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POLYMORPHISM OF OSTEOARTICULAR MANIFESTATION OF BRUCELLOSIS INFECTION. A REVIEW

Brucellosis is a common zoonosis which still remains as a major health problem in certain parts of the world. Kazakhstan remains among the most disadvantaged territories of brucellosis from Commonwealth of Independent States countries. The involvement of the musculoskeletal system is one of the most common systemic manifestations in brucellosis infection. The frequency of osteoarticular involvement of brucellosis varies between 10% and 85%. Osteoarticular involvement includes spondylitis, sacroiliitis, osteomyelitis, peripheral arthritis, bursitis, and tenosynovitis. Sacroiliitis is the most common osteoarticular finding in adults. A high degree of suspicion in the diagnosis of brucellar spondylitis is essential to reduce the delay for the treatment. Thus, it should be essentially included in the differential diagnosis of longstanding back pain particularly in regions where brucellosis is endemic. Screening serologic tests for brucella should be used more widely even in presence of low index of suspicion, especially in endemic areas. According to studies, when diagnosed with chronic brucellosis, the results of serological studies were unreliable: the result of the standard agglutination test (SAT) - Wright's reaction was negative in 32.7% of cases in patients with chronic brucellosis. Imaging studies, including radiography, computed tomography (CT), magnetic resonance (MR) imaging, and bone scintigraphy, have been used for diagnosis. Radiography is limited to evaluating the focal form of spinal brucellosis and advanced disease at the joints. For instance, MR imaging has a low specificity to predict the exact cause of an osteoarticular lesion, and in case of arthralgia or symptoms of osteomyelitis or spondylodiscitis, the index of suspicion should be high in regions where the disease is endemic.

Keywords: Brucellosis, osteoarticular manifestation, brucellar sacroiliitis, spinal brucellosis, Spondylodiscitis, discitis

Introduction

Brucellosis is a relatively common zoonosis worldwide, caused by small coccobacilli of Brucella species, which are intracellular gram-negative facultative bacteria. B. melitensis and B. abortus are the main causes of human brucellosis. Human brucellosis is a systemic infection that involves many organs and tissues in the pathological process[1,2]. The relevance of this problem is the late diagnosis, which indicates the lack of alertness and knowledge among medical personnel regarding brucellosis even in areas where the infection is widespread [3]. According to Professor Amireev S.A. in Kazakhstan (20000 cases of brucellosis, 1986-1994 y.) despite the typical clinical manifestations of acute brucellosis, in 1/3 of the patients the initial diagnoses were incorrect: 12% of the patients were mistakenly diagnosed as pneumonia, 7% of the patients as an acute respiratory infection, and some patients even received treatment diagnosed with viral hepatitis, acute rheumatic fever and others [4].

This fact once again proves the polymorphism of the clinical manifestation of brucellosis and the low awareness doctors of all specialties. If such difficulties exist during the diagnosis of acute brucellosis, verification of chronic brucellosis in the presence of systemic manifestations and with low sensitivity of laboratory tests is a real medical problem.

The incidence of brucellosis in the world has increased in recent years. From the literature it is evident that the current rate is lower than the actual incidence because of under diagnoses and underreporting. Although the diagnosis of brucellosis is usually not difficult, its misleading and multifarious manifestations, especially in case of localized, subacute or chronic infections might lead to misdiagnosis and delayed treatment [1].

Brucellosis is the most frequent zoonotic infectious disease in the world, affecting more than 500 000 people each year. Its prevalence is more than

10/100 000 population in some endemic countries In endemic countries, brucellosis is more prevalent in the 15–35 years age group [3,4]. In a recent study by T. Buzgan et al. (1028 cases of brucellosis, Turkey) 53.4% of patients were between 13 and 34 years of age [5]. In a recent study by Gu¨l et al. from Turkey (140 patients between January 1997 and December 2006), a mean age of 27 ±3.6 years was reported in a population comprising 80.7% male and 19.3% female. Gender differences between these results could be explained by the diversity of populations, because the latter study was performed in a military hospital [6,7].

According to research Gu¨ r et al. (283 cases, Turkey) 138 (49%) were female, 145 (51%) male and 53 (19%) were younger than 15 years old [8].

An alarming fact is that brucellosis mainly affects a young rural contingent from among indigenous ethnic groups (90%), including children under 14 years of age. The professional composition of patients has undergone significant changes: the proportion of people constantly associated with animal husbandry (shepherds, milkmaids, hunters and others) is steadily decreasing: from 36.5% in 1961-1965 to 13.8% in 1994 of the total Today, there is a tendency to increase the proportion of persons professionally not associated with animal husbanddry. However, according to a study by prof. Amireeva S.A. the majority of patients with acute and subacute brucellosis (76%) had professional contact (permanently or temporarily) with animals, its raw materials, or animal products [9].

