

Original Article

A 10-year retrospective comparative analysis of the clinical features of brucellosis in children and adultsLiyuan Ma¹, Jinhai Ma², Xiaoyuan Chen², Linghua Dong²¹ Department of Pediatrics, Southern University of Science and Technology Hospital, Shenzhen, Guangdong, China² Department of Pediatrics, General Hospital of Ningxia Medical University, Yinchuan, Ningxia, China**Abstract**

Introduction: Brucellosis is a zoonosis with a wide spectrum of clinical manifestations. However, it is still unclear whether the clinical manifestations in children are significantly different from those in adults.

Methodology: Patients with brucellosis and treated at the General Hospital of Ningxia Medical University between 2009 and 2019 were divided into two groups; children (88) and adults (354). Thereafter, the records of the two groups were analyzed retrospectively.

Results: The findings showed that: 1. School-age children, young and middle-aged individuals were more likely to suffer from brucellosis and most were male; 2. Fever and arthralgia were the most common manifestations in the two groups. In addition, fatigue and low back pain were rare in children although fever and lymphadenopathy were more common in this group. However, hepatomegaly and splenomegaly were common in both groups; 3. The most common complication was osteoarthritis and peripheral arthritis occurred more frequently in children. On the other hand, spondylitis was the most common in adults (this particularly involved the lumbar and sacral vertebrae); 4. An increase in the erythrocyte sedimentation rate, levels of the C-reactive protein and liver enzymes was common in both two groups; 5. There was no significant difference in the positive rate of the standard agglutination test between children (96.59%) and adults (95.20%). However, the positive rate of blood culture was higher in children (65.85%) than in adults (51.00%).

Conclusions: Brucellosis causes damage to multiple systems and differences in clinical characteristics were found between children and adults.

Key words: Brucellosis; characteristics; complications; osteoarticular; laboratory findings; children and adults.

J Infect Dev Ctries 2021; 15(8):1147-1154. doi:10.3855/jidc.13962

(Received 20 September 2020 – Accepted 15 February 2021)

Copyright © 2021 Ma *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Brucellosis is a zoonotic disease caused by *Brucella* spp. Over the recent years, the incidence of human brucellosis has increased rapidly across the globe although the incidence of the disease in northern China has relatively decreased while that in southern China has increased to some extent [1]. Notably, sheep and cattle infected with *Brucella* spp. are the main sources of infection although pigs, dogs, deer and horses may transmit the disease. However, transmission of brucellosis from person to person is rare. In addition, the clinical manifestations of brucellosis are complex, non-specific and can infect any organ system, which may lead to misdiagnosis and delayed treatment. Moreover, the disease can cause severe human disability although it has a low mortality rate. Brucellosis is also associated with various complications and osteoarthritis is among the most common. Notably, osteoarthritis can lead to joint pain and even paralysis hence affecting movement. Over the recent years, research has focused on the clinical characteristics of brucellosis. However, different

studies reported contradicting results and there is currently no comparison of the clinical features of brucellosis between children and adults. Additionally, public awareness and knowledge of brucellosis is relatively low.

Therefore, the present study collected information on a large number of brucellosis cases in children and adults within a period of 10 years (2009-2019) with an aim of clarifying the differences in the clinical manifestations of the disease between children and adults.

Methodology*Study population*

The study collected the medical records of patients (88 children and 354 adults) who were first diagnosed with brucellosis at the General Hospital of Ningxia Medical University between 2009 and 2019. Two groups were used in the study. i.e. children and adults. The group with children consisted of individuals aged 0-14 years while the adult category consisted of patients older than 15 years. In addition, the study excluded

patients with other bacterial, fungal or viral infections, tuberculosis, typhoid and paratyphoid fever, rheumatic immune diseases, tumors, necrotizing lymphadenitis, hyperthyroidism and other diseases. Patients with incomplete examination items in the medical records and errors in laboratory data were also excluded. The following parameters were mainly studied; epidemiological history (including gender, age, season and contact history), clinical manifestations, complications, laboratory examination records at admission (including routine blood tests, routine biochemical tests, Erythrocyte Sedimentation Rate - ESR-, C-reactive Protein -CRP-, blood culture, the Rose Bengal Plate Test -RBPT- and the Standard Agglutination Test -SAT-). Thereafter, the clinical characteristics in children and adults were analyzed retrospectively. Notably, the basis of diagnosis of brucellosis included epidemiological history, clinical manifestations, positive RBPT, a positive titer of SAT (1:100 or higher) or *Brucella* spp. isolated from blood

