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ORIGINAL RESEARCH PAPER

The incidence and clinical manifestations of human brucellosis in a referral hospital in Southern Saudi Arabia between 2015 and 2019

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ABSTRACT

We determined the incidence and clinical manifestations of human brucellosis from patients who attended a referral hospital in South of Saudi Arabia. A record-based retrospective study was conducted from January 2015 to December 2019 at King Abdulla Hospital, Bisha, Saudi Arabia. Information on patients' demographic characteristics, detailed records of signs and symptoms, and the laboratory findings were reviewed. Of 6,586 patients included, 15.8% (n = 1,041) were infected with brucellosis. The age of infected individuals ranged from five to 95 years, with an average of 35.1 ± 21.2 years. Most infected patients were male (72.3%). Young adults (26–44 years) were the most common age group with the disease (34.1%). The annual rate of infection significantly decreased ($P < 0.0001$) from 33.2% in 2015 to 12.5% in 2019. An escalating number of brucellosis cases was seen in the spring and peaked during the summer. Fever (35.3%), joint pain (25.5%), generalized body ache (10.7%), and neurological symptoms (10.0%) were the most frequent clinical manifestation associated with brucellosis. Joint pain was commonly found among children (44.4%). Neurological findings were more frequent among adult patients. The study concluded that brucellosis is endemic in Southern Saudi Arabia and needs local health authority to implement preventive and educational program measures. Infected patients may present with diverse, nonspecific clinical manifestations that require intuition from clinicians to detect the disease.

KEYWORDS

human brucellosis, clinical findings, Southern region, Saudi Arabia

INTRODUCTION

Human brucellosis is a zoonotic infectious disease that remains a significant health problem in many parts of the world [1]. The disease is caused by several *Brucella* species, commonly by *Brucella abortus* (transferred by goats, sheep, camels, cattle), *Brucella melitensis* (transferred by cows, buffalo, camels, and yaks, also by sheep and goats), and *Brucella suis* (transferred by pigs) [2, 3]. Individuals acquire *Brucella* infection through direct or indirect contact with infected animals, or consumption of their food products [4, 5].

Brucellosis causes systemic infection that can involve any body organ, with diverse nonspecific clinical manifestations [6, 7]. Patients commonly present with the nonspecific symptoms of fever, chills, backache, fatigue, myalgia, and arthralgia, which can be shared by other infectious diseases [1]. In pregnant women, brucellosis may contribute to spontaneous

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abortion and intrauterine fetal death [8]. Therefore, the diagnosis of human brucellosis is based on clinical appearance coupled with laboratory findings of bacterial pathogens [5].

Human brucellosis remains an uncontrolled public health problem in many parts of the world, such as in the Middle East countries, Africa, and Southwest Asia [7, 9]. Although there are 500,000 new cases of human brucellosis reported each year worldwide, these numbers underestimate the true incidence of the disease [6]. Saudi Arabia continues to be an endemic zone, and the disease is reported in many parts of the country, despite extensive control efforts [1, 10, 11]. According to a report in Saudi Arabia, a mean of 4,164 cases per year reported from 2004 to 2012, with an incidence rate of 12.5 per 100,000 population in 2012 [4]. Studies across different geographical regions of Saudi Arabia have reported high prevalence rates of the disease [4, 12–14]. Most of the human brucellosis cases in Saudi Arabia inhabitants are in rural areas where a wide range of livestock is bred [15]. However, the incidence is higher in rural areas, where people's traditional habits involve contact with cattle and consumption of their raw milk products [4, 15]. Although data about brucellosis in Southern Saudi Arabia is limited, the current evidence suggests that the disease may be widespread in this geographical area [14, 16]. We retrospectively analysed the epidemiological and clinical manifestations of human brucellosis among patients over a five-year period in Bisha, Southern region of Saudi Arabia.