Infection of a person with brucellosis can occur not only as a result of his direct contact with animals affected by brucellosis, but through livestock products, in particular, in the process of removing and processing skins infected with brucellosis in areas that are often quite remote from the immediate location of the source of infection. The primary transmission route of brucellosis is by the ingestion of unpasteurized dairy products in endemic countries, whereas in developed countries infection occurs mostly due to occupational exposure [3,4,10]. In Kazakhstan (20000 cases of brucellosis, 1986-1994 y.), the contact route of transmission of the infection still prevails (79-86%), which over time is becoming increasingly less important in favor of the nutritional route. By the end of 9th decade of the 20th century, an alimentary route of infection is much less common (0.1–9.1%) [9]

The disease spreads to humans by the ingestion of raw dairy products, the consumption of infected meat from domestic livestock (sheep, goats, cattle, water buffalo, camels and pigs) and close contact with their secretions and carcasses [5].

Alimentary infection is caused by using raw and not sufficiently thermally processed livestock products (milk, dairy products, especially goat milk and feta cheese, barbecue, etc.). The long stay of brucella in milk determines its epidemiological role especially goat milk. There are known cases of human disease that has been caused by consuming unboiled milk. Brucella lives in meat and minced meat for 14 to 40 days, depending on storage temperature and salt concentration. This factor is of particular importance for workers in the meat processing industry and for the consumer [11].

In some epidemiologic studies from Turkey (1028 cases of brucellosis), a history of raw dairy product consumption has been reported for between 62.6% and 94.6% of cases [5]. The consumption of raw dairy products in other studies has been reported as occurring in 23.6% of cases in Spain by Colmenero et al. (530 cases),[12] 69% in Kuwait by Mousa et al. (379 cases),[13] 34.7% in the Balkan Peninsula by Bosilkovski et al. (418 cases), [14] and 22.4% in Iran by Roushan et al. (469 cases) [1]. A history of a local traditional food in Turkey – raw meat ball – consumption was reported in 55% in the series of Gu¨ r et al. (283 cases) [8]. High-risk occupations for the disease are shephards, butchery, farming, and people associated with veterinary medicine [3,4].

Although it is seen widely throughout the world, it is hyperendemic in the Mediterranean Basin and Arabian Peninsula, India, Mexico, and Central and South America. Brucellosis has been eradicated in England, in many northern European countries, and in Australia, New Zealand, and Canada [7,15]. The increase in the incidence of brucellosis of people in Kazakhstan is a direct consequence of the sharp deterioration of the epizootic situation: a direct link has been established between the infection of livestock and the incidence of people [9].

According to reports on the MEDinform website, which contains official statistics of the Ministry of Health of Kazakhstan, in 2000, 1918 cases were recorded (incidence rate of 12.9 / 100,000), and in 2004 their number increased to 3596 (incidence rate of 23.95 / 100,000). Interestingly, despite the improvement in the diagnosis and verification of brucellosis in 2018, 998 new cases were recorded, the incidence rate decreased to 5.46 per 100,000 population [16]. However, these figures do not fully reflect the actual situation in our country, because the high incidence of brucellosis in people does not always agree with the official statistics of the veterinary service. In Kazakhstan, the following pattern remains: the predominance of small cattle as a source of

infection, and in recent years it has been expressed more and more. Accordingly, there is a slight decrease in the value of cattle in infecting people. In almost all zones of Kazakhstan, except the western, small cattle are of primary importance in infecting people. In the western regions of Kazakhstan, the role of small and cattle is approximately the same (43% and 50%, respectively, and the rest is other ways of infection) [9]. There is a lot of speculation about reducing the incidence of brucellosis by 3.5 times over the last 10 years. Firstly, incomplete laboratory diagnosis in suspected brucellosis. According to the rules of the standard definition of the case of a particularly dangerous infectious disease, the following laboratory tests are necessary to confirm the diagnosis of "brucellosis": the Hadlson reaction, agglutination reaction, ELISA, passive hemagglutination reactions, antigen neutralization reactions, Coombs reaction, complement fixation reaction, method of detecting antigen-binding brucellous specificity lymphocytes (diagnostic value 95% in acute brucellosis), polymerase chain reaction using blood serum, blood cells, bone marrow, lymph node biopsy and other biomaterials, as well as bacteriological blood tests for brucellosis. But unfortunately, most cases use only screening methods to determine brucellous infection: the Hudlson reaction and agglutination test, which have low diagnostic value. Secondly, the low caution of infectious doctors and general practitioners. This may be due to the distinctive feature of modern brucellosis - the increase in morbidity among unprofessional groups, including children, along with persons associated with livestock production and processing of livestock products. Thirdly, the prevalence of the alimentary route of infection when the agent enters the body when the infected food is consumed (dairy, less often meat products). The alimentary route of infection is carried out when raw and insufficiently thermally processed livestock products (milk, dairy products, especially goat milk and feta cheese, barbecue, etc.) are consumed. This leads to an erroneous interpretation of epidemiological history. Thus, the decline in morbidity in Kazakhstan is surprising at a time when there are no epidemiological prerequisites for this phenomenon. All the above-mentioned reasons are still hypotheses that need further study.

