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Differentiation of *Brucella*-Induced Epididymo-orchitis from Nonspecific Epididymo-orchitis in an Endemic Area for Brucellosis

Masoomeh Sofian[1], Arezoo Aghakhani[2], Mohammad Banifazl[3], Ali Eslamifar[2], Fatemeh Zolfaghari[1], Hossein Sarmadian[1], Amitis Ramezani[2]

[1]Tuberculosis and Pediatric Infectious Research Center, Arak University of Medical Sciences, Arak, Iran; [2]Clinical Research Department, Pasteur Institute of Iran, Tehran, Iran; [3]Iranian Society for Support of Patients with Infectious Disease, Tehran, Iran.

Distinction between brucellar epididymo-orchitis (BEO) and nonspecific epididymo-orchitis (EO) is an important medical issue. This study was conducted to compare demographic, clinical and laboratory features, treatment and outcome of patients with BEO and nonspecific EO in Arak city, Markazi Province, Iran. We compared the clinical and laboratory characteristics of 40 BEO and 40 non-specific EO patients. The diagnosis of brucellosis was based on the symptoms, compatible clinical findings and standard tube agglutination test. Epididymo-orchitis was diagnosed by swelling and tenderness of scrotal skin, testis and epididymis, which was confirmed by sonography. BEO can be distinguished from nonspecific EO based on having a history of living in rural areas, contact with domestic animals, and consumption of unpasteurized dairy products. Other criteria include seasonal pattern, gradual onset ($P<0.05$), sweating ($P<0.001$), arthralgia ($P=0.02$), associated lower urinary tract symptoms ($P=0.004$) and lower rate of leukocytosis and abnormal urine analysis ($P=0.002$). Our results showed that brucellosis should be considered as a cause of EO in endemic areas like Iran. Combination antibiotic therapy to manage BEO is usually effective and all patients in this study responded quite satisfactory to the treatment.

Keywords: **Brucellar epididymo-orchitis, nonspecific epididymo-orchitis, Iran.**

INTRODUCTION

Brucellosis, a bacterial infection, is a worldwide zoonotic disease, which under certain circumstances can directly or indirectly be transmitted to humans. It causes considerable economic losses among those keeping domestic animals as a source of meat and dairy products. It is also a burden on health system due to the cost of treatment and chronic serious sequelae of the disease [1]. Millions of individuals are at risk worldwide, especially in developing countries, where the infection rate in cattle is of a high incidence. However the rate of brucellosis incidence in developed countries is low and it is sporadically reported in persons who are infected by occupational exposure to infected animals [2].

The frequency of brucellosis in different areas of Iran is estimated to be 0.5-10.9% [3], and *Brucella melitensis* is the most prevalent causing species. The disease is highly endemic in certain parts of the country such as Markazi Province of Iran showing a five-year incidence of about 40/100000 [3].

In humans, brucellosis causes a systemic infection with various clinical signs and symptoms. The main symptoms of this infection are undulant fever, chills, night sweating and fatigue [4]. Malaise, anorexia, headache, arthralgia, sexual impotence and depression have also been seen in some cases [4]. Focal forms of brucellosis, presented in 20-40% of patients, have been described almost in all organs and systems, with osteoarticular and genitourinary forms being more common [4-6].

Corresponding author: Amitis Ramezani, Clinical Research Dept. Pasteur Institute of Iran; 13164, Pasteur Ave., Tehran, Iran.
Email: amitisramezani@hotmail.com

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Genitourinary complications have been described in 2-40% of patients, and epididymo-orchitis (EO), the most frequent one, has been observed in 2-20% of males with brucellosis [6-9]. The outcome of brucellar epididymo-orchitis (BEO) is usually favorable; however, any delay in diagnosis or improper approach may cause major complications, like testicular abscess [10].

Distinction between BEO and nonspecific epididymo-orchitis (EO) is essential, as treatment and outcome of these issues are completely different. In the present study, we analyzed the epidemiological, clinical and laboratory findings, and treatment and outcome of BEO in comparison with nonspecific EO in patients, from Arak city, Markazi Province, Iran, an endemic area for brucellosis.

