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BRUCELLA CANIS: UNDERSTANDING THE TRANSMISSION, INFECTION AND MANAGEMENT OF BRUCELLOSIS CANINE IN PUBLIC HEALTH

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ABSTRACT

Transmission of Brucella canis to humans typically occurs through contact with infected dogs or their fluids, or via direct exposure in laboratories. The zoonotic risk is notably high for individuals handling breeding dogs in kennels or coming into contact with infected animals, although transmission in other situations is believed to be uncommon. We report a rare outbreak of brucellosis caused by B. canis, which, to our knowledge, is the first documented case in the literature. This outbreak affected six individuals (three children and three adults), a female dog, and three puppies with whom the family had close daily interaction. Brucella canis is a bacterium that primarily affects dogs, causing canine brucellosis, a contagious infection with potential implications for public health. This abstract provides an overview of the infection, its transmission, symptoms, and preventive measures. Canine brucellosis is mainly transmitted through contact with infected bodily fluids and can lead to reproductive issues in dogs, such as infertility and abortion. While rare, brucella canis can also be transmitted to humans, leading to flu-like symptoms. Responsible dog breeders should regularly test their animals and take precautions no prevent the spread of the infection. Public health authorities play a vital role in monitoring and controlling the transmission of brucella canis. Understanding and adhering to preventive measures can help protect both animal and human health. Precautions.No clinical signs are pathognomonic of canine brucellosis, although reproductive failure and infertility should be suspected. Transmission is mainly through contact with vaginal discharges, abortion materials and fluids of bitches and semen and/or urine of males. Since clinical examinations are inadequate for diagnosis, isolation of the organism and serological tests are the only reliable way to confirm a presumptive diagnosis. In this case the bitch had a history of abortion 3 years previously, gave birth to weak puppies which died after 3 days one year later, but was never diagnosed with brucellosis. Of the last pregnancy in 2008, two puppies were born dead and three (two males, one female) were apparently normal.

Keywords: Brucellosis, Coccobacilli, Genotypes, Lymphadenopathy

INTRODUCTION

Brucellosis has been documented in the Mediterranean area and historically linked with military operations. George Cleghorn, a British army surgeon, recorded instances of the disease in 1751 in his work 'Observations on the Epidemical Diseases in Minorca from the Year 1744 to 1749' [1]. Its recognition as a distinct medical condition occurred during the Crimean War on Malta. Detailed descriptions were provided by Sir David Bruce, Hughes, and Sir Themistocles Zammit in 1886. B. abortus, responsible for undulant fever in humans and cattle abortions, was first identified by Bernhard Bang in 1897. B. suis, associated with brucellosis in humans, was isolated from swine by Traum and Huddleson. Evans noted the relationship between Micrococcus melitensis (Brucella melitensis) from cows and pigs, leading to the genus's naming in honor of Major-General Sir David Bruce [2]. B. neotomae was isolated from rats by Stoenner and Lackman. Carmichael and Bruner discovered B. canis in dogs. More recently, B. pinnipedialis and B. ceti, new Brucellae from marine mammals, have raised concerns about potential zoonotic threats. B. microti has been reported in terrestrial animals. The identification of various Brucella strains in marine mammals and humans emphasizes the significance of zoonotic transmission [3].

Brucellosis, a communicable ailment resulting from bacteria belonging to the Brucella genus, has the potential to impact diverse animal species. Dogs may, on occasion, contract the disease from B. abortus, B. melitensis, or B. suis, as well as from the endemic form caused by B. canis [4]. In canines, it induces reproductive issues and presents as non-specific lameness or discospondylitis. In humans, B. canis can be the source of chronic debilitating conditions typical of its genus, including undulant fever, splenomegaly, and lymphadenopathy [5]. The utilization of the MLVA (multilocus variable-number tandem repeat analysis) assay proves beneficial in examining epidemiological correlations among Brucella isolates and tracing their geographic origins. In this study, MLVA-16 was employed to scrutinize the epidemiological connections among 63 isolates sourced from dogs and humans [6]. The classification revealed three major clusters (A, B, and C) encompassing 50 distinct genotypes (GT1-50), with 43 unique genotypes represented by individual isolates. This suggests that these strains lack apparent epidemiological links, implying that canine brucellosis is largely sporadic in China [7].