MATERIALS AND METHODS

Characteristics of the study area

Bisha is the largest area located in the northern part of the Aseer region (260 km far from Abha, the capital of Aseer) in the South of Saudi Arabia. The average annual temperature is estimated to be 24.5 °C, and the rainfall is about 130 mm, or 5.1 in per year. In Bisha, there are 58 urban centers, and about 240 villages. In Bisha and its suburbs, there is a large livestock population. The local communities, particularly in the rural areas of Bisha, have a traditional habit of drinking raw cow's milk.

King Abdullah Hospital is a referral hospital in Bisha, with a capacity of 365 beds. The hospital annually provides different healthcare services to approximately 17,000 hospitalized patients and 215,000 outpatients who live in the north part of the Aseer region and neighbouring areas [17].

Study design and population

A retrospective records-based study was conducted over five years from January 2015 to December 2019 at King Abdullah Hospital. The study participants were patients of all age groups who were hospitalized or presented to outpatient clinics of the hospital. The age groups were children (less than 15 years), youth (15–25 years), young adults (26–44 years), adults (45–64 years), and elderly (65 and above).

Collection of data

The data were obtained from the hospital and laboratory database. Information on patients' demographic characteristics, detailed records of signs and symptoms, and the laboratory findings supporting the diagnosis of brucellosis were collected. The data were provided in an anonymous format, without violating the personal privacy of the patients. The diagnosis of brucellosis was based on patients' history of contact with cattle or of living in an endemic area, medical history, and clinical manifestations, coupled with seropositivity of the *Brucella* test.

Laboratory procedures

Processing of blood samples. A sample of at least 5 mL of venous blood was collected from each patient in a plain vacutainer tube. The samples were centrifuged at 15.000 rpm for 10 minutes to obtain the sera for serological investigation. All sera were immediately screened for the presence of *Brucella* antibodies using the rapid slide agglutination test. Serum samples that showed agglutination were further diluted in a set of test tubes to determine the exact titer of *Brucella* antibodies. These tests were performed using Crescent Diagnostics kits (Crescent Diagnostics, Jeddah, Saudi Arabia) for the detection of *B. melitensis* and *B. abortus* antibodies. The assays were carried out following the manufacturer's instructions.

Rapid slide agglutination test. The agglutination test was done on two clean slides using *B. abortus* and *B. melitensis* antigens as per standard procedure [18]. In brief, exactly 50 µl of each patient's serum and control were placed into separate circles on each slide. A single drop (about 50 µl) of *B. abortus* antigen was mixed with the patient serum in control wells on the first slide. At the same time, the procedure was repeated using the *B. melitensis* antigen. Then, the slide mixtures were rotated on a mechanical rotator for 2 min, and the agglutination was examined under bright, indirect light. All positive sera were subsequently tested using a tube titration method.

Standard tube agglutination method. The technique was performed as previously described in the literature [6, 18]. A series of nine clean test tubes were labeled and placed in a rack. Using an automatic micropipette, 1.9 mL of 0.85% normal saline was delivered to the first tube, and 1.0 mL to each of the remaining tubes. An exact 0.1 mL of patient serum was added to the first tube and mixed. After mixing the tube, 1.0 mL of the diluted serum was subsequently transferred to the second to the eighth tubes, from which 0.1 mL was discharged. The final dilutions in the eight tubes ranged from 1:20 to 1:1,280. Tube number nine was used as an antigen control by adding 0.1 mL normal saline. Approximately 0.5 mL of *Brucella* antigen was delivered to each tube. The tubes were shaken gently and incubated for 24 hours in a water bath at 37 °C. After incubation, positive results were indicated by visible agglutination. Titer values

were obtained from the last tube showing agglutination. A titer of 1:160 or greater was considered to be positive for specific *Brucella* antibodies [19].

Statistical analysis. Microsoft Excel 2011 (Mac, Impressa Systems, Santa Rosa, California, USA, 2010) was used to translate and store the data. Simple descriptive statistics were used to analyse the data. GraphPad Prism version 7 for Windows (GraphPad Software, La Jolla California, USA) was used for statistical analysis in developing graphs and charts. The chi-square test was used to compare categorical variables, with a *P*-value of <0.05 considered to be statistically significant.