Because brucellosis is one of the great imitators in the world of infectious diseases, it can mimic various multisystem diseases, showing wide clinical polymorphism, which frequently leads to misdiagnosis and treatment delays, further increasing the complication rates [3,4].

Clinically it may progress as a subclinical, acute, subacute or chronic infection. Since Brucella spp. are intracellular bacteria, relapse is often seen [3, 4, 10, 17].

Brucelles can persevere in the host 's body for a long time. Most commonly, the brucella reservoir is lymph nodes, bone marrow, and spleen. They play the role of "microbial depot," from where the infection is re-generalized: the patient after a long period of well-being, when he seems to have recovered, in supercooling, trauma, cold, stress, getting physiotherapeutic procedures, symptoms of the disease again appear. Centers of infection can be a source of another endogenous reinfection even after a significant period of time (months and years). Chronic inflammation can follow an acute, and sometimes the inflammatory process from the very beginning has the features of a chronic one. When acute clinical manifestations of brucellosis die away, focal manifestations come to the forefront (damage to individual organs - for example arthritis, spondylitis), followed by degenerative-dystrophic changes (after arthritis - arthrosis, osteochondrosis).

Clinical manifestations are the basis for the diagnosis of brucellosis. After an initial physical examination, we use serological tests [Wright test and 2-mercaptoethanol (2-ME)], cultivation and imaging methods to verify the diagnosis. To definitely diagnose brucellosis, the organism needs to be isolated from blood, bone marrow, wounds, purulent discharge or other body tissues and fluids, with culture or molecular/histological assessment [18]. The major pathological feature of Brucella spondylitis is nodular lesions consisting of epithelioid cells, which can be seen in the nidus under a light microscope. Affected areas may show histiocytosis, proliferative nodules, and granuloma, as well as large numbers of neutrophils, lymphocytes, monocytes, and eosinophils. The typical mechanism of brucellosis infection is direct contact with the skin or mucosa, although infection can also occur via inhalation of airborne droplets into the respiratory tract. Brucellosis can also invade the spine; this occurs in 2–53% of cases [17,19,20]. An important aspect in the pathogenesis of Brucella, apart from its virulence factors and the environmental factors contributing to infection, is host genetic background, which is crucial in determining the susceptibility or resistance to brucellosis [21]. Cell-mediated and humoral immune responses, in which several cytokines are involved, play pivotal roles in protection against

brucellosis [10]. Production and release of cytokines rely mostly on human genetic factors, so variations in the regulatory sequences of the cytokine genes can greatly affect the cytokine balance. A growing number of studies report higher prevalence of single nucleotide polymorphisms (SNPs) in the cytokine-encoding genes of patients with brucellosis. These SNPs are possibly the agents responsible for susceptibility to brucellosis and can be important in the clinical course and prognosis of the disease [22-25]. However, the extent to which these genetic variations can influence the development, progression, and outcome of brucellosis is yet to be known [10]. These nucleotide polymorphisms in the genes encoding the cytokines of patients with brucellosis are not excluded; they cause a systemic clinical manifestation [26].

The most common clinical presentations of human brucellosis are fever, sweating, musculoskeletal pains, lymphadenopathy or hepatosplenomegaly. The musculoskeletal system is particularly involved. Presentations of brucellosis are variable, deceptive and often non-specific, and they can mimic other infectious and non-infectious diseases [5].