Among a total of 20 isolates, seven shared genotypes were identified, each represented by two to eight isolates, indicating epidemiological correlations among strains within each shared genotype. Notably, five shared genotypes were traced back to 16 strains from Beijing, signifying multipoint outbreaks and multiple sources of infection in the origin of canine brucellosis in Beijing. Based on a comprehensive

analysis of clinical B. canis infection, preliminary findings suggest an association between human B. canis infections and Mycoplasma pneumoniae infection, leading to decreased patient immunity.

While B. canis may hold limited epidemiological significance for the healthy population, it remains a significant threat to the canine breeding industry and individuals in close contact with dogs. MLVA-11 data reveal the clustering of B. canis strains into 16 genotypes, organized into five evolutionary branches [11]. This underscores the extensive geographic coverage and characteristics of co-existing introduced and locally native lineages, contributing valuable insights to the prevention and control of canine brucellosis and enhancing public awareness of the health risks posed by B. canis [8].

Description of the Disease

Etiology

Brucellae, categorized as Gram-negative coccobacilli or short rods, exhibit dimensions ranging from 0.6 to 1.5 um in length and 0.5 to 0.7 um in width. Typically found singly, they may occasionally appear in pairs or small groups, maintaining a consistent morphology except in aged cultures where pleomorphic forms may manifest. Genus Brucella bacteria are characteristically non-motile, lacking spores, Pili, and true capsules. They operate as aerobes and are devoid of spore formation. In the case of B. Canis, it lacks a biovar, demonstrating growth independence from carbon dioxide during initial isolation, and susceptibility to thionin rather than basic fuchsin. During the initial isolation, B. Canis colonies consistently present in phase R (rough) or M (mucoid), with no reported occurrence in phase S (smooth). B. Canis exhibits no agglutination in the presence of Brucella A-M monospecific antisera but agglutinates with specific antisera targeting the R antigen of B. Ovis (REO 198 strain). Additionally, cross-reactions with surface antigens of other Brucella species in a non-smooth phase are plausible. B. Canis does not produce H2S, lacks oxidation of substrates based on L-Asparagine or D-Xylose, does not reduce nitrate, and does not undergo lysis in reactions with various phages, except with the P/C phages [9].

Epidemiology

B. canis infection has been observed globally, with the identification of the causative agent in some countries and suspected presence based on serological responses in others. Canine brucellosis is reported as endemic in regions like Central and South America, Asia, and the Southern USA, particularly prevalent among stray dogs and in kennels. The introduction of the disease into a kennel leads to rapid spread. In Europe, reports of B. canis infections mainly reflect clinical symptoms in dogs or humans. No comprehensive cross-sectional study assessing the prevalence of the disease has been conducted in any

European country. Limited data and surveillance hinder an accurate understanding of endemic countries. Since 2017, sporadic cases, clusters, or outbreaks have been reported in EU countries, including Switzerland, Ukraine, the Netherlands, the UK, and Turkey. Retrospective laboratory data from 2016 to 2022, mainly from Western Europe, show 3.7% of samples tested positive for Brucella spp. DNA, with higher rates in Spain and Poland. However, caution is needed in interpreting results due to the non-validated PCR kit and uneven sample submission.Currently, there's no mandatory pre- or post-import testing for B. canis in Europe. Detection often follows clinical manifestations if veterinarians are informed. Movements of dogs between countries, exacerbated during the COVID pandemic, contribute to disease spread. Recent risk assessments in the UK, France, and Finland led to regulatory changes, making cases reportable. Notably, canine brucellosis isn't a notifiable disease for the World Organization for Animal Health (OIE) and EU countries, impacting case reporting. In the UK, positive B. canis laboratory results are now reportable [11].

Global prevalence

Brucellosis is a zoonotic infection caused by various Brucella species, affecting both humans and animals, including cattle, dogs, sheep and goats. Recent studies reveal a higher global incidence than previously estimated, with 1.6–2.1 million new human cases annually. Resource-limited regions, such as the Mediterranean, Middle East, Central Asia and certain parts of Africa, report elevated incidence rates. Iran, Kyrgyzstan, Tajikistan, Kazakhstan, Azerbaijan, Turkmenistan, Armenia and Uzbekistan are among the countries with the highest reported incidences of brucellosis.