MATERIALS AND METHODS

Eighty patients aged 3-88 years (mean age: 39±20 years), diagnosed with EO, were enrolled in this study from January 2007 to January 2011. Forty patients had BEO, and 40 had nonspecific EO. Informed consent was obtained from all patients. The project was approved by ethical committee of Arak University of Medical Sciences. We studied the characteristics of BEO in comparison with nonspecific EO, and both groups were compared in terms of clinical findings, demographic characteristics, seasonal pattern, symptoms onset, duration of illness, pattern of fever, associated lower urinary tract symptoms, urine analysis, leukocyte count, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), response to treatment and patients outcome. The definition of EO was based on the finding of swelling and tenderness of testis, epididymis, and scrotal skin, with sonography confirmation. The brucellosis was diagnosed based on compatible signs and symptoms, standard tube agglutination (STA) test dilution≥1:160, and in presence of 2-Mercaptoethanol (2ME) agglutination≥40.

Statistical analysis. The Chi-square and t^2-tests were used along the SPSS 16 Package program for statistical analysis (Chicago, IL, USA). Data are presented as mean±SD or, when indicated, as an absolute number and percentage.

RESULTS

The mean age of BEO patients was 40±21.5 years and the mean age of nonspecific EO patients was 37.95±19.5 years. 47.5% of patients in the BEO group had a history of contact with domestic animals and 50% of them reported consumption of unpasteurized dairy products. The *Brucella* infection group showed a well-defined seasonal pattern, as all cases occurred in the late spring and early summer. In contrast, no particular seasonal pattern or history of contact with domestic animal was reported in the nonspecific group. Most of the individuals in the BEO group were residents of rural areas compared to those in nonspecific group (62.5% vs. 37.5%, P=0.04). All BEO patients suffered EO during a primary brucellosis infection and 2 subjects (5%) reported infection among members of the same households. The duration of the symptoms was less than 1 week in all nonspecific EO and 65% of BEO patients, and from 1 week to 1 month in remaining 35% of BEO cases; so acute symptoms onset was significantly more prevalent in nonspecific EO group. Thirty seven out of 40 BEO (92.5%) and 33 out of 40 nonspecific EO patients (82.5%) had fever, which was typically undulatory in BEO group (P=0.17, NS). On the other hand sweating and arthralgia were observed more frequently in BEO patients compared to nonspecific EO group. Peripheral arthritis was seen in 8 (20%) BEO, but in only 1 (2.5%) EO patients, and knees were the most common site of the infection in both groups (P=0.01). Twelve (30%) BEO and 8 (20%) nonspecific EO patients had bilateral clinical involvement. Unilateral involvement of organ was observed in 28 (70%) BEO (30% right-sided and 40% left-sided), and 32 (80%) nonspecific EO patients (45% right-sided and 35% left-sided).

Twenty six (65%) nonspecific EO and 13 (32.5%) BEO patients had lower urinary tract symptoms including dysuria and urinary frequency.

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Urethral discharge was observed in 5 (12.5%) nonspecific EO patients but none of BEO patients manifested this symptom.

CRP was positive in 30 (75%) of EO and 27 (67.5%) of BEO patients (p>0.05). ESR was above 40 mm/h in 17 (42.5%), between 20 and 40 mm/h in 16 (40%) and below 20 mm/h in 7 (17.5%) EO patients, while in BEO group, 11 (27.5%) had an ESR level below 20 mm/h, 16 (40%) between 20 and 40 mm/h, and 13 (32.5%) above 40 mm/h (p>0.05).

Leukocytosis (>10000 WBCs/mm^3) was found in 25% of BEO and 82.5% of EO patients (P<0.001). Eleven (27.5%) EO and 8 (20%) BEO patients had platelet counts less than 150×10^9/L and anemia (hemoglobin<14 g/dL) was detected in 22 (55%) BEO and 18 (45%) EO cases which both were not significant between 2 groups. Severe thrombocytopenia (thrombocytes<50×10^9/L) was not seen in any patient, but one BEO patient presented with leukopenia (leukocytes<4.5×10^9/L). Urine analysis was abnormal in 30% of BEO patients while 65% of EO patients had abnormal urinary sediment. The testicular abscess was detected in 5 (12.5%) EO and 1 (2.5%) BEO patients. Orchiectomy was required only for 1 nonspecific EO patient.