culture. Moreover, the definition of abnormalities in laboratory test results was based on established reference values for children and adults. Furthermore, Magnetic Resonance Imaging (MRI) was performed on the patients with back pain and positive serological tests for brucellosis. MRI was performed using a 1.5-T MRI scanner (General Electric Signa Excite High-speed Scanner, Milwaukee, USA) using appropriate coils. In addition, if any joint showed signs of inflammation with radiographic abnormalities, joint involvement was considered. Moreover, pain in the scrotum, testis and epididymis as well as a positive ultrasound examination were used to diagnose testitis and epididymitis. On the other hand, diagnosis of meningitis included a positive cerebrospinal fluid culture for *Brucella* abnormal cerebrospinal fluid upon examination and/or neurological symptoms. Additionally, diagnosis of endocarditis was based on revised diagnostic criteria for infective endocarditis.

Table 1. Demographic and exposure history of children and adults with brucellosis.

| Characteristics | N=442 | |
|---|-------------------------|-----------------------|
| | n | % |
| Age groups (years) | | |
| ≤ 1 | 15 | 3.39 |
| 2-3 | 21 | 4.75 |
| 4-7 | 14 | 3.17 |
| 8-14 | 38 | 8.60 |
| 15-25 | 43 | 9.73 |
| 26-35 | 38 | 8.60 |
| 36-45 | 77 | 17.42 |
| 46-55 | 109 | 24.66 |
| 56-65 | 68 | 15.38 |
| ≥66 | 19 | 4.30 |
| Demographic | Children (N=88) | Adults (N=354) |
| Age, years [mean ± sd (range)] | 6.37 ± 4.52 (0.57-14) | 45.51 ± 14.13 (15-79) |
| Gender | | |
| Male | 61 (69.32)* | 268 (75.71) |
| Female | 27 (30.68) | 86 (24.29) |
| Seasonal Distribution | | |
| Spring | 34 (38.64) | 128 (36.16) |
| Summer | 39 (44.32) | 100 (28.25) |
| Autumn | 7 (7.95) | 51 (14.41) |
| Winter | 8 (9.09) | 75 (21.19) |
| Exposure history | Children (N=65) | Adults (N=317) |
| Contact with cattle and sheep | 54 (83.08) | 261 (82.33) |
| Contact with a family member with Brucellosis | 6 (9.23) | 9 (2.84) |
| Processing beef and mutton | 0 | 11 (3.47) |
| Contact with dead livestock | 0 | 6 (1.89) |
| Eating raw beef and mutton | 1 (1.54) | 4 (1.26) |
| Drinking unsterilized milk | 1 (1.54) | 2 (0.63) |
| Rearing pigs | 0 | 3 (0.95) |
| Rearing foxes | 0 | 1 (0.27) |
| Contact with the faeces of cattle and sheep | 0 | 1 (0.27) |
| Denial of exposure history | 3 (4.62) | 19 (5.12) |

Children group: aged 0-14 years; Adults group: >15 years of age.

Statistical analysis

Data processing and statistical analysis was conducted using the SPSS 22.0 statistical analysis package. In addition, measurement data was expressed as mean \pm standard deviation ($s \pm x$) while counting data was expressed as percentages (%). The t-test was also used to assess the significance of differences between the means. On the other hand, percentages of cases were compared using the Chi-square test. $p < 0.05$ was considered to be statistically significant.

Results

The results revealed that brucellosis was more common in school-age children, young and middle-aged individuals. The average age of children was 6.37 ± 4.52 (0.57-14) while that of adults was 45.51 ± 14.13

(15-79). In addition, 69.32% of the children were male and the ratio of males to females was 2.26:1. On the other hand, 75.71% of the adults were male and the ratio of males to females was 3.12:1. The results therefore suggested that the disease mainly affected the males. Moreover, the presence or absence of a history of exposure was recorded in 65 children and 317 adults. Additionally, most of the individuals in both groups came into contact with sheep and cattle. Individuals were be infected from such factors as eating raw meat, drinking unsterilized milk and coming into contact with dead livestock (Table 1).