Ethical Approval. The study was approved by the Research Ethics Local Committee, College of Medicine, University of Bisha (UBCOM-RELOC), Bisha, Saudi Arabia. (Ref. no.: UBCOM/ H-06-BH-087 (04/20)).

RESULTS

Demographic characteristics of the population

Of the 6,586 individuals screened for brucellosis, 15.8% (1,041) tested positive for the antigen. Men constituted the majority of the patients (72.3%; 753). The age of the infected individuals ranged from five to 95 years old, with an overall average of 35.1 ± 21.2 years. Young adults were found to be the age group most likely to have brucellosis (34.1%; 355), followed by children (28.5%; 296), adults (23.1%; 241), elderly (11.25; 117), and youth (3.2%; 33) (Fig. 1A).

The proportion of brucellosis by year

Table 1 shows the incidence of brucellosis by year. The highest proportion of brucellosis was found in the year 2015, at 33.2% (208/616). This rate significantly decreased ($P \leq 0.0001$) to 12.5% in the year 2019 (Fig. 1B). During

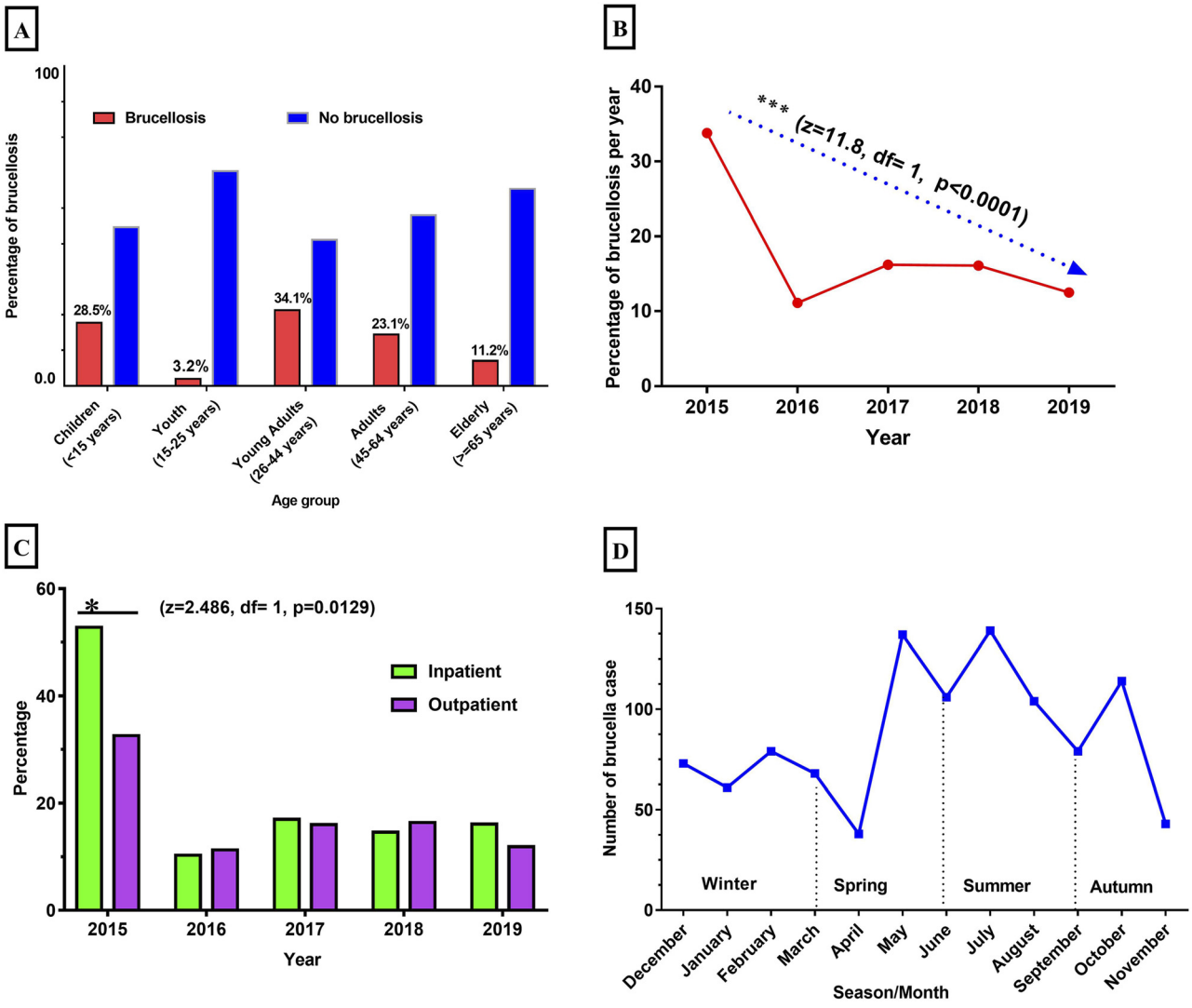

Fig. 1. Socio-demographic information of human brucellosis in Bisha, Southern region of Saudi Arabia (2015–2019). (A) Frequency of reported cases per patient age groups. (B) Annual incidence rates of brucellosis. (C) Proportions of brucellosis among hospitalized patients and outpatients. (D) Seasonal distribution of *Brucella* cases

Table 1. Annual incidence rates of brucellosis (2015–2019) among patients referred to King Abdullah Hospital, Bisha, Saudi Arabia

Year	The overall prevalence of brucellosis	Inpatient		Outpatient	
		Total number	*n* (%) of brucellosis	Total number	*n* (%) of brucellosis