Table 1. Comparison of epidemiologic, clinical and laboratory characteristics of the *Brucella* induced epididymo-orchitis and nonspecific epididymo-orchitis

	***Brucella* induced epididymo-orchitis (n=40)**	**Nonspecific epididymo-orchitis (n=40)**	**P Value**
Fever	37 (92.5%)	33 (82.5%)	NS
Sweating	36 (90%)	1 (2.5%)	0
Arthralgia	20 (50%)	0 (0%)	0.02
History of brucellosis in family members	2 (5%)	0(0%)	NS
Place of residence (rural/urban)	25/ 15 (62.5%/37.5%)	12 /28 (30%/70%)	0.04
Acute symptoms onset (≤7 days)	26 (65%)	40 (100%)	0
Lower urinary tract symptoms	13 (32.5)	26 (65%)	0.004
Bilateral involvement of testis	12 (30%)	8 (20%)	NS
Abnormal urine analysis	12 (30%)	26 (65%)	0.002
Leukocytosis (>10000 WBCs/mm^3)	10 (25%)	33 (82.5%)	0
ESR>20 mm/h	29 (72.5%)	33 (82.5%)	NS
CRP (+)	27 (67.5%)	30 (75%)	NS
Genitourinary instrumentation	2 (5%)	3 (7.5%)	NS
Abscess formation	1 (2.5%)	5 (12.5%)	0.021

Data are indicated as number (%); ESR, Erythrocyte sedimentation rates; CRP, C - reactive protein; NS: Not significant

All patients were treated with rifampin plus doxycycline for 3 months, in combination with streptomycin or gentamicin for 1 week. Combination antibiotic therapy resulted in complete resolution of the disease in all BEO patients, without serious side effects, except one who developed testicular abscess and fistula formation, which was resolved after extended antibiotic therapy.

Comparison of clinical and laboratory characteristics of the BEO and nonspecific EO patients revealed that place of residence, contact with domestic animals, seasonal pattern, sweating, arthral-

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gia, abnormal urine analysis, lower urinary tract symptoms, symptom onset and leukocytosis were significantly different between these two groups (Table 1).

DISCUSSION

In this study, we analyzed the epidemiological, clinical and laboratory findings, and treatment and outcome of BEO in comparison to nonspecific EO group. Our results showed that BEO can be distinguished from nonspecific EO based on having a history of living in rural areas, contact with cattle and consumption of unpasteurized dairy products. Other criteria include seasonal pattern, gradual onset ($P<0.05$), sweating ($P<0.001$), arthralgia ($P=0.02$), associated lower of urinary tract symptoms ($P=0.004$), lower rate of leukocytosis and abnormal urine analysis ($P=0.002$). Antibiotic therapy resulted in complete resolution of all BEO patients, except in 1 case who developed testicular abscess. EO is a prevalent clinical condition [11, 12] and its inappropriate management may lead to critical complications, such as testicular abscess, testicular infarction and male infertility in up to 39% of cases [7, 13, 14]. In endemic countries, brucellar epididymo orchitis has been described in 2%-20% of patients with brucellosis and accounts for 10% to 20% of all cases of epididymo orchitis [9, 15, 16]. Several studies on *Brucella*-induced epididymo orchitis have been performed in the Kingdom of Saudi Arabia (KSA) [17], Greece [7], Spain [18], Turkey [10] and Iran [15] to determine epidemiological, clinical and laboratory finding of the disease. In a study by Colmenero *et al.* [18], 14.5% of BEO patients had leukocytosis, and urine analysis was normal in 69% of the patients. The onsets of symptoms were subacute and the presence of lower urinary tract symptoms was very un-common. Our results are in concordance with Colmenero *et al.* [18] reports. Similar data have been reported by other scholars [7, 9, 17, 19].