Among the pediatric patients, 82.95% had fever, and the average temperature was 39.18 ± 0.67 °C On the other hand, 61.58% of the adults had fever and the average temperature was 39.26 ± 0.69 °C The results

Table 2. Clinical manifestations and complications in children and adults with brucellosis.

| Characteristics | Children (N=88) | Adults (N=354) | p-value |
|--|-----------------|----------------|---------|
| Clinical manifestation | | | |
| Fever | 73 (82.95) | 218 (61.58) | < 0.001 |
| 37.3 °C-38 °C | 8 (10.96%) | 19 (8.72%) | NS |
| 38.1 °C-39 °C | 22 (30.14%) | 82 (37.61%) | NS |
| 39.1 °C-41 °C | 43 (58.90%) | 117(53.67%) | NS |
| Fatigue | 11 (12.50) | 160 (45.20) | < 0.001 |
| Hyperhidrosis | 34 (38.64) | 122 (34.46) | NS |
| Anorexia | 20 (22.73) | 123 (34.75) | NS |
| Low back pain | 19 (21.59) | 174 (49.15) | < 0.001 |
| Single joint pain | 35 (39.77) | 49 (13.84) | < 0.001 |
| Multiple joint pain | 15 (17.05) | 83 (23.4) | NS |
| Abdominal pain | 3 (3.41) | 9 (2.54) | NS |
| Nausea | 3 (3.41) | 40 (11.3) | 0.025 |
| Vomiting | 3 (3.41) | 17 (4.80) | NS |
| Rash | 5 (5.68) | 6 (1.69) | NS |
| Cough | 22 (25.00) | 61 (17.23) | NS |
| Headache | 10 (11.36) | 60 (16.95) | NS |
| Dizziness | 3 (3.41) | 50 (14.12) | 0.003 |
| Muscle pain | 5 (5.68) | 33 (9.32) | NS |
| Hepatomegaly | 19 (21.59) | 53 (14.97) | NS |
| Splenomegaly | 32 (36.36) | 99 (27.97) | NS |
| Lymphadenopathy | 29 (32.95) | 16 (4.52) | < 0.001 |
| Complications | | | |
| Spondylitis | 0 | 131 (37.01) | < 0.001 |
| Intraspinal, paraspinal or psoas abscess | 0 | 46 (12.99) | < 0.001 |
| Arthritis other than spondylitis | 50 (56.82) | 105 (29.66) | < 0.001 |
| Synovitis | 12 (13.64) | 8 (9.09) | < 0.001 |
| Joint effusion | 11 (12.50) | 7 (1.98) | < 0.001 |
| Orchitis | 2 (2.27) | 22 (6.21) | NS |
| Epididymitis | 0 | 12 (3.39) | NS |
| Endocarditis | 0 | 1 (0.28) | NS |
| Pericarditis | 1 (1.14) | 3 (0.85) | NS |
| Pneumonia | 12 (13.64) | 34 (9.60) | NS |
| Pleural effusion | 3 (3.41) | 18 (5.08) | NS |
| Meningitis | 7 (7.95) | 12 (3.39) | NS |
| Nervous disorder | 0 | 2 (0.56) | NS |
| Hemophagocytic syndrome | 5 (5.68) | 2 (0.56) | 0.003 |
| Optic papillitis | 0 | 1 (0.28) | NS |
| Coagulation disorders | 1 (1.14) | 0 | NS |

NS means $p > 0.05$, no statistical difference.

Table 3. Laboratory results, positive rate of the SAT test and blood culture in children and adults with brucellosis.