Regional epidemiology–California;United States of America In Latin America, Mexico and Peru have reported many cases. A study conducted by Fritz et al. on the epidemiology of brucellosis in California found that the disease is particularly prevalent among older Latino men, with a significant link to the consumption of unpasteurised Mexican-style soft cheese and B. melitensis was the most common species detected in cases. There were 492 cases reported in California from 1993 to 2017, underscoring the health risks of brucellosis. This study emphasises the importance of public health initiatives to inform the Latino community, especially the older population, about the risks associated with importing and consuming unpasteurised dairy products, particularly those from Mexico.

Regional epidemiology–Europe; In the 28 EU countries, the annual incidence rate for 2017–2018 was 0.09 per 100,000 people. The European Food Safety Authority (EFSA) noted a decline in brucellosis cases from 735 in 2008 to 352 in 2011, highlighting successful intervention measures . In Europe, Brucella canis has emerged as a cause of canine brucellosis, indicating a zoonotic threat to public health.

The lack of comprehensive surveillance and awareness of B. canis among veterinarians and dog owners complicates disease management. The current diagnostic tools for detecting B. canis infection are insufficient in sensitivity and specificity, underscoring the need for better diagnostic methods. The lack of universal reagents and standards for serological tests adds to the challenge of accurately diagnosing this infection. To address these issues, this study emphasises the importance of developing awareness materials, profession-specific guidance and enhanced diagnostic techniques to curb the spread of B. canis and increase awareness among the public and professionals .

Regional epidemiology–Bosnia and Herzegovina; Between 2008 and 2018, 263 cases were studied in Bosnia and Herzegovina, decreasing from 102 in 2008 to 3 in 2018. The findings of this study regarding epidemiological characteristics align with the data from other global studies. Specifically, there was a notable male predominance; the most affected age group was between 25 and 49 years, and most patients either hailed from rural settings or had previous exposure to animals.

Regional epidemiology–Turkey; A study was conducted in Turkey to investigate the prevalence of brucellosis in children. The primary risk factor identified was occupational exposure, with 71.1% of the studied families engaging in animal breeding. Additionally, having a family member previously diagnosed with brucellosis accounted for 15.6% of the total risk. The study also emphasised that consuming raw milk and dairy products, such as cheese, is the primary transmission route in most instances. These findings are consistent with previous studies conducted in other regions of Turkey.

Regional epidemiology–Iran; Brucellosis is present in most parts of Iran, with 80,000 cases reported annually since 1989. It has been reported in Iran that healthcare workers are accidentally exposed to Brucella strains during routine animal vaccination programs. Brucellosis incidence in Iran varies by region and has decreased in recent years. Males aged 25–29 years are more commonly affected by the disease, with western provinces reporting higher prevalence. The seasonality of brucellosis cases is notable, with spring months seeing increased diagnoses. Occupational risks for healthcare workers, including accidental exposure during animal vaccination programs, highlight the need for targeted prevention strategies. Brucella melitensis biovar 1 remains the dominant causative agent in Iran, and risk factors include the consumption of unpasteurised dairy products and living in rural areas. Efforts to control and manage brucellosis in Iran require a multifaceted approach that addresses regional variations and occupational exposures [5].

Regional epidemiology–Jordan; In Jordan, brucellosis is prevalent among young adults in rural areas and those working in livestock-related occupations, particularly during the spring and summer. Al-Amr

et al. revealed variations in seropositivity rates, with occupational exposure being a significant risk factor. This research also highlights the substantial health burden of brucellosis in Jordan, exceeding that in North America and Western Europe, with 31.1% of febrile illnesses in Jordan attributed to the disease. These findings are crucial in informing and enhancing disease control and prevention strategies, offering valuable insights into the epidemiology of brucellosis in Jordan and contributing to reducing its impact.

