Brucellosis is a zoonosis transmitted to humans from infected animals, mainly after consumption of unpasteurized milk and milk products and less often after direct contact with infected animals via inhalation, especially by children and by slaughterhouse, farm, and laboratory workers. Although brucellosis in domestic animals has been controlled in most developed countries it remains an important public health problem in several parts of the world. The disease is endemic in Iran as well as in other Middle East and Mediterranean countries, and in Latin America. In a study in Iran most cases were caused by Brucella melitensis usually belonging to biotype 1. The aim of this study was to examine the epidemiological features, clinical and hematological characteristics, complications and treatment outcome of brucellosis in Yazd.

We reviewed the records of 686 patients 1 to 70 years of age with the diagnosis of brucellosis over a 6-year period between 1995 and 2001. The Nikoopour clinic is the center for infectious diseases control in Yazd and is also the referral center for patients from other cities, mainly Maybod, Ardakan, Taft, Mehriz, and Sadough. Confirmed cases were defined those with clinical symptoms and signs suggestive of brucellosis in which Brucella was recovered from blood. The presumptive diagnosis of brucellosis in patients with negative cultures was based on a standard tube agglutination test (STA) (1:320). A Brucella abortus suspension was used for the STA test.

There was a significant difference in the number of patients during the 6 years of the study; the most were in 1998 with 266 cases (38.8%) and the least in 2001 with 18 cases (2.6%). Males were more commonly affected than females and the male-to-female ratio was 1.32. Only 3.2% of the patients were (5 years of age, and 23.8% than females and the male-to-female ratio was 1.32. Only 3.2% of the patients were (5 years of age, and 23.8% were 5 to 14 years). A seasonal variation in the distribution of cases was observed, and the most common cases were observed in summer. Mean (±SD) duration of symptoms prior to diagnosis was 14.1 (±14.6) days (median 11 days, range 7-70 days).

Nearly all patients were febrile, most with moderate fever. Other common symptoms included fatigue, arthralgia, night sweats, gastrointestinal manifestations such as abdominal pain and constipation and diarrhea and weight loss. A substantial number of patients (61%) developed arthritis or arthralgia. The joints more commonly affected included the knee in 49%, hip in 41%, ankle in 18%, wrist in 13%, and small joints of the hand in 15%. Monoarthritis and oligoarthritis was noted. A substantial number of patients (36%) developed sacroiliitis. Arthritis of the cervical spine was rare. The response of joint symptoms to treatment was immediate and by two weeks of treatment nearly all patients had significant improvement. Hepatomegaly was reported in 5% patients. Splenomegaly was recorded in 20% cases and was also mild to moderate. Unilateral or bilateral epididymoorchitis was seen in 11 (2.8%) cases in males.

The antibody titers to Brucella determined by standard tube agglutination were as follows: 1/2560, 28 (4.08%); 1/640, 162 (23.62%); 1/320, 204 (29.74%); 1/160, 111 (16.18%); 1/80, 38 (5.54%); 1/40, 11 (1.6%). All of the patients had symptoms and signs suggestive of brucellosis. In patients who had an initial SAT titer of 1/80 the diagnosis was documented with a positive blood culture in 9 or with increased titer to 1/320 or greater on reexamination 1-2 weeks later.

All patients received a combination of two or three antibiotics. Duration of treatment was 8-12 weeks. None of the patients was readmitted to our clinic with a relapse. Only four patients had been previously treated in other places and presented for the first time to our clinic with a relapse. Two had received doxycycline and streptomycin for 2 weeks and two received doxycycline and rifampin for 2 weeks. All four patients relapsed twice 1 to 2 months after discontinuation of therapy. They were then treated with doxycycline and streptomycin for 4 weeks and then with doxycycline and rifampin for 8 weeks and had no relapse during 6 months of follow-up.

Remarkable and unusual complications were noted in two patients who developed chronic meningitis.
and endocarditis. The first patient developed a prolonged history of fatigue and weight loss and night sweats and low-grade fever. Blood cultures were negative and STA titer in the first 2 months was negative or 1/40. However, in the third month STA was detected at 1/640 and the CSF STA test was 1/80. The second patient presented with fever and sweats and weight loss, but the serum titer of the STA test was 1/40 and blood cultures were negative. However, one month after initiation of signs and symptoms the STA titer was detected at 1/640 and ultimately a heart murmur was detected.

Brucellosis is a systemic disease with protean manifestations. Its features may mimic those of other febrile illnesses. Brucellosis remains an important public health problem in our area and can cause serious complications, resulting in significant morbidity. The clinical characteristics of brucellosis in our series are similar to those reported by previous studies. Musculoskeletal manifestations were recorded in the majority of patients and included arthralgia and arthritis, which most commonly affected the large joints of the lower extremities. Sacroiliitis was a frequent manifestation of brucellosis in our patients, but arthritis of the small joints of the hand was infrequent. The response of joint symptoms to treatment was immediate in our patients and none suffered long-term complications.

The most common hematological manifestations of brucellosis in our group of patients were a normal CBC followed by anemia and lymphocytosis. These hematological manifestations of brucellosis have been reported in previous studies. Leukopenia was less frequently encountered in our series.

A remarkable finding of the study was the insignificant STA titer (1/80) in a considerable number of patients (49, 7.14%), in whom the diagnosis was confirmed with a positive blood culture (9 cases) or with an increase in titer to 1/320 or greater on reexamination 1 to 2 weeks later. A falsely low or equivocal STA titer occasionally occurs in patients with acute brucellosis and the diagnosis can be made with the detection of IgM antibodies with ELISA or culture or repeat STA later.

Neurological complications of brucellosis are uncommon and occur in <5%. In our study only one patient developed chronic meningitis. Blood cultures were negative and the STA titer in the first 2 months was (1/40). However, in the third month STA were detected at 1/640 and the CSF STA test was 1/80.

Our patients were treated with different therapeutic regimens and duration of treatment was variable since this was a retrospective study spanning 6 years. However, none of the patients who received a combination of rifampicin plus either doxycycline or trimethoprim-sulfamethoxazole ± streptomycin (for the first month) for 8 weeks or longer had a relapse. Therefore, it appears that the combination of at least two of the above antibiotics for a period of 8 weeks is an effective treatment for brucellosis. The patients who presented with a relapse had previously received a combination of two antibiotics for 2 weeks. The relapse occurred in these patients within 1 to 2 months from completion of initial treatment. High relapse rates have been reported with short-term (3 week) two-drug regimens even when an aminoglycoside was initially included.

In conclusion, brucellosis has a wide range of clinical manifestations. It may affect any organ system and imitate a variety of clinical entities. Physicians practicing in endemic areas must be familiar with this disease so that early recognition results in lower morbidity. The diagnosis may present difficulties since blood cultures or the agglutination test may not always be positive. Treatment with at least two antibiotics for not less than eight weeks appears to be effective. An organized effort must be undertaken in endemic areas for brucellosis control through vaccination of animals and finally eradication through testing and slaughter of infected animals.

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References

A neonatal case of citrullinemia with urolithiasis

To the Editor: Citrullinemia is a rare autosomal recessive inborn error of urea cycle metabolism caused by a deficiency of argininosuccinate synthetase. At least half of genetically affected newborns present in the first several days of life. Major clinical symptoms and signs of hyperammonemia in the neonatal period are difficulty in feeding, vomiting, tachypnea, lethargy, convulsion and coma. The neonatal forms are serious and many times are associated with a high level of mortality. We describe a neonatal case of citrullinemia associated with urolithiasis.