| Laboratory abnormalities | Children (N=88) | Adults (N=354) | p-value |
|-----------------------------------|------------------|-----------------|---------|
| WBC > 9,500 cells/mm ³ | 6 (6.82) | 34 (9.60) | NS |
| WBC < 3,500 cells/mm ³ | 17 (19.32) | 27 (7.63) | 0.001 |
| NEUT > 70% | 2 (2.27) | 36 (10.17) | 0.018 |
| LYM > 40% | 72 (81.82) | 92 (25.99) | < 0.001 |
| MXD > 10% | 14 (15.91) | 120 (33.90) | < 0.001 |
| EOS < 0.4% | 54 (61.36) | 154 (43.50) | 0.003 |
| PLT < 125 g/L | 11 (12.50) | 36 (10.17) | NS |
| PLT > 350 g/L | 16 (18.18) | 30 (8.47) | 0.008 |
| AST > 36 U/L | 65 (73.86) | 135 (38.14) | < 0.001 |
| ALT > 52 U/L | 43 (48.86) | 100 (28.25) | < 0.001 |
| UREA > 6.1 mmol/L | 4 (4.55) | 83 (23.45) | < 0.001 |
| CREA > 92 mmol/L | 0 (0.00) | 20 (5.65) | 0.019 |
| K ⁺ < 3.5 mmol/L | 5 (5.68) | 26 (7.34) | NS |
| Na ⁺ > 135 mmol/L | 7 (7.95) | 50 (14.12) | NS |
| ALB < 30 g/L | 4 (4.55) | 57 (16.10) | 0.005 |
| ESR > 15 mm/h | 66 (75.00) | 277 (78.25) | NS |
| CRP > 10 mg/dL | 47 (53.41) | 275 (77.68) | < 0.001 |
| Anemia | 42 (47.73) | 67 (18.93) | < 0.001 |
| Positive SAT test | 85 (96.59) | 337 (95.20) | NS |
| Positive blood culture | 54/82 (65.85) | 127/249 (51.00) | 0.019 |

WBC: White Blood Cell count; NEUT: Neutrophil; LYM: Lymphocyte; MXD: Monocyte; EOS: Eosinophils; PLT: Platelets; ALB: Albumin; AST: Aspartate Transaminase; ALT: Alanine Transaminase; CREA: Creatinine; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive Protein. NS means $p > 0.05$, no statistical difference.

therefore showed that a majority of the individuals mainly had moderate to high fever. In addition, fever was the most common symptom in both groups and other manifestations included joint pain, fatigue, anorexia and low back pain. Moreover, fatigue and low back pain were rare in children although fever and lymphadenopathy were more common in this group, compared to the adults and the difference was statistically significant. Additionally, osteoarticular brucellosis was the most common complication, affecting 56.82% of the children and 66.67% of the adults. Other complications included pneumonia, meningitis and epididymitis (Table 2).

Additionally, the White Blood Cell (WBC) count of most patients in both groups was within the normal range. Moreover, the increase in ESR, CRP as well as

liver enzymes and the decrease in eosinophils were common in the two groups. However, the increase of lymphocytes and liver enzymes as well as the decrease of eosinophils, anemia and thrombocytopenia were more common in children, compared to adults. However, hypoproteinemia, increase in monocytes, CRP, urea and creatinine were rare in children compared to adults and the difference was statistically significant. Furthermore, hypokalemia and hyponatremia were rare in both groups and the RBPT test was positive in all the patients. The positive rate of the SAT test was high in both children (96.59%) and adults (95.20%) although there was no significant difference between the two ($p > 0.05$). In addition, the titer range was 1:50-1:800 and blood culture was carried out in 82 children and 249 adults. The findings

Table 4. The bones and joints affected in children and adults with brucellosis.

| Osteoarticular | Children (N=50) | Adults (N=236) | p-value |
|---|-----------------|----------------|---------|
| Spondylitis | 0 | 131 (55.51) | < 0.001 |
| Joints involved except the spine | | | |
| Knee joint | 31 (62.00) | 39 (16.53) | < 0.001 |
| Hip joint | 21 (42.00) | 38 (16.10) | < 0.001 |
| Ankle joint | 9 (18.00) | 15(6.36) | 0.016 |
| Elbow joint | 3 (6.00) | 10 (4.24) | NS |
| Sacroiliac joint | 3 (6.00) | 13 (5.51) | NS |
| Wrist joints | 2 (4.00) | 8 (2.26) | NS |
| Shoulder joint | 1 (2.00) | 13 (3.39) | NS |
| Sternoclavicular joint | 0 | 2 (0.85) | NS |
| Small joints of hands and feet | 0 | 3 (1.27) | NS |
| Symphysis pubis | 0 | 1 (0.42) | NS |
| Calcaneus | 1 (2.00) | 1 (0.42) | NS |

NS means $p > 0.05$, no statistical difference.

showed that the positive rate of blood culture in children (65.85%) was higher than that in adults (51.00%) and the difference was statistically significant ($p = 0.019$) as shown in Table 3.

Moreover, osteoarthritis developed in 50 children and 236 adults. Notably, peripheral arthritis was most frequent in children, especially in the knee joint (62.00%) and hip joint (42.00%). On the other hand, spondylitis (55.51%) occurred more in adults and the lumbar and sacral vertebrae were the most frequently affected, especially the L3–L4 and L4–L5 levels. However, the thoracic and cervical vertebrae were the least affected. Other affected joints included the sacroiliac, ankle and wrist joint (Tables 4 and 5).

Discussion

The present study collected data from the medical records of 88 children and 354 adults with Brucellosis and their clinical characteristics were compared. The minimum age of patients in this study was 6 months while the maximum was 79 years, indicating that all the

age groups can be infected. The findings revealed that school-age children, young and middle-aged adults were more likely to suffer from brucellosis with a remarkable difference between the proportion of males (more) and females, consistent with the findings from other studies [2]. Additionally, the incidence rate was high in spring and summer but low in autumn and winter. Given that domestic animals are usually in the breeding season during this period and there is also an increase in human activity, the increased contact with infected animals as well as their secretions and excreta might be the reason behind the elevated number of infections in spring and summer. Furthermore, the results showed that more than 80.00% of patients had contact history with livestock such as cattle and sheep. Since many of the people raising cattle and sheep in China are men, it is highly likely that they would be more susceptible to brucellosis, as indicated by the results. In addition, most people in these areas mainly eat beef and mutton and use unpasteurized milk to make milk products. Additionally, some of the residents eat roast or instantly boiled mutton that has not been thoroughly cooked and also drink unpasteurized milk hence increasing the risk of infection. Contact with a family member with brucellosis may also be a high risk factor.

Moreover, differences in immunity, physiological structure and function between children and adults may have caused the variations in clinical manifestations. In this study, more than half of the patients had fever, which was the most common clinical symptom, consistent with other studies [3]. Notably, the fever lasted for at least 4 days and persisted for at most 1 year and this was easily confused with other febrile diseases of unknown origin. Other common symptoms included lower back pain, profuse sweating, fatigue and anorexia. Additionally, a few of the patients had headache, abdominal pain, cough as well as swelling and pain in the testis and epididymis. These results were similar to those obtained from previous studies [4,5]. Furthermore, the clinical symptoms were complex and varied with lower back pain being more common in adults than in children. This may have been related to the fact that adults are more likely to develop Brucellar spondylitis. In addition, it is difficult for children to describe their medical history, which may lead to challenges in collecting information on symptoms such as fatigue, anorexia and arthralgia. Therefore, abnormal crying in children and limited physical activity should be noted by clinicians and their families should be carefully interrogated.

Table 5. The Level of lesions in Brucellar spondylitis.

| Level of lesions | n (%) |
|------------------|------------|
| C3-C4 | 3 (2.29) |
| C4 | 1 (0.76) |
| C4-C6 | 1 (0.76) |
| C5-C6 | 4 (3.05) |
| C6-C7 | 2 (1.53) |
| C7-T2 | 1 (0.76) |
| T6-T7 | 1 (0.76) |
| T8-T9 | 1 (0.76) |
| T10 | 1 (0.76) |
| T11 | 1 (0.76) |
| T11-T12 | 2 (1.53) |
| T12 | 1 (0.76) |
| T9-L2 | 1 (0.76) |
| T12-L1 | 4 (3.05) |
| L1-L2 | 5 (3.82) |
| L2 | 1 (0.76) |
| L2-L3 | 11 (8.40) |
| L3-L4 | 31 (23.66) |
| L2-L4 | 4 (3.05) |
| L3-L5 | 4 (3.05) |
| L3-S1 | 1 (0.76) |
| L4 | 2 (1.53) |
| L4-L5 | 23 (17.56) |
| L4-S1 | 2 (1.53) |
| L5-S1 | 16 (12.21) |
| S1 | 1 (0.76) |
| T11-T12+L2-L3 | 1 (0.76) |
| T11-T12+L3-L4 | 1 (0.76) |
| L1-L2+L5-S1 | 1 (0.76) |
| L1-L2+L4-L5 | 1 (0.76) |
| L2-L3+L5-S1 | 1 (0.76) |

After infection with *Brucella*, T cells in the liver, spleen and lymph nodes are sensitized. In addition, macrophages become chemotactic and release inflammatory factors that gather around the bacteria, continuously phagocytosing and killing *Brucella*. This leads to the formation of an infectious granuloma that might have been responsible for the splenomegaly observed in about a third of the patients in this study. The findings also showed that lymphadenopathy and hepatomegaly were common, corroborating with previous research [6].

Additionally, osteoarthritis was reported in 56.82% of the children and 66.67% of the adults. This was the most common complication, consistent with other studies [7,8]. Notably, Adetunji *et al.* [9] showed that at least 27% of brucellosis patients were likely to develop osteoarthritis. The peripheral joints involved included the ankle, knee, hand and foot joints as well as the calcaneus. On the other hand, the axial joints involved included the sacroiliac, spine, pubic symphysis and sternocostal joints. Herein, the peripheral joints were mostly affected in children, especially the knee (62.00%) and hip joints (42.00%). In addition, no cases of spondylitis were reported in children, but in other studies, children were treated for lower back pain and MRI showed lumbar involvement [10]. Moreover, the axial joints were more affected in adults, especially the spine joint (37.01%). However, the sacroiliac joint, sternoclavicular joint and pubic symphysis were also affected. In brucellar spondylitis, MRI revealed that patients mostly presented with lumbar and sacral vertebral involvement particularly in the L3–L4 and L4–L5 levels with 32 (24.43%) and 24 cases (18.32%), respectively, similar to previous reports [11]. The lumbar spine is an important load-bearing structure of the human spine with a better activity than that of the cervical and thoracic spine. Given the many cancellous bones and the abundant venous plexus in the lumbar spine, it was easier for the bacterial embolus to stay here. Furthermore, 84.73% (111 cases) of the patients in this study had single level brucellar spondylitis while 12.98% (17 cases) had multiple-level brucellar spondylitis. Moreover, 5 patients suffered from non-contiguous spondylitis in different levels of the spine, similar to the findings from a previous study [12]. Notably patients with an affected spine and sacroiliac joint can present with back pain and sciatic nerve root pain which can radiate to the lower limbs. These clinical symptoms are usually similar to those of lumbar disc herniation and this may lead to misdiagnosis. In addition to osteoarticular brucellosis, pneumonia was

also common although meningitis, epididymitis, endocarditis and other complications were rare.

In this study, 2 children and 34 adults were diagnosed with orchiepididymitis. According to previous studies, women infected with *Brucella* suffer from oophoritis, salpingitis, endometritis and others complications, resulting in abortion [13] although the above were not reported in this study. Understanding the damage caused to the reproductive system is helpful in reducing adverse outcomes in pregnancy. Additionally, neurobrucellosis is usually rare and in this study, only 4.30% of the patients (7 children and 12 adults) were diagnosed with meningitis. Early diagnosis and treatment can be achieved based on the neurological symptoms as well results from the cerebrospinal fluid and serological tests. Moreover, the clinical manifestations of neurobrucellosis include headache, dizziness, vomiting, numbness of limbs, fatigue, disturbance of consciousness and seizures. Transverse myelitis was also previously reported as a main symptom [14]. In addition, heart damage from brucellosis can manifest as pericarditis and endocarditis. In the present study, 5 cases of heart damage were reported and they were characterized by fever, fatigue, precordial discomfort and an abnormal heart rate. However, these symptoms were mostly mild and the severe ones were rare. The results also showed that hemophagocytic syndrome, secondary to *Brucella* infection, was more common in children, corroborating with the findings from a previous study [15].

Furthermore, the most common abnormalities from laboratory tests were an increase in ESR, CRP and liver enzymes as well as a decrease in the percentage of eosinophils, in the two groups. In addition, pediatric patients had a significantly higher percentage of lymphocytes ($p < 0.001$) compared to the adults. The percentage of lymphocytes was also higher in healthy children aged 4–6 days and 4–6 years. On the other hand, adult patients had significantly higher neutrophil counts ($p = 0.018$) compared to their pediatric counterparts. Additionally, abnormalities in liver enzymes were more common in children although the adults had higher levels of urea and creatinine. This may have been due to the relatively large volume of the reticuloendothelial system and the low incidence of underlying diseases in children. Moreover, ESR combined with CRP can assist in the diagnosis of *Brucella* infections due to the inflammatory response caused by infection with the bacterium. A previous study showed that adult patients with brucellosis had a significantly higher Neutrophil to Lymphocyte ratio (NLR) compared to children. Existing literature also highlights that higher NLR