Osteoarticular disease is the most common complication of brucellosis and has been described in 10%–85% of patients [3, 4]. Osteoarticular involvement rates of between 58.8% and 79.5% have been reported, [8, 27-29] but lower rates of between 9.3% and 22.8% have also been reported [30, 31-44]. In the T. Buzgan et al. study (1028 cases, Turkey) osteoarticular involvement was observed in 21.8% of acute cases, 34.7% of subacute cases, 25.7% of chronic cases, and in 27.3% of relapsed cases, with an overall rate of 25.3%. The enormous range between reports in the literature may be due to characteristics of the study populations, the radio-diagnostic methods used, and the different diagnostic criteria employed [5]. According to research Gu¨ r et al. (283 cases, Turkey) osteoarticular complications were the most frequent, found in 195 (69%) cases, followed by cutaneous (17%), genitourinary (8%), nervous (7%), respiratory (5%) and hematological (4%) complications. Cutaneous, hematological and respiratory complications in childhood; osteoarticular and cardiac complications in adults; and genitourinary, neurological and gastrointestinal complications in middle aged were more prominent [8] (Table 1).

Table 1 – The incidence of osteoarticular manifestation in patients with a diagnosis of chronic brucellosis according to different authors

The authors	Osteoarticularmanifestations	Sacroiliitis	Spondylitis	Spondylarthrosis	Spondylodiscitis	Spondylosis	Osteochondrosis	Arthritis	Arthralgia
Esmaeilnejad-Ganji SM et al. (Iran, 2019)[19]	10-85%	80%	54%		6-85%			14-26%	
Kasatkina I. L. et al. (Kazakhstan, 1976) [83]	45-92%	-	10,2%	12,2%	5,8%	8,6%	37,6%	15,1%	42,2-86%
Solera et al. (35 Cases, Spain) [29]	10-85%	-	100%	-	-	-	-	-	54%
V.kh. Fazylov et al.(26 patients, Tatarstan [30]	65,4%	65,4%		80,8%				34,6%	
Tu L. et al. (72 Cases China) [28]	-	-	2-53%	-	-	-	-	-	-
Jiang et al. (850 Cases China)[46]	69,8	-	13,1%	-	2,2%	-	-	26%	65%
K.B.Kurmanova et al. (45 Cases, Kazakhstan) [16]	100%	-	3%	-	0,5%	-	-	-	100%
G.M. Kurmanova et all (186 Cases, Kazakhstan) [60]	79,4%	46,7%	6,5%			-	-	-	30,8%

According to the prof. Amireeva S.A. (2500 Cases, Kazakhstan, 1991-1994) 46.8% of patients have persistent involvement of large joints The preferential damage of the bone-joint system in brucellosis was the most frequent cause of the erroneous rheumatological diagnosis [9]. At the same time, there was no incomplete targeted collection of epidemiological history and analysis of clinical manifestation, as well as late use of laboratory methods of research in each suspected case of brucellosis.

Spinal brucellosis. The spine is one of the most common organs involved in brucellosis infection with a rate varying from 2%-54%, and the lumbar vertebrae are the most frequently affected [35,36]. It mainly manifests as spondylitis, spondylodiscitis and/or discitis. Back pain is the most common compliant in spinal brucellosis and reported by about half of the patients [37, 38]. In patients with acute brucellosis, the morphology of the infected vertebrae is normal. The endplates, which have a rich blood supply, are the first vertebral bodies to be affected. Inflammation eventually spreads to the entire vertebral body, accompanied by early vertebral infections wherein inflammatory congestion and edema are the principal pathological changes, in addition to increased amounts of water in the vertebral bodies.

However, (at first) no obvious spinal deformities or bone destruction attributable to changes in the vertebral morphology are evident. When the disease enters its subacute and chronic stages, immune cells interact with the infected foci and bone destruction occurs. Infected vertebral bodies undergo complex changes, including hyperosteogenesis and sclerosis. Thus, the signal intensities of vertebral bodies are uneven, even when osteoporosis in diseased vertebrae and obvious changes in vertebral body morphology are absent [26]. The clinical and imaging manifestations are very similar to those of spinal tuberculosis, including narrowing of vertebral gaps, destruction of vertebral bodies, formation of bony bridges, and widening of the shadow of the vertebral column [29,31]. Cases with delayed or aggravated illness caused by early clinical misdiagnosis are frequent [32]. One of the targeted studies regarding Brucellosis spondylitis is described in the article by Solera et al., In which there are reliable data on the polymorphism of clinical manifestations. Thirty-five patients aged 14–74 years (average, 54 years) who had brucellar spondylitis were treated between January 1991 and December 1997. The time from onset of symptoms to diagnosis of spondylitis ranged from 1 week to 8 months (median, 9 weeks). Back or neck pain (100% of patients), fever (66%), and constitutional symptoms (57%) were the most common symptoms. Cultures of blood specimens from 26 patients (74%) were positive for Brucella melitensis. The duration of antimicrobial therapy (median, 120 days; range, 45–535 days) varied according to clinical response and the presence of epidural and paravertebral masses. One of the 35 patients underwent surgical treatment of a spinal epidural abscess. Therapy failed for 9 patients, and 5 had a relapse. There were no deaths or severe sequelae in this study. Brucellar spondylitis causes considerable suffering and absenteeism from work, but long-term clinical responses are favorable [39].