2015 (n = 616)	208 (33.8)	36	19 (52.8)	580	189 (32.6)
2016 (n = 1,311)	146 (11.1)	195	20 (10.3)	1,116	126 (11.3)
2017 (n = 1,368)	221 (16.2)	223	38 (17.0)	1,145	183 (16.0)
2018 (n = 1,530)	246 (16.1)	240	35 (14.6)	1,290	211 (16.4)
2019 (n = 1,761)	220 (12.5)	261	42 (16.1)	1,500	178 (11.9)
Total (n = 6,586)	**1,041 (15.8)**	**955**	**154 (16.1)**	**5,631**	**887 (15.8)**

2015, a significantly higher rate ($P = 0.0129$) of brucellosis was found among hospitalized patients than among outpatients. In contrast, the level of infection was similar between these two groups of patients for other years (Fig. 1C).

Figure 1D illustrates the seasonal distribution of brucellosis. An increasing incidence of the disease was seen in spring and peaked during the summer months, while the number of brucellosis cases decreased during autumn and winter.

Clinical manifestations associated with brucellosis

The clinical findings associated with brucellosis were collected from 411 patients of different age groups (Table 2). Among these patients, the most frequent clinical manifestations were fever (35.3%), joint pain (25.5%), generalized body ache (10.7%), neurological symptoms (10.0%), and abdominal pain (8.0%). In comparison between different age groups, the highest rate of fever was reported in the children's age group. Joint pain was also commonly found among children (44.4%), followed by the elderly (30.4%), and youth (23.1%). The most frequent clinical finding in the adult age group was neurological complaints (21.1%). Other clinical signs and symptoms varied between absent and 19.6% among all groups (Table 2).

DISCUSSION

This was the first study that analysed the epidemiological and clinical manifestations associated with brucellosis among patients in Bisha, Southern region of Saudi Arabia. According to this study, the incidence of brucellosis decreased significantly from 33.8% in 2015 to 12.5% in 2019. This result suggests that the disease is still at a high level and requires extensive effort from local health authorities to reduce the rate. This study found the overall percentage of human brucellosis to be 15.8% over the five-year period. This figure is similar to the 15.9% reported in the Najran region at the Southern border of Saudi Arabia [6]. However, it is slightly higher than the 12.8% reported in another study conducted at Aseer Central Hospital in Abha City, the capital of the Aseer region [14]. It is also much higher than the 8.6% reported in Wadi Al Dawaser in the central region of Saudi Arabia [20]. A previous study reported that the incidence rate of brucellosis among the main regions of the country was 12.5 per 100,000 population in the year 2012 [4]. Such findings illustrate that brucellosis is endemic in many geographical regions of Saudi Arabia. These variations could be attributed to the existence of infected animals, occupational contact, or to the traditional habits of local communities in the use of cattle dairy products [4, 14, 21].

Table 2. Frequency of signs and symptoms associated with human brucellosis among patients (n = 411) of different age groups

Finding	Total cases (n = 411)	Age group				
		Children (n = 117)	Youth (n = 13)	Young adults (n = 140)	Adults (n = 95)	Elderly (n = 46)
Fever	145 (35.3%)	75 (64.1%)	4 (30.8%)	30 (21.4%)	24 (25.3%)	12 (26.1%)
Joint pain	105 (25.5%)	52 (44.4%)	3 (23.1%)	15 (10.7%)	21 (22.1%)	14 (30.4%)
Generalized body ache	44 (10.7%)	8 (6.8%)	2 (15.4%)	23 (16.4%)	9 (9.5%)	2 (4.3%)
Neurological symptoms	41 (10.0%)	5 (4.3%)	0 (0.0%)	13 (9.3%)	20 (21.1%)	3 (6.5%)
Abdominal pain	33 (8.0%)	8 (6.8%)	2 (15.4%)	14 (10.0%)	9 (9.5%)	0 (0.0)
Testicular pain	21 (5.1%)	0 (0.0)	0 (0.0)	14 (10.0%)	4 (4.2%)	3 (6.5%)
Headache	21 (5.1%)	2 (1.7%)	0 (0.0)	13 (9.3%)	5 (5.3%)	1 (2.2%)
Muscular pain	20 (4.9%)	0 (0.0)	1 (7.7%)	5 (3.6%)	5 (5.3%)	9 (19.6%)
Back pain	19 (4.6%)	5 (4.3%)	0 (0.0)	10 (7.1%)	4 (4.2%)	0 (0.0)
Vomiting	15 (3.6%)	6 (5.1%)	2 (15.4%)	3 (2.1%)	4 (4.2%)	0 (0.0)
Fatigue	13 (3.2%)	2 (1.7%)	0 (0.0)	5 (3.6%)	3 (3.2%)	3 (6.5%)
Nausea	12 (2.9%)	1 (0.9%)	0 (0.0)	8 (5.7%)	3 (3.2%)	0 (0.0)
Abortion	8 (1.9%)	0 (0.0%)	0 (0.0)	8 (5.7%)	0 (0.0)	0 (0.0)

Therefore, continuous implementations of local and national surveillance programs are important to control and prevent the disease burden.

In the present study, most of the infected individuals were male. Similarly, studies in other regions of Saudi Arabia have documented the predominance of brucellosis among men [14, 20, 22]. This could be due to the greater involvement of men than women in farming domestic animals in rural areas, and handling their products [21]. Comparatively, an earlier study in the Southern region of Saudi Arabia reported higher rates of infections among women [16]. It is well known that women are at high risk of acquiring brucellosis in communities where they have the opportunity to come into contact with animals and their products [23].

Young adults constituted the age group having the highest rate of brucellosis in this study. This is inconsistent with previous studies, where the age group of adults below 45 was found to be most likely to acquire the disease [4, 14]. This age group plays an important role in rearing animals and may regularly encounter infected animals. Young adults are the age group most likely to carry out activities related to domestic animals, such as milking cows and slaughtering cattle [23]. In addition, young adults are the most common age group to work as veterinary practitioners, or as slaughterhouses and abattoirs workers, and therefore have direct contact with raw meat and infected animals.