values are observed in inflammatory processes compared to the non-inflammatory ones, therefore NLR may be used in the diagnosis and follow-up of brucellosis cases [16]. An additional study also suggested that increased serum levels of hepcidin (compared to the CRP levels) in patients with brucellosis can be used as a diagnostic biomarker of inflammation and active disease [17]. Furthermore, the decrease or disappearance of eosinophils may be important in the early diagnosis of brucellosis as suggested by other studies [18]. Notably, thrombocytopenia is relatively rare, usually moderate and is attributed to bone marrow suppression or hypersplenism. A previous study reported on a girl with severe thrombocytopenic purpura as a symptom of brucellosis [19]. In this study, some patients (12.90%) developed hyponatremia. In addition, Bala *et al.* [20] proposed that hyponatremia may be caused by inappropriate secretion of the antidiuretic hormone due to infection with *Brucella*. Additionally, the positive rate of SAT was similar in children and adults although the positive rate of blood culture in children (65.85%) was higher than in adults (51.00%) and the difference was statistically significant ($p = 0.019$). It is noteworthy that infection with *Brucella* can cause persistent bacteremia. It is therefore common practice in pediatrics to collect blood for culture, in children with unknown fever, to enable diagnosis earlier in the bacteremia stage. Nonetheless, the positive rate of blood culture in the present study was slightly higher than that reported in other studies [21]. This may be related to the fact that Ningxia belongs to the epidemic area, therefore the medical staff and those involved in cattle and sheep production are more aware of brucellosis. Moreover, the results of pathogen culture in the hospital showed that all the bacteria were *Brucella ovis*.

While the study uncovered some informative findings, it had a number of limitations. The present study performed a retrospective chart review by collecting information from electronic medical records. In addition, misdiagnosis and missed diagnosis are common in the disease given that some patients may see doctors repeatedly without being diagnosed with brucellosis. Therefore, the number of patients that were lost is unknown. Additionally, the incidence of complications in children may be lower than that actually reported due to their inability to express discomfort. Nonetheless, the study presents one of the largest contemporary case studies and the data is a 10-year summary of *Brucella* infections. The study also provides a comparative analysis of the clinical features

of brucellosis in children and adults. This therefore complements the understanding of the disease and creates awareness to both health care providers and the general population on the public health threat posed by the disease.

Conclusions

The clinical characteristics of brucellosis are complex and different in children and adults. In addition, osteoarthritis was the most common complication in both groups in this study. Additionally, the results showed that the joints affected and the form of joint involvement differed in children and adults. Moreover, the incidence of laboratory abnormalities differed between the two groups. Therefore, given that brucellosis is nonspecific and easily misdiagnosed, careful inquiry on the patients' epidemiological history and active etiological examination will be helpful for effective diagnosis and treatment.

References

1. Yang H, Zhang S, Wang T, Zhao C, Zhang X, Hu J, Han C, Hu F, Luo J, Li B, Zhao W, Li K, Wang Y, Zhen Q (2020) Epidemiological characteristics and spatiotemporal trend analysis of human brucellosis in China, 1950–2018. *Int J Environ Res Public Health* 17: 2382.
2. Jia B, Zhang F, Lu Y, Zhang W, Li J, Zhang Y, Ding J (2017) The clinical features of 590 patients with brucellosis in Xinjiang, China with the emphasis on the treatment of complications. *PLoS Negl Trop Dis* 11: e0005577.
3. Hassounch L, Quadri S, Pichilingue-Reto P, Chaisavaneeyakorn S, Cutrell JB., Wetzel DM, Nijhawan AE (2019) An outbreak of brucellosis: an adult and pediatric case series. *Open Forum Infect Dis* 6: ofz384.
4. Jiang W, Chen J, Li Q, Jiang L, Huang Y, Lan Y, Li Y (2019) Epidemiological characteristics, clinical manifestations and laboratory findings in 850 patients with brucellosis in Heilongjiang Province, China. *BMC Infect Dis* 19: 439.
5. Liu Z, Shen T, Wei D, Yu Y, Huang D, Guan P (2020) Analysis of the epidemiological, clinical characteristics, treatment and prognosis of human brucellosis during 2014–2018 in Huludao, China. *Infect Drug Resist* 13: 435–445.
6. Serpa JA, Knights S, Farmakiotis D, Campbell J (2018) Brucellosis in adults and children: a 10-year case series at two large academic hospitals in Houston, Texas. *South Med J* 111: 324–327.
7. Dieckhaus KD, Kyebambe PS (2017) Human brucellosis in rural Uganda: clinical manifestations, diagnosis, and comorbidities at Kabale regional referral Hospital, Kabale, Uganda. *Open Forum Infect Dis* 4: ofx237.
8. Shi Y, Gao H, Pappas G, Chen Q, Li M, Xu J, Lai S, Liao Q, Yang, Yi Z, Rouzi Z., Yu H (2019) Correction: Clinical features of 2041 human brucellosis cases in China. *PLoS ONE* 14: e0219110.
9. Adetunji SA, Ramirez G, Foster M, Arenas-Gamboa AM (2019) A systematic review and meta-analysis of the prevalence of osteoarticular brucellosis. *PLoS Negl Trop Dis* 13: e0007112.

10. Wang X, Yan Y, Wu F, Su G, Li S, Yuan X, Lai J, Zhou Z (2018) Sixteen Chinese pediatric brucellosis patients onset of fever in non-epidemic areas and 8 developed with osteoarticular involvement. *Clin Rheumatol* 37: 145-149.
11. Liang C, Wei W, Liang X, De E, Zheng B (2019) Spinal brucellosis in Hulunbuir, China, 2011-2016. *Infect Drug Resist* 12: 1565-1571.
12. Zhao RG, Ding R, Zhang Q, (2020) Safety and efficacy of polyetheretherketone (PEEK) cages in combination with one-stage posterior debridement and instrumentation in lumbar *Brucella* spondylitis. *Clin Neurol Neurosurg* 199: 106259.
13. Ntirandekura JB, Matamba LE, Kimera SI, Muma JB, Karimuribo ED (2020) Association of brucellosis to abortions in humans and domestic ruminants in Kagera ecosystem, Tanzania. *Transbound Emerg Dis*: 13516. [Online ahead of print]
14. Anadure RK, Goel J, Sahu S, Vidhale T (2019) Recurrent encephalopathy with transverse myelitis: an uncommon presentation of neurobrucellosis. *J Neurosci Rural Pract* 10:703-706.
15. Pekpak E, Sirvan CB (2017) Secondary hemophagocytic lymphohistocytosis in a child with brucellosis. *J Pediatr Hematol Oncol* 39: e501-e503.
16. Tekin R, Aktar F, Yılmaz K, Tekin S, Ayaz C (2020) Comparison of inflammatory markers between adult and pediatric brucellosis patients. *Rev Soc Bras Med Trop* 53: e20190356.
17. Hashemi SH, Esna-Ashari F, Nemat GF, Tayebinia H, Mamani M (2018) Increased serum levels of hepcidin and C-reactive protein in patients with brucellosis. *Trans R Soc Trop Med Hyg* 112: 509-512.
18. Jiao P, Chu W, Ren G, Hou J., Li Y, Xing L (2015) Expression of eosinophils be beneficial to early clinical diagnosis of brucellosis. *Int J Clin Exp Med* 8: 19491-19495.
19. Alexandros M, Aikaterini P, Nikolaos C (2017) Severe thrombocytopenic purpura in a child with brucellosis: case presentation and review of the literature. *Case Rep Infect Dis* 3:3416857-3416857.
20. Bala KA, Doğan M, Kaba S, Akbayram S, Aslan O, Kocaman S, Bayhan Gİ., Üstyol L, Demir N (2016) The syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) and brucellosis. *Med Sci Monit* 22: 3129-3134.
21. Zheng R, Xie S, Lu X, Sun L, Zhou Y, Zhang Y, Wang K (2018) A systematic review and meta-analysis of epidemiology and clinical manifestations of human brucellosis in China. *Biomed Res Int* 2018: 5712920.

Corresponding author

Jinhai Ma, PhD

Chief Physician of General Hospital of Ningxia Medical University, No. 804 Shengli Street, Xingqing District, 750003, Yinchuan, Ningxia, China

Phone: 86-13995306967

Fax: 86-951-6743231

Email: makhcn@163.com

Conflict of interests: No conflict of interests is declared.