Several studies have reported a well-defined seasonal pattern in BEO patients [20, 21]. The incidence is highest in spring and summer and lowest in winter. Memish *et al.* [17] reported half of the patients during March to June. In our study, most of the cases were observed during late spring to early summer (months of June, July, and August). This can be due to parturition of home-owned animals in these months and consumption of home-made dairy products. Our results are in agreement with the study by Papatsoris *et al.* [7], which showed that *B. melitensis*-induced EO patients had a history of contact with animals, drinking raw milk or consuming freshly prepared dairy products, along with the signs and symptoms of typical undulatory fever, absence of lower urinary tract symptoms and serious leukocytosis .

In the study by Akinci *et al.* [22], BEO patients showed unilateral involvement of testis, but bilateral involvement was rarely detected. In another report EO was mostly unilateral (52.1% left-sided and 43.7%, right-sided); and bilateral in only 4% [18]. Memish *et al.* [17] reported that 6 out of 26 brucellosis patients had unilateral EO; the remaining 20 had only orchitis (bilateral in two, right-sided in ten, and left-sided in eight). The present study demonstrated that 30% of BEO patients had bilateral and 70% unilateral (30% right-sided and 40% left-sided) involvement of testis.

Abnormal laboratory findings are usually low and nonspecific in BEO patients. ESR is relatively elevated in most patients and the hemoglobin level is lower than normal range due to prolonged infection [10]. Leukocytosis is usually observed, although it's not a typical presentation of BEO [23]. Ibrahim *et al.* [19] considered it as a significant feature, differentiating brucellar and nonspecific EO. They found leukocytosis in only one of 10 BEO patients. In Akinci *et al.* [22] study, leukocytosis was detected in 18% of the patients. Yurdakul *et al.* [8] found slight leukocytosis in only 14.3% of patients with BEO. On the other hand, some studies have reported leukocytosis as an important feature of *Brucella* induced epididymo-orchitis [23, 24]. In two separate studies this feature was observed in 71.4% and 84.6% of BEO patients [23, 24]. In our

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study, a minor leukocytosis occurred in 25% of the 40 BEO cases. These results suggest that we should be more cautious in using leukocytosis for distinguishing these 2 types of EO. Papatsoris *et al*. reported elevated ESR in all nonspecific EO and 76% of BEO patients [7]. In another study, ESR in BEO patients was within the range of 9-81 mm/h, and 92.9% of cases had ESR>20 mm/h (10). In our survey, elevated ESR>20 mm/h was observed in 72.5% of BEO and 82.5% of nonspecific EO patients indicating no significant difference between these two groups. High CRP levels were the significant laboratory findings in some studies [10, 22]. Celen *et al*. [10] found high CRP levels in 96.3% of BEO patients. Although in our study, elevated CRP levels were observed in 67.5% of BEO patients, but this ratio was not significantly different from that of nonspecific EO patients. So in our investigation, ESR and CRP were not considered as discriminating features to differentiate brucellar and non-specific EO. The rate of abnormalities in urine laboratory test of BEO patients is usually low. In the present study, only 30% of the patients had mild proteinuria, hematuria, pyuria, or some combination of these. Similar findings have been reported by other scholars [7, 9, 19].

The therapeutic failure or relapses have been reported in up to 40% of BEO cases and up to 5.1% of individuals required orchiectomy [7-9, 16, 17, 22, 23]. Treatment and prognosis of BEO remains a serious clinical problem; appropriate combination of antibiotics is suggested to improve prognosis and prevent relapses [9]. Oral administration of rifampin and doxycycline combination, or doxycycline plus streptomycin for at least 6 weeks has been successfully used for the treatment of BEO [9, 16, 17, 23]. In the present study, all patients were treated with rifampin plus doxycycline for 3 months, in combination with streptomycin or gentamycin for 1 week. Antibiotic therapy resulted in complete resolution of the symptoms in all BEO patients without serious side effects, except in 1 patient who developed testicular abscess with fistula formation that resolved after extended antibiotic therapy. None of the patient required orchiectomy.

In conclusion, our findings suggest that brucellosis is still a cause of EO in endemic areas like Iran. BEO can be differentiated from nonspecific EO based on seasonal pattern, gradual onset, sweating and arthralgia, lower percentage of urinary tract symptoms, and lower rate of leukocytosis and abnormalities in urine analysis. Combination of antibiotics for treatment of BEO was effective and response to medical management was quite satisfactory.

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