formed osteophytes, or from sacro-iliitis)
- Headache, insomnia, irritability, occasional depression
- Small, firm splenomegaly and hepatomegaly; possible discrete symmetrical lymphadenopathy, especially in children
- Leucopenia, with relative lymphocytosis

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started immediately. However, in most patients (especially those with *B. abortus* infections), the acute illness is self-limited after 2–3 weeks.

Subacute brucellosis may follow within the first three months after the acute illness; but sometimes there is no acute phase, and the illness has an insidious onset. The patient develops characteristic recurring waves of pyrexia (often most marked in the evening), each showing a step-like rise towards a plateau, then a gradual fall over a 2-week period: hence the term, undulant fever. It is not known whether these exacerbations are due to recurrent bacteraemias, or to release of brucella toxin from lesions.

The fever is accompanied by severe malaise and fatigue and sometimes by manifestations of specific organ involvement (including bones, joints and meninges; see below, page 87). The patient remains well between attacks (which may recur over many months), and most patients eventually recover spontaneously.

Localized disease: bacteraemia occurs in brucellosis, and occasionally the disease may present insidiously with evidence of localized infection in specific organs, notably bones and joints (Figure 2).

Chronic brucellosis: in a few patients, symptoms recur for prolonged periods. Usually, their temperature is normal (though it might be slightly elevated in the evenings), and the main symptoms are recurrent headaches, malaise, anorexia, wasting, cough and sweating, mimicking early pulmonary tuberculosis. Slight, firm splenomegaly or hepatomegaly may occur, and less commonly discrete, symmetrical lymphadenopathy, especially in children. These patients may easily become anxious and depressed, especially as the paucity of signs may lead to their being labelled neurotic by their doctors.

Course and prognosis

In the pre-tetracycline era, brucellosis was associated with considerable disability from frequent relapses and complications, lasting many months; but the mortality was low (under 5%), and limited to the septicaemic types. The gravity of the disease varies with the species of *Brucella* responsible. *B. melitensis* infections are the most severe and also have the greatest tendency to chronicity, whereas *B. abortus* and *B. suis* infections are generally milder. *B. suis* infection is more often complicated by suppurative bone and visceral lesions. As the result of tetracycline therapy, mortality is now negligible and the course and complications are usually controlled within a few days or weeks.

Diagnosis

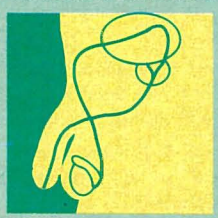
Brucellosis should be suspected in any patient with prolonged pyrexia, musculoskeletal pains and a slightly enlarged firm spleen, especially if there is a history of consumption of raw milk or milk products, or occupational exposure to infected animals or their secretions or excretions. Identification of leucopenia reduces the number of possible clinical alternatives. However, for a definite diagnosis, the presence of *Brucella* must be confirmed, either directly or indirectly.

Culture: attempts should be made to isolate the organism from three or more blood cultures, taken into special culture medium (the laboratory should be notified beforehand). The cultures are best taken on several successive days, during the early evening rise in temperature. If kept for 6 weeks, up to 80% of cultures will be positive in acute cases. In chronic cases, cultures of the following may be useful:

- bone marrow
- urine
- exudates
- aspirates
- biopsy specimens.

Serological tests can confirm the presence of specific antibodies within 2 days and are therefore widely used. They include the routine standard agglutination test (SAT), on the blood serum (and also on any exudates, e.g. joint effusions, abscesses, or body fluids such as CSF in meningitis, etc). SAT is usually the early method of diagnosis (preferably later confirmed by isolation of *Brucella* on culture). A titre of $\geqslant$80 is diagnostic. If lower titres, or negative results are obtained in a patient in whom brucellosis is suspected clinically, SAT should be repeated at intervals (of about 5 days), to look

Effects of localized *Brucella* infection

Location		Clinical features
Bones and joints		Chronic osteitis, osteoperiostitis, osteomyelitis, with late 'cold' abscess formation in any part of skeleton Spondylitis: usually in lumbo-dorsal vertebral body or margin, occasionally in a disc and adjacent vertebrae – radiograph reveals a rarefied focus, circumscribed by a denser proliferative process and excessive new-osteophyte formation, with 'vertebral bridging' Onset occurs months after defervescence, mostly in elderly men – a paravertebral abscess may form – heals spontaneously in 3–12 months (weeks with tetracycline) Subacute arthritis: common, usually monoarticular in a larger joint (e.g. knee). Exudate is lymphocytic – *Brucella* and agglutinins are present; resolves in under 6 weeks
Heart		Acute or subacute ulcerative endocarditis (usually affects aortic valve, even if previously normal)
Respiratory tract		Bronchopneumonia Pleurisy, usually dry and fleeting. Empyema is very rare
Genitourinary tract		Epididymo-orchitis, in about 5% of males; usually late, unilateral, quickly resolving Granulomatous renal disease
Liver		Granulomatous hepatitis with jaundice (uncommon) Hepatolienal syndrome very uncommon
Nervous system		Meningitis; (but meningism is more common) acute or subacute meningitis syndrome during febrile stage; CSF is lymphocytic – *Brucella* and agglutinins present Tardive meningo-encephalitis, occurs months after defervescence, sudden or insidious onset, usually ending in recovery Compression myelitis or myelopathy: cord compression, usually by subdural osteomyelitic abscess of the dorsal spine. Onset is insidious, months after defervescence; clears spontaneously, after many months (weeks with tetracycline) Sciatica from compression-radiculitis by vertebral or sacro-iliac osteophytes or inflammatory disease

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for a rise in titre. If the results are persistently negative, other serological tests are required to reveal (or exclude), possible non-agglutinating IgG antibodies.

Serology, at different stages of disease, reflects the pattern of immunological response to infection. Both IgM and IgG antibodies appear in acute brucellosis (or acute exacerbations). IgM peaks in a few weeks, but may persist after recovery; whereas IgG rises slowly, peaking in about a year, but eventually disappears after recovery. Thus persistence of specific IgG points to active infection.

Most supplementary tests depend on identifying IgG, and are therefore occasionally useful in diagnosing chronic brucellosis. However, it must be remembered that in chronic disease the results of serological tests are much more difficult to interpret and may be impossible if occupational exposure is continuous (e.g. veterinary surgeons). The tests employed include 2-mercaptoethanol (2-ME) agglutination test, the anti-human globulin (AHG) test and the complement fixation test (CF). In general, the most useful test is serum anti-brucella immunoglobulin (IgM, IgG, IgA) estimation by radioimmunoassay (RIA), or enzyme-linked immunosorbent assay (ELISA). The total amount of immunoglobulin indicates the presence (or absence), of brucellosis, whereas the relative titres indicate the disease stage. Thus, in acute disease, the titre of IgM is greater than that of IgG or IgA, while in chronic disease IgG or IgA titres exceed those of IgM.

Treatment

In the treatment of brucellosis, the proven antibiotic of choice is tetracycline (or its derivatives), usually given orally, 2–3 g/day in 4–6 divided doses, for about 3 weeks. Parenteral tetracycline is seldom needed. (Adequate amounts of vitamin B-complex, a liberal diet and initial bed rest are also recommended.) For children the dose is 50 mg/kg/day; but the significant risk of teeth-staining should be borne in mind; the risks of the disease, both in pregnancy and in children, usually outweigh this. The available alternatives are still unreliable.

Defervescence occurs within 4–5 days. Loading doses should be avoided, as they are more likely to lead to a severe Jarisch-Herxheimer reaction. In such a severe reaction, corticosteroid therapy may be life-saving. Relapses seldom occur, and usually respond to repeat courses of tetracycline.

In exceptional cases, for example, repeated relapses in spite of treatment, or acute or subacute endocarditis, tetracycline treatment can be supplemented with streptomycin, 1 g/day i.m., or gentamicin, 6 mg/kg i.m. or i.v. for the first 2–3 weeks of a 6-week course. Co-trimoxazole, 2–3 x 400/80 mg tablets b.d. for 1–2 months, has been used as an alternative therapy for brucellosis, but is less effective than tetracycline.

Prevention

The following precautions will minimize the risk of brucellosis infection.

- Pasteurize or boil all milk for human consumption.
- Maintain scrupulous hygiene and wear protective clothing when handling potentially-infected animals.
- Vaccinate young animals.
- Screen animals for *Brucella* infection and slaughter any animal with positive reactions on testing. □

FURTHER READING

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