Spondylitis. Spondylitis or vertebral osteomyelitis is inflammation and infection of vertebrae which has a prevalence rate of 2%-60% and mostly observed in men aged > 40 years Old [15, 18]. According to study Jiang et al, arthralgia was detected in 69.8% of patients and spondylitis was found in 111 of 850 patients. According to this study, lumbar spine involvement was observed in 105 patients, the cervical spine was affected in 9 patients, and the thoracic spine was involved in 6 patients [33]. Lumbar (60%), sacral (19%) and cervical (12%) vertebrae were the most common affected sites, respecttively, in a survey by Bozgeyik et al (152 cases, Turkey), [34]. There are two types of spinal brucellosis, focal and diffuse. In focal involvement, osteomyelitis is localized in the anterior aspect of an endplate at the discovertebral junction, but in the diffuse type, osteomyelitis affects the entire vertebral endplate or the whole vertebral body [34, 40]. Spondylitis is the dangerous complication of brucellosis, due to its association with epidural, paravertebral and psoas abscess and potential (in causing nerve compression.)In one report, rapidly progressive spinal epidural abscess was observed following brucellar spondylitis, which was primarily misdiagnosed as a lumbar disc herniation [49]; delay in diagnosis and treatment were responsible for rapid progression of the disease.

Spondylodiscitis. Spondylodiscitis is an inflammatory disease of vertebral structures involving intervertebral discs and adjacent vertebral bodies and joints. It is the most severe form of osteoarticular involvement of brucellosis, and can have single or multi-focal involvement. The main complaint is back pain that is known to be the most prevalent complaint in the general population. Diagnosis of spondylodiscitis is difficult and is often characterrized by delay from the debut of symptoms. Granulomatous spondylodiscitis may be caused mycobacterium tuberculosis, be a complication

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Sacroiliitis. Large joints, like sacroiliac, are the most common regions of musculoskeletal involvement of brucellosis. Sacroiliitis, inflammation of sacroiliac joint, has been observed in nearly 80% of patients with focal complications and more frequently in adults [46]. It is reported that the rate of sacroiliitis is high in those patients who are infected with B. melitensis spp. [47,48].

Sacroiloiits with brucellosis is(unilateral or bilateral)and is manifested by severe pain in the sacral region, aggravated by movement, especially when walking and when the body is tilted forward; in severe cases, patients lie motionless on their backs, afraid to move, so as not to cause increased pain [11]. Sacroiliitis was also simultaneously seen with dactylitis, olecranon bursitis, humerus osteomyelitis and iliac muscle abscess, and with other systemic diseases, like endocarditis, pyelonephritis and thyroiditis. A study showed that high-resolution MRI has a higher sensitivity than scintigraphy in the diagnosis of brucellar sacroiliitis [18].

Peripheral joints. Brucellosis with peripheral skeleton involvement is less prevalent compared with vertebral features. It can manifest as arthralgia, enthesopathy, osteomyelitis, arthritis, bursitis, tendonitis and tenosynovitis [18]. Arthritis occurs in 14%-26% of the patients suffering from acute, subacute or chronic brucellosis [49-50]. Articular Syndrome is significantly more often observed in secondary-chronic brucellosis 79.4%) as compared with primary chronic brucellosis 47 (59.6%, P <0.01) in the form of arthritis, arthrosis arthritis, bursitis, tenosynovitis, periostitis, perichondritis with characteristic symptoms. Knee, hip and ankle joints are among the most common peripheral regions affected by brucellosis and these patients present with arthritis. Shoulders, wrists, elbows, interphalangeal and sternoclavicular joints may also be involved [18]. Multiple joint arthritis caused by brucellosis was reported in 17% of patients in a study. In 44.3% with primary chronic brucellosis and in 41.2% with secondary chronic brucellosis small joints of the hands and feet were affected [51].

According to T. Buzgan et al. (1028 cases, Turkey), study, the most common symptoms of brucellosis were arthralgia (73.7%), fever (72.2%) and fatigue (71.2%) and peripheral arthritis (14.3%), when in children arthralgia was detected in 85.9% of patients, and peripheral arthritis was found in 21.8% of children. Peripheral arthritis occurred more frequently than in the adult group (21.4% vs. 14.3%), while sacroiliitis was less frequent (2.6% vs. 6.2%) and spondylitis was not seen [52]. Brucellosis can involve the peripheral joints through septic (with presence of pathogen) and reactive (lack of the pathogen) mechanisms [53, 54]. Septic arthritis caused by brucellosis has been reported in the literature and it has been recommended that patients with septic arthritis living in the endemic areas, be examined in terms of brucellosis [55, 56]. Septic arthritis in brucellosis progresses slowly and starts with small pericapsular erosions. Blood culture is positive in 20%–70% of such patients. Although synovial fluid assessment is the most useful diagnostic method, the isolation of the pathogen from synovial fluid is not easy [57]. Knee arthritis has obvious symptoms and is less difficult to diagnose and treat due to easy access. However, the diagnosis and treatment of hip arthritis is more difficult and delay in diagnosis and treatment may lead to serious and (irreversible) complications, such as dislocation and necrosis of the femoral head [58,59]. Brucellosis should be considered in the differential diagnosis for a patient presenting with knee or hip arthritis symptoms in endemic regions to prevent misdiagnosis and serious complications. Due to the synovial involvement of the

disease, pathological evidence may not be found on radiograph in the early phase of infection.

Other Articular manifestations and complications. One of the clinical manifestations of infection is the development of osteoarthritis. In the study of G.M. Kurmanova et al. ((186 Cases, Kazakhstan), changes in the joints radiography were revealed, indicating that in patients with primary chronic brucellosis (21.5 ± 4.6%), with secondary chronic brucellosis (46.7 ± 4, 8), a progressive process was detected up to deforming osteoarthritis with osteophytosis of the knee joints (21.5 ± 4.6%). %); hip deforming arthritis was found in patients with primary chronic brucellosis (20.3 ± 4.5%), with secondary chronic brucellosis (41.1 ± 4.8%); In patients with primary chronic brucellosis (19.0 ± 4.4%) and secondary chronic brucellosis (30.8 ± 4.5%), humroacular periarthritis was confirmed[60]. In a study by Ebrahimpour et al.[59], brucellosis was attributed to sternoclavicular (4.5%), wrist (2.4%), elbow (1.07%) and shoulder (0.6%) arthritis Table 2.

Table 2 – The frequency of manifestations of articular syndrome

The joints/the authors	G.M. Kurmanova et all [60]	V.kh. Fazylov et al. [30]
Humeral	18.7%	27%
Elbow	13.1%	
Wrist band	15%	30.8%
Small joints of the hands	17.8%	
Hip	13.1%	34.6%
Knee	45.8%	46.1%
Ankle	15.9%	
Small joints of the feet	23.4	11.5%

Delay in the diagnosis of brucellosis result in prolong disease duration which can lead to osteomyelitis or osteolytic lesions. Brucellar osteomyelitis has been observed in closed femur fracture and a pathologic fracture of humeru [60,61]. It was also seen in association with extra-articular prosthetic hardware[62]. It was reported the first case of brucellar osteomyelitis of pubic symphysis, who was symptom free within two-year follow-up despite inappropriate initial antibiotherapy [63].

Diagnosis of brucellosis.

The main issue in the fight against brucellosis remains the timely and complete identification of farm animals suffering from brucellosis. However, existing generally accepted laboratory methods do not always allow to determine the real epidemic and epizootic picture in our country.

Currently, the most common methods for detection of Brucella include culture techniques, serological tests and PCR-based assays. Real-time PCR seems to be highly reproducible, rapid, sensitive and specific. Additionally, this assay is easily standardized and minimises the risk of infection in laboratory workers. It is therefore a useful method for both the initial diagnosis of human brucellosis and the differentiation among inactive, seropositive, and active states. Queipo-Ortuño et al. reported that the sensitivities of a SYBR Green I LightCycler-based real-time PCR assay with serum samples was 93.3%, which is higher than 90% and 65% obtained by PCR-ELISA with whole blood samples and blood cultures, respectively . This group further developed a Light Cycler-based real-time PCR assay to detect Brucella DNA in serum samples. This assay was found to be 91.9% sensitive and 95.4% specific when tested with 65 negative control samples and 62 serum samples from patients with active brucellosis. Isolation of Brucella spp. is considered the gold standard technology, but it is lengthy, and requires high-level biosafety laboratories and certificated personnel [64,65].

Serological testing is widely used in the clinical diagnosis of Brucellosis, but serological tests can yield false negatives when detecting the early course of Brucellosis, and it can only indirectly diagnose Brucellosis based on a high antibody titre [66]. According to research, when "brucellosis" was diagnosed, the results of serological studies were unreliable. The result of SAT (Wright 's reaction) was negative in patients with diagnosis "Primary-chronic brucellosis" in 41.5% cases and "Secondary-chronic brucellosis" in 32.7% cases. Regarding the results of the Roz Bengal antigen test, which has great sensitivity, the ability to detect specific brucellosis antibodies at short notice after infection, more than half of patients (51.3%) with primary-chronic brucellosis and slightly less than one third of patients (28.6%) with secondary-chronic brucellosis were negative. ELISA for brucellosis were positive only in 40-50% of patients. Blood culture isolation in about 2.4-4% of patients, which once again proves the instability of laboratory diagnostics [67].

PCR-based assays are highly sensitive, specific, and rapid, and have been applied for the detection

of Brucellosis in humans and other animals, and identification of Brucella in animal products and the environment [68,69] However, PCR-based assays require expensive thermal cycling instruments and can take more than 1 h, which limit their application in point-of-care detection of Brucella, especially in undeveloped rural areas.

Recombinase polymerase amplification (RPA) offers a new approach to achieve rapid and point-of-care detection of Brucella [70]. A total of 52 Brucella field strains were detected by real-time PCR and RPA in parallel, and compared with real-time PCR, the sensitivity of the RPA assay was 94%. Thus, this RPA assay may be a rapid, sensitive, and specific tool for the prevention and control of Brucellosis [71].

Despite the availability of advanced laboratory research methods in the world sometimes these methods may not be reliable or some developing countries like Kazakhstan these new high-sensitivity types of polymerase valuable reaction may be absent. In that case a radionuclide scan can be a useful tool to verify the diagnosis.MRI may be the best method to diagnosis and localize the cause of spondylodiscitis, epidural abscess, or compression on the spine and spinal nerves related to brucellosis. Epidural abscess is a rare complication of spinal brucellosis but can lead to severe outcomes, such as permanent neurological deficits, or even death if not treated timely [18]. Imaging issues in the diagnosis of brucellosis spondylitis is fundamental and there are several scientists who have investigated this aspect to improve our understanding of the disease and minimize the erroneous diagnosis. They used data from x-ray, CT, and MRI 72 brucella patients with spondylitis who received treatment from 2010 to 2017 were subjected to a retrospective analysis; diagnoses were made by evaluating laboratory and pathological data. The results of this study showed the following features: X-ray films revealed changes in intervertebral space heights, the number of lateral osteophytes, and bone destruction, which were more severe in the following order: lumbosacral vertebrae (56 cases, 77.8%), cervical spine (6 cases, 8.3%), thoracic spine (5 cases, 6.9%), and multisegmental mixed vertebrae (5 cases, 6.9%). CT revealed osteolytic destruction attributable to early-stage Brucella spondylitis (endplate and vertebral lamellar osteolysis), usually associated with multiple vertebral involvement, with the middle and late disease stages being characterized by osteophytes in the vertebral margins and bony bridges, endplate sclerosis, and vertebral osteosynthesis. Tu L. et al. encountered 54 cases (75%) with endplate lamellar osteolysis, 37 (51.4%) with vertebral lamellar osteolysis, 59 (81.9%) with marginal osteophytes, 10 (13.9%) with bony bridges, 25 (34.7%) with vertebral laminar sclerosis, and 17 (23.6%) with vertebral osteosynthesis. MRI revealed early, low-intensity, differential T1WI vertebral and intervertebral signals, with occasional iso-signals, T2WI iso-signals or high-intensity signals; and T2WI-FS vertebral and intervertebral high-intensity signals, commonly from vertebral soft tissues and rarely from paravertebral abscesses [26]. As MRI can detect early abnormal signals from vertebral bodies, intervertebral discs, and soft tissue, this is the first-choice imaging when evaluating patients with spinal brucellosis, and enhanced MRI scans improve diagnostic accuracy. The imaging features of spinal brucellosis need to be distinguished from those of spinal tuberculosis. The incidence of spinal tuberculosis can attain 40–50%, being the most common manifestation of pulmonary tuberculosis, often triggering vertebral body destructtion and other serious complications. The clinical and imaging manifestations are very similar to those of brucellosis spondylitis, making misdiagnosis easy. The typical manifestations of spinal tuberculosis are bone destruction, dead bone, narrow intervertebral spaces, paraspinal abscesses, and deformities of the spinal posterior process [26]. Radionuclide bone scintigraphy is an important technique in determination of musculoskeletal region of brucellosis. Increased uptake of the involved region on bone scintigraphy is more in favor of brucellar spondylodiscitis than tuberculous spondylodiscitis [38,72]. MRI is the choice for diagnosis of spondylodiscitis, epidural abscess and cord or root compression relevant to brucellosis [17, 73, 74]. In MRI, the lesion is found as destructive appearance (Pedro Pons'sign) at antero-superior corner of vertebrae accompanied by prominent osteosclerosis, which is a pathognomonic finding [75,76]. Spinal spondylitic brucellosis often involves the endplates of the junctions between the vertebral bodies and the intervertebral discs. The shape of the vertebral body is not affected, the posterior process does not exhibit compression or deformity, no bony hyperplasia is evident at the edges of vertebral bodies, bone death is rare, the intervertebral spaces are not obviously narrowed in those with early-stage disease, abscesses in the vertebrae and the psoas major muscle are rare, and abscess heterogeneity is limited. In general, only adjacent vertebrae are affected, the vertebral bodies suffer only minor destruction, and adjacent organs are not involved [62].

Differential diagnosis requires the evaluation of biopsy samples. Furthermore, brucellosis titer test positivity and anti-brucellosis positivity are useful diagnostic criteria [77].

Diagnostic difficulties. Sacroiloiits with brucellosis is(unilateral or bilateral)and is manifested by severe pain in the sacral region, aggravated by movement, especially when walking and when the body is tilted forward; in severe cases, patients lie motionless on their backs, afraid to move, so as not to cause increased pain. In patients with≥ 3months back and age at onset ≤45 years should differentiate it from Brucellor back pain. AS and SpA is inflammatory type which is worse in morning, prolong period of inactivity and decreases with physical activity and exercise. In such cases, clinicians, especially orthopaedic surgeons, must understand the disease, especially imaging features, to ensure accurate diagnosis through a combination of epidemiological history, clinical manifestations, and laboratory data. The polymorphism of the clinical manifestation and the variety of osteoarticular manifestations greatly complicates the timely diagnosis and treatment of brucellosis. It is known that brucellosis is prone to a chronic recurrent course with frequent disability, which determines the social significance of the infection. The low diagnostic value of serological tests, which are used by many clinicians as screening methods for detecting brucellosis, complicates early diagnosis more and more. The low alertness of brucellosis infection, not only among therapists and other specialties, but also among infectious disease doctors, is a big problem due to the lack of awareness of doctors about all the clinical manifestations of this infection against the background of incomplete laboratory diagnosis, which leads to an erroneous diagnosis.

A characteristic feature of brucellous infection is the prolonged wave-like course of the disease with repeated relapse and remission. It should be remembered that in chronic brucellosis there is suppression of antibody formation and the value of serological methods decreases and this increasingly devalues serological methods of study. In Kazakhstan, despite changes in the population of patients with brucellosis over the last 10 years due to the increase in the share of urban residents among patients, A large number of patients still live in rural areas where it is not possible to fully examine, including the use of the method of detecting antigen-binding lymphocytes of brucellosis specificity and polymerase chain reaction, Especially the bacteriological examination with waiting for the results of the tests up to 40 days. The organization requires modern laboratories equipped with expensive analyzers, but the rural hospital cannot afford such costs. It is necessary to note the fact that there are no infectious doctors in rural hospitals who can correctly interpret the results of laboratory studies and given the epidimological history, knowing the full range of clinical manifesttations will be able to verify the diagnosis in a timely manner. All these factors are the main problems of early correct diagnosis of brucellosis, which can eventually lead to partial or complete loss of working capacity of the patient.

Conclusion

Thus, brucellosis occupies a special position among other infectious diseases due to the peculiarity of the pathogen: high contagiousness or infectious ability of brucella; their resistance to non-specific factors of body protection; the ability to survive (and for years) even multiply within immunocompetent cells (macrophages); negligible protective role of anti-brucellosis antibodies, more precisely the formation of only relative immunity and the presence of re-infection in an endemic zone. Brucellosis is an important health problem in Kazakhstan. The disease has a significant morbidity and mortality. Additionally, since the disease primarily affects persons in their productive age, it causes important workpower losses. Eradication of the disease in humans can only be achieved by the control of the disease in animals; this necessitates a multidisciplinary approach involving both humans and animals. In addition to isolation and serological tests, non-specific tests such as CRP and ESR should also be used in treatment follow-up. In summary, brucellosis is easily misdiagnosed, although it is important to achieve an early diagnosis to prevent further complications. Blood cultures and Brucella spondylitis serology tests are required when patients with spinal lesions do not respond to standard treatment. The features of Brucella spondylitis in X-ray, CT, and MR images must also be better understood to minimize misdiagnosis and to use in combination with epidemiological and laboratory data. A high level of chronic infection and polymorphism of osteoarticular manifestations of brucellosis complicates differential diagnosis with inflammatory diseases of the joints and spine, which negatively affects the process of timely diagnosis and treatment, which ultimately affects the effectiveness of treatment and the further quality of life of patients.

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