Regional epidemiology–India; A study by Holt et al. Revealed that brucellosis, a zoonotic disease caused by Brucella species, is endemic in rural areas of India, with a seroprevalence of 15.1% (95% CI: 15.9–19.8%). This finding emphasises the disease's prevalence in regions where agriculture and livestock farming are common, facilitating disease transmission due to close human–animal interaction. Seroprevalence, denoting the presence of Brucella antibodies in individuals' blood, highlights substantial exposure within the rural population. Moreover, the study's 95% confidence interval underscores the statistical reliability of this seroprevalence estimate. In conclusion, Holt et al.'s research underscores brucellosis as a significant health concern in rural India, necessitating effective control measures and increased community awareness to address this zoonotic disease's impact [7] .

Regional epidemiology–Punjab, Pakistan; In Punjab, Pakistan, a study by Nawaz et al. on the epidemiology of brucellosis revealed a seroprevalence of 13.13%, with higher rates in males aged 25–40. Risk factors were lack of education, involvement in farming, keeping animals at home, animal slaughter and consumption of raw milk. This study further emphasises the necessity of raising awareness regarding disease transmission and risk factors among individuals with direct animal exposure, particularly livestock farmers. Furthermore, it underscores the importance of avoiding unpasteurised dairy products to mitigate the spread of this often underestimated zoonotic disease, which has a high regional morbidity rate [6].

Regional epidemiology–China; A study in China examined the epidemiological features, morbidity and endemic nature of human brucellosis and observed a notable increase in the population. Four-year study revealed divergent trends in the incidence of brucellosis across China, with a nationwide average annual incidence of 3.0 per 100,000 people. While the rate substantially decreased in Xinjiang, it more than doubled in Inner Mongolia, contributing to the higher incidence rate in Northern China. Notably, males aged 45–64 in this region are more than twice as likely to be affected by their female counterparts.

Regional epidemiology–sub-Saharan Africa Brucellosis is endemic to many regions of the world, including sub-Saharan Africa. According to the literature published between 2010 and 2019, the prevalence of brucellosis in livestock ranged from 0.2% to 43.8% in cattle, 0.0% to 20.0% in goats, and

0.0% to 13.8% in sheep. In humans, the prevalence of brucellosis in the sub-Saharan African region ranges from 0% to 55.8%, highlighting the significant presence of brucellosis infection in this area [10].

TRANSMISSION

Brucella has the potential for transmission through horizontal or vertical routes. Pregnant animals harbor higher concentrations of Brucella organisms in their uterus. The primary sources of infection include aborted fetuses, placental membranes, and uterine discharges. Infection transmission to newborns can occur through the shedding of organisms in the milk of infected animals. The organism can persist in the environment, particularly in cold and moist conditions, for several months. Animals can contract the infection by ingesting contaminated feed and water or by coming into contact with aborted fetuses, fetal membranes, and uterine discharges. The prevention and control of brucellosis is of paramount significance, and a thorough understanding of its mode of transmission is indispensable in achieving this objective. Brucellosis can be transmitted to humans through several paths [11].

DIAGNOSIS

Diagnostic techniques for brucellosis primarily rely on serology, with the LPS smooth chains eliciting significant immunological responses across various hosts. The main challenge in diagnosis stems from the resemblance between the O-antigenic side chain of Brucella LPS and those of other organisms like Yersinia enterocolitica O:9, Vibrio cholerae, Escherichia coli O:157, and Francisella tularensis. Although alternative antigens have been explored to enhance specificity, they have mostly yielded unsatisfactory results. Blood culture serves as the gold standard for bacterial infection diagnosis, including brucellosis, but its success rate ranges only between 40% to 70%. While the traditional Biphasic Ruiz-Castaneda system has historically been used for Brucella sps isolation from clinical samples, it has largely been replaced by the lysis centrifugation technique and automated culture systems, which offer higher rates of positive blood culture. Additionally, bone marrow cultures may provide greater sensitivity and faster results, particularly in patients with prior antibiotic exposure. Brucella can also be cultured from pus, tissue, cerebrospinal fluid (CSF), and pleural/joint/ascitic fluid [12].

Serodiagnosis

Regarding serodiagnosis, in the absence of culture, the diagnosis of brucellosis relies on agglutination tests such as the Rose Bengal test, serum agglutination test, Coombs test, complement fixation test, and the recently introduced immunocapture test [13]. The Rose Bengal test serves as a screening tool, with positive results confirmed by serum agglutination tests. This agglutination test relies on antibody

reactivity against smooth lipopolysaccharide, boasting high sensitivity (>99%) and rare false-negative results [14]. To enhance specificity, the test may be subjected to serial dilutions (1:2 through 1:64) of serum samples. The Standard Tube Agglutination Test (SAT), developed by Wright and colleagues, remains popular due to its simplicity. SAT measures the total quantity of agglutinating antibodies (IgG and IgM). However, interpretation can be challenging, particularly in patients with low levels of agglutinating IgG antibodies [14]. SAT titers above 1:160 are considered diagnostic, rising to 1:320 in endemic areas. Coombs test is suitable for confirmation in relapsing patients, although it is complex and technique-dependent. Enzyme-linked immunosorbent assay (ELISA) and Fluorescence polarization assay (FPA) offer alternatives to conventional serological tests, with varying levels of sensitivity and specificity. The Immunochromatographic Brucella IgM/IgG lateral flow assay (LFA) presents a rapid point-of-care option with high sensitivity and specificity for Brucella IgM and IgG. Additionally, the Brucella Capt BCAP assay detects both agglutinating and non-agglutinating antibodies with high sensitivity, potentially serving as a substitute for Coombs test and a marker for disease activity [15].

Diagnostic challenges and public health response

Brucellosis poses numerous diagnostic challenges that significantly hinder public health initiatives. The challenges mentioned are intricately tied to the level of interaction individuals have with animals carrying the infection or their derivatives. Here are several critical factors to consider:

Misdiagnosis and underdiagnosis: One of the main obstacles in diagnosing brucellosis is the risk of misdiagnosis or underdiagnosis. The symptoms of the disease, such as fever, fatigue and joint pain, are non-specific and can be similar to those of various other illnesses. Consequently, healthcare professionals might either miss identifying the diagnosis or mistake it for other ailments, resulting in delays in administering suitable treatment [16].

Resource-poor settings: Diagnostic inaccuracies, particularly misdiagnosis and underdiagnosis, are notably prevalent in regions with limited access to advanced diagnostic equipment and healthcare infrastructure. Consequently, the disease burden in such resource-poor settings may be considerably underestimated, resulting in inadequate public health responses [17].

Overestimated case numbers: The paradoxical nature of diagnosing brucellosis is such that the difficulty in doing so can lead to an overestimation of case numbers in regions where healthcare systems rely on less specific diagnostic methods. This overestimation can in turn foster heightened risk perceptions and unwarranted panic among the general population [18].

In response to these challenges, several crucial measures need to be implemented:

Improved diagnostic methods: The development of reliable diagnostic tests for brucellosis is imperative, as current methods are often inaccurate and slow. Research and development initiatives should focus on creating tests that can accurately differentiate brucellosis from other febrile illnesses and are suitable for use in resource-limited settings. These tests should also be easily accessible to improve early diagnosis and treatment of the disease [19].

Enhanced surveillance: The implementation of comprehensive surveillance systems is crucial for the purpose of closely monitoring the occurrence and geographic proliferation of brucellosis. This entails identifying outbreaks at an early stage and gaining insight into the disease's epidemiological patterns within particular demographics [20].

Increased awareness: Increasing awareness and education among healthcare professionals, especially in endemic areas, is imperative for addressing brucellosis, a zoonotic ailment with significant public health ramifications [21]. It is crucial to enhance comprehension of the disease's clinical presentations and diagnostic complexities to ensure precise and prompt diagnoses, thereby facilitating effective public health interventions. Strengthened surveillance, improved diagnostic tools, and heightened awareness within healthcare settings are essential in mitigating the repercussions of brucellosis, particularly in resource-constrained regions where its prevalence is often elevated. These concerted efforts are pivotal for curtailing disease transmission and reducing its adverse effects on affected communities [22].

Clinical manifestations

The clinical manifestations of brucellosis vary significantly, making the diagnosis challenging. Symptoms range from flu-like illnesses to more severe complications involving multiple organs. The non-specific nature of symptoms and the difficulty in obtaining samples for laboratory testing contribute to challenges in diagnosing the disease [23]. Haemorrhagic anaemia is an important clinical manifestation of brucellosis in children. Brucella infections can lead to microangiopathic haemolytic anaemia and severe thrombocytopenia in children. The ability of Brucella to change from a non-haemolytic to a haemolytic phenotype may influence its pathogenicity and contribute to the correlation between acute brucellosis and haemolytic anaemia in humans [24]. The expression of haemolysin genes in Brucella may have accumulated mutations during growth, resulting in the repair of the default genes and the ability to express haemolysin, which can affect pathogenicity. However, a conclusive explanation for the

development of haemolytic anaemia during Brucella infection is still missing. The presence of haemolysin genes and haemolytic anaemia in humans has been reported [25].

Current treatment methods for brucellosis

Doxycycline and rifampin are commonly used antibiotics for treating brucellosis. They form the basis for treating all types of human brucellosis. Following suitable antibiotic therapy, full recovery is expected in acute, uncomplicated brucellosis. Adults and children over eight usually take doxycycline, the preferred antibiotic due to its dosing frequency and fewer gastrointestinal side effects, orally for six weeks [26]. To minimise the risk of relapse, aminoglycosides are often added during the initial 2–3 weeks of therapy. Although gentamicin shows promise, further research is needed to establish the optimal dosage and duration. Rifampicin is another effective alternative. A six-week oral administration of both doxycycline and rifampicin showed similar efficacy in treating uncomplicated brucellosis. Fluoroquinolones are considered secondary alternatives because of their high efficacy [27].

While the WHO-recommended brucellosis treatment has evolved, the optimal approach remains unclear. This review suggests that a combination of doxycycline and aminoglycosides is common for uncomplicated brucellosis. Short-term treatment is discouraged because of the high failure and relapse rates. For complicated cases of spondylitis, neurobrucellosis or endocarditis, a prolonged triple therapy regimen involving streptomycin, gentamicin, doxycycline and rifampicin is more effective [28].

In resource-limited areas, various combinations of oral drugs such as tetracycline/rifampicin, doxycycline/ofloxacin or ciprofloxacin/rifampicin can be used. Rifampicin should be used cautiously and never alone to avoid multidrug-resistant tuberculosis. In children, co-trimoxazole combined with gentamicin or rifampicin is recommended, and quinolones should be used cautiously as a monotherapy [29].

For dogs with B. suis infection, a combination of rifampicin and doxycycline was administered. Euthanasia should be considered in severe cases to prevent zoonotic exposure. In B. canis-infected dogs, dual therapy is recommended despite the high relapse rates, particularly in males [30].

In production animals, brucellosis treatment is typically avoided, and the affected animals are usually culled. This varied information underscores the complexity of brucellosis treatment and different approaches, depending on the species affected [31].

Consideration of patient specifics, drug accessibility, and local resistance trends is crucial when selecting antibiotics for brucellosis [32]. It is imperative to closely monitor and follow up to ensure successful

treatment and prevent relapse. Despite these efforts, mild brucellosis cases often experience treatment failure and relapse (5–15%), underscoring the importance of continuous monitoring and repeated serological testing over a one-year period [33].

The inappropriate use of antimicrobials has been associated with the emergence of multidrug-resistant Brucella strains in endemic regions globally. This, in turn, poses a public health threat and hampers the availability of effective treatments. To manage brucellosis effectively, regular antimicrobial susceptibility testing, employing techniques like microdilution, E-tests, Kirby Bauer, and real-time PCR, is essential to determine the minimum inhibitory concentrations (MICs) of drugs and evaluate Brucella resistance profiles [34].

CONCLUSION

In summary, comprehending the biological aspects of a disease is crucial for its efficient management, involving personalized therapies and early detection. Ongoing research into disease mechanisms informs vaccine development, highlighting the importance of continuous drug discovery due to the substantial time required. The rapid expansion of multi-omics and bioinformatics has greatly contributed to patient profiling and potential drug targeting, supporting the development of new drugs and vaccines. The collaboration across sectors represents a significant stride toward a comprehensive control program, requiring active participation and endorsement from the community. A multidisciplinary approach facilitates transparent data exchange and the implementation of an empirical surveillance model for precise brucellosis tracking. Bridging the gap between socioeconomic challenges and research priorities involves prioritizing funding for infrastructure and human resources. International collaboration is crucial, exemplified by the recent $82 million grant from the World Bank to India for zoonosis and endemic disease prevention. This collective endeavor is indispensable for the effective management and control of zoonoses on a global.

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