In this study, there were no significant differences in the brucellosis rates of outpatients and hospitalized patients, except during the year 2015 when the disease incidence was statistically higher among hospitalized patients. One possible reason might be that most of the brucellosis patients in 2015 had severe complications or were at the chronic stage of the disease. In the literature, the prevalence and characteristics of the chronic stages of brucellosis among hospitalized patients have been well-documented by others [24].

Several studies in endemic areas have determined the prevalence rates of brucellosis and found the disease to be affected by climatic features and geographic location [2, 14, 24]. In this study, the maximum rates of human brucellosis were shown to occur in the spring and summer seasons, and similar findings were reported by Aloufi et al. [4]. In the Southern part of the Aseer region, the incidence of human brucellosis increased during the summer season [14]. This could be explained by the increased drinking of raw milk and the use of milk products during spring and summers [24]. However, the consumption of a large amount of milk and dairy products from infected animals during the summer season was observed in the Aseer region [14]. Notably, many Saudi families traveled to rural areas during the spring and early summer to visit and relax, and enjoyed drinking raw camel's milk.

The present study reported various nonspecific clinical presentations of brucellosis, with fever (35.3%) and joint pain (25.5%) being the most frequent symptoms. Also, 64% of infected children presented with fever. These results are almost in agreement with previous findings in Saudi Arabia. For instance, a study in the central region of Saudi Arabia found the main clinical features associated with brucellosis were febrile illness alone (44%) or fever with arthritis (42%) [25]. In the northern region of the country, Fallatah et al. found that the most common clinical features in brucellosis patients were fever (79.2%) and joint pain (70.4%), and that (48.4%) had bone pain [12]. These findings are in line with a study from the eastern region, where the most common symptoms were fever and musculoskeletal pain [1]. Likewise, previous studies from endemic countries have highlighted brucellosis as a significant cause of fever [24, 26]. Therefore, in endemic areas, it is important for treating doctors to suspect brucellosis among febrile patients.

Consistent with other research [27, 28], this study found that neurological complaints were often associated with brucellosis. Several neurological disorders involving motor deficits, weakness in extremities, sensory loss, cranial nerve deficits, sciatica, hearing and vision defects, meningitis, and seizures have been reported in the literature [28, 29]. Thus, neurobrucellosis should be considered in patients presenting with fever of unknown origin, coma, and neurological complaints. Concerning reproductive health problems, the study reported that 5.1% of males had testicular pain and 1.9% of females suffered from spontaneous abortion. Mujuni et al. found that the overall seropositivity of *Brucella* antibodies was significantly higher among sera from women with spontaneous abortion than among women who had full-term delivery [8].

In a comparison of clinical manifestations associated with brucellosis among different age groups, neurological symptoms were commonly found among adult patients (21.1%). Elsewhere, a study identified diverse neurological manifestations with brucellosis [27]. On the other hand, joint pain was most common among children, followed by the elderly and youth. However, the relationships of these complications between specific age categories are not clear. Further research to evaluate the complications and pathological effects of brucellosis in different age groups is essential to avoid the consequence burdens of the disease.

CONCLUSIONS

The study has shown that human brucellosis is endemic in Bisha, in the Southern region of Saudi Arabia, and that it has clear seasonal variations. Although the incidence of the disease has gradually decreased over the last five years, it is still at a high level. There is a need for an effective educational program for community members, stockbreeders, livestock owners, and healthcare workers to raise awareness about the risk factors associated with brucellosis and its substantial economic and health burden. Moreover, implementing control measures via a vaccination strategy, identification of infectious livestock, and modes and transmission of the disease is essential. Although fever was the most frequent symptom, patients may present with diverse nonspecific clinical manifestations that require high intuition from a clinician to suspect the disease. Thus, obtaining a history of epidemiological exposure, clinical

manifestations, and laboratory investigations can simplify the diagnosis of brucellosis in endemic areas.

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