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Human Brucellosis in Iran: Incidence, Complication, Diagnosis, Treatment and Prevention

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Brucellosis is an important zoonotic disease with a worldwide distribution. Despite its control in many countries, it remains endemic in Iran. Routine serological surveillance along with high clinical suspicion and screening of family members of index cases would be essential in delineating the real magnitude of human brucellosis in endemic countries. Laboratory testing is indispensable for diagnosis. Advances in newer rapid, sensitive, and specific testing methodologies and alternate treatment strategies are urgently needed. A safe and effective vaccine in human is not yet available. Prevention is dependent upon increasing public awareness through health education programs and safe livestock practices. Co-operation between health and veterinary services should be promoted actively .This review contains all these issues in general, and the incidence, diagnosis and therapy in particular, in the Iran.

Key words: Zoonotic, Brucellosis, Iran, Prevalence.

Brucellosis is an infectious zoonotic disease that is accompanied with chronic weakening infections in humans and reproductive impairment in household animals. It is the most prevalent zoonotic disease in the world, accounting for the annual incidence of more than 500,000 cases[1,2]. In spite of discovery of the disease over 100 years ,and its transmission , over 100 years before, and its transmission, the disease remains a universal problem, mainly so in developing countries, in particular, in the Mediterranean area, including Iran, Turkey, the Arabian Peninsula, the Indian subcontinent, Mexico, and parts of Central and South America[2,3]. Since the finding of *B. melitensis* by Bruce, brucellosis has been an emerging disease. The transmission of *Brucella* infection and its prevalence in a region depends upon several factors like food habits, methods of processing milk and milk products, social customs, husbandry practices, climatic conditions, socioeconomic status, and environment hygiene. Environmental sanitation is particularly important in the context of air borne transmission. Brucellosis is almost always transmitted to man from infected domestic animals. On the other hand, it has been documented beyond doubt, the opportunity of human to human transmission of *Brucella* infection[4]. Human brucellosis was once thinking

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to be predominantly transmitted through animal contact. However, it is now being realized increasingly those animal products such as milk and meat also playing an important role in the disease transmission. Dairy products prepared from unpasteurized milk such as soft cheeses, yoghurts, and ice creams may contain high concentration of the bacteria that consumption of these products are from important causes of brucellosis. It is the commonest mode of transmission in case of *B.melitensis* and *B.abortus* infections in general population. In Middle East countries and Mongolia Camel milk is also considered to be the most source of the infection. Bacterial load in animal muscle tissues is low, but eating of undercooked traditional delicacies such as liver has been implicated in human infection. Some particular food habits, such as eating aborted fetuses seen in Ecuador, may have role in causing human brucellosis. Crushing the umbilical cord of newborn lambs and kids with the teeth is another risky habit. Consuming fresh goat's milk combined with herbal extracts to obtain relief from chronic ailments have been reported a more risky habit. Skinning stillborn lambs and kids and aborted fetuses, which may be heavily contaminated with *Brucella* spp., also presents a high risk of brucellosis[4]. Skin abrasions or inhalation of airborne animal manure particles are from other means of infection.Contamination of skin wounds may be a problem for persons working in slaughterhouses or meat packing plants or for veterinarians. Hunters may be infected through skin wounds or by accidentally ingesting the bacteria after killing deer, elk, moose, or wild pigs. In addition, laboratory acquired *Brucella* infection due to accidental ingestion, inhalation and mucosal or skin contact is a major health hazard for the laboratory workers handling the cultures of the virulent or attenuated strains. The disease has been recognized as one of the common laboratory-transmitted infections and has been reported to occur in clinical, research, and production laboratories[6-7]. Increased business and leisure travel to endemic countries have led to diagnostic challenge in areas where brucellosis is uncommon. Although *B.melitensis* accounts for most recorded cases, *B. abortus* and *B. suis* cause substantial morbidity in countries in which they persist in domestic animals, markedly in Asia and Latin America. *B. canis* rarely causes overt human disease, and *B. neotomae* and *B. ovis* have not been identified as causes of infection in humans. *B.melitensis* has 3 biotypes; biotype 1 is prevalence in Iran. *B. abortus* has 7 biotypes; biotype 3 is prevalence in Iran. *B. suis* has 5 biotypes but it isn't prevalences in Iran[8]. The presence of brucellosis in wild animals, with a potential for continuous transfer to domestic animals and from them to humans is another epidemiological issue[9] . Those with a professional risk of acquiring infection include livestock producers, abattoir workers, shepherds, farmers, veterinarians, and laboratory personnel. Brucellosis is common in rural areas because farmers live in close contact with their animals and often consume fresh unpasteurized dairy products. However, the vending of dairy products may also bring the disease to urban areas. Pasteurization of milk and the monitoring and culling of herds of sheep, goats, cows, and pigs for brucellosis have considerably reduced the incidence of such outbreaks. Great importance has been assigned to such methods of control and great and justifiable pride is taken by countries such as New Zealand who have earned the designation brucellosis free. Upon such achievements, progress in international human health depends, as do agricultural efforts and investments worth many millions of dollars. A more recent matter of international concern is the possibility that this agent might be used as a biological instrument of terror since in aerosolized form merely 10-100 organisms might be capable of producing infection of humans and animals. The pathogenicity in human brucellosis is attributed to factors like LPS, adenine and guanine monophosphate, virB, 24 kDa protein, and urease enzyme. *Brucellae* may enter the host via ingestion or inhalation, or through conjunctiva or skin abrasions. The *Brucellae* colonize in different organs with predilection for lymphoreticular system. Both antibody and cell-mediated immune responses develop in most patients, but the cellular immunity is the essential component. Initially, the macrophages mediate control of infection without specific activation, but after the first 2 weeks of infection, sensitized T lymphocytes specifically activate the macrophage response. This considerably reduces the survival rate of *Brucella* organisms in the liver and spleen of most infected

individuals. The organisms evade further processing once ingested by the macrophages wherein they may find a safe harbor for replication, evading other arms of the immune response. Humoral immune mechanisms may participate in the control of acute infection, although the nature of that participation is not yet well understood. The capacity of humoral immune mechanisms to influence the course of the infectious reaction is likely limited because of the intracellular repose achieved by *Brucella* organisms. Nonetheless, the level of immunoglobulin M (IgM) antibodies begins to rise at the end of the first week of infection and usually peaks at approximately 1 month, when immunoglobulin G (IgG) antibodies begin to appear. The level of IgG antibodies often declines in the ensuing months, while IgM antibody titers may remain elevated for years. In some instances there is persistent elevation of IgG antibodies in association with chronic active infection. In other instances IgG a spike of IgG titers occurs after a phase of decline in concentration, suggesting a relapse of illness. Immunoglobulin A (IgA) antibodies are elaborated late and also may persist for very long intervals[10, 11] .

Incidence of brucellosis in Iran

Iran is an endemic area for brucellosis. In Iran 40% of the population living in villages have close contact with domestic/wild animal population owing to their occupation. The situation in Iran is improving, according to data from the National Commission on Communicable Diseases Control. In 1979 the annual incidence exceeded 38 cases per 100000; 170 in 1989 24 in 2000, 39 in 2005,in 2006 the annual incidence had fallen to 23.8 cases per 100000 and in 2009 the annual incidence arrived 24 cases per 100000 (Fig. 1). The most number of human brucellosis was recorded in 1990(Fig. 2), one of the reasons of increasing brucellosis in Iran from 1979 to 1989 was Iran-Iraq war that resulted in massive transferring of domestic animals. The other reasons were improvement of reporting system, and unsuitable vaccination of domestic animals. Recently the incidence of brucellosis has been decreased but still, human brucellosis remains a huge burden for Iran, because of traditional dairy producing, animal husbandry and incomplete vaccination problems. Traditional Ice-creams play a key role in re-emerge new brucellosis cases in Iran. In recent years the most incidence of brucellosis has been absorbed in Lourstan, Eastern Azerbaijan, Arak provinces (Fig. 3). That is because these regions are the main center of animal husbandry in Iran. Occupation distribution of human brucellosis in industrialized countries have been indicated that most of the cases occurring in the slaughterhouse workers and butchers, whereas, In Iran Frequency of human brucellosis in different occupational in 2009, indicates that housewives has higher incidence rate then others (Fig. 4).

Gender distribution of human brucellosis in 2009 have indicates that 45% and 55% cases occurring in female and male respectively(figure.5)**,** but 28% and 72% of cases have been occurring in urban and rural respectively(figure.6)**.** Age's distribution in fig.8 indicates higher incidence of brucellosis is in age group 15-24 years old. Two thirds of cases human brucellosis happing in spring and summer (Fig. 7), although human brucellosis

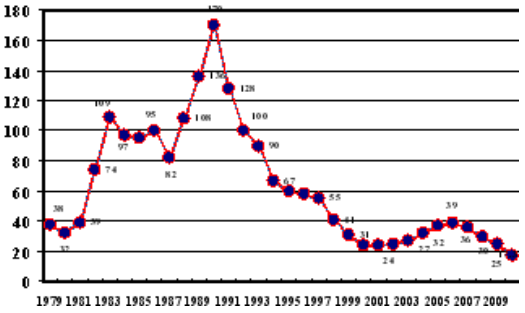

Fig. 1. Iran incidence of human brucellosis from 1979 to 2010

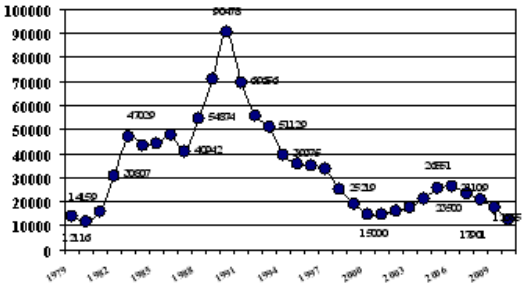

Fig. 2. Total cases of human brucellosis in Iran from 1979 to 2010, in 1979, brucellosis patients accounted for 0.0404% of the country's total population of 35 million and in 2008 they comprise 0.0255% of the country's 70 million people

affects all age groups, it is said to be rare in childhood. However, in Iran, where brucellosis is endemic, pediatric cases are seen[12, 13]. In a study Congenital brucellosis in a preterm neonate reported [14]. 75% and 25% of cases of brucellosis have been occurring through direct and indirect contact respectively (Fig. 9).

Risk factors for human brucellosis in Iran, including consumption of raw milk (94.7%), fresh cheese (100%), uncooked meat (95.1%), animal skin contact (100%), contact with placenta (27.2%) and living with animal, the existence of another infected family member, animal husbandry , laboratory worker and veterinary profession. and consumption of unpasteurized dairy products (OR=3.7, p=0.014). Keeping cattle and cattle vaccination have been reported also as important risk factors[15-17].

The prevalence of animal brucellosis in Iran reached 44% in 1956 and dropped to 5% following control program that started in 1958. Because of reluctance in control, the reactor rate increased again to 17.4% in 1977. A control program started in 1983 with consequent decrease of the prevalence to 1.25% in 1987. In 1991, the prevalence rate was 0.85%. The prevalence rate in sheep and goats was 13.7% in 1970, 6.4% in 1980 and 10.18% in 1991[18]. A positive correlation was observed between the frequency of brucellosis and density of cattle (OR=1.81, *P*= 0.007)[19]. seroprevelance of brucellosis in sheep and goat, cattle and human and the correlation between human and animal brucellosis in Birjand, a sub tropical city in east of Iran was evaluated. During 2002-2006 ,among 472106 individuals referred to health-care of Birjand and among 12113 cattle and 7199 sheep and goat that have been tested by veterinary organization of South Khorasan province, the prevalence rate of brucellosis have been reported, in Human 37/ 100,000, in sheep and goat 340/10, 000 and in cattle

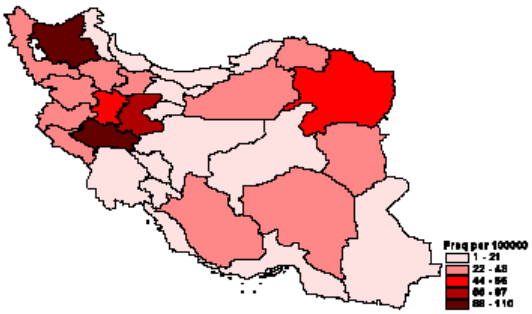

Fig. 3. Iran incidence map of human brucellosis in 2009.the provinces of Lorestan, East Azerbaijan and markazi with an annual incidence rate of 88-110 per 100,000, had the highest rate of brucellosis patients in the country in (March 2008-March 2009), and Sistan-Baluchestan Province, with an annual incidence rate of 1-21 per 100,000, had the lowest rate in (March 2008-March 2009)

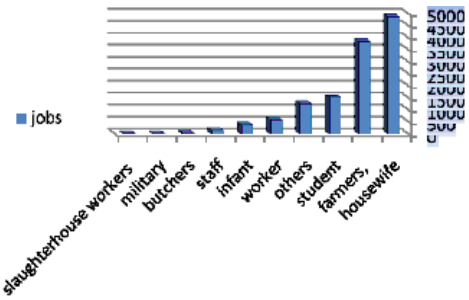

Fig. 4. Occupation distribution of human brucellosis in 2009; Human brucellosis occur in industrialized countries most in the slaughterhouse workers and butchers, wherease, In Iran Brucellosis involved most in housewife, farmers, ranchers and people who consume not pasteurized dairy products

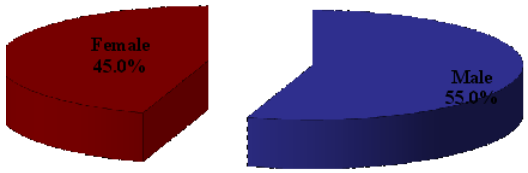

Fig. 5. Gender distribution of human brucellosis in 2009

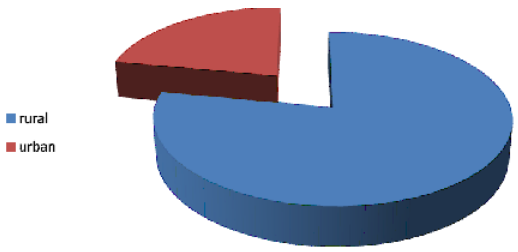

Fig. 6. Urban and rural distribution of human brucellosis in 2009

56/ 10,000. Brucellosis prevalence in cattle and buffaloes based on a survey of studies published between 2002-2006 on 12 113 animals tested in Iran by Rose Bengal plate test was 6.8% [18].

B. Global Epidemiology

Worldwide, reported incidence of human brucellosis in endemic disease areas varies widely, from <0.01 to >200 per 100,000 population. For example, Egypt, Jordan, Oman, Saudi Arabia, and Syrian Arab Republic reported a combined annual total of more than 90,000 cases of human brucellosis in 1990[4, 20]. The low incidence reported in known brucellosis-endemic areas may reflect the absence or the low levels of surveillance and reporting programs[21]. Recent re-emergence in Israel indicates the difficulty of eradicating this infection[22-24]. Sheep and goats and their products are the main sources of infection by *B. melitensis* in humans, but *B. melitensis* infection in cattle is emerging as a potential problem in some southern European countries, Israel, Kuwait, and Saudi Arabia[25-27]. *B. melitensis* infection is particularly problematic because *B. abortus* vaccines do not protect effectively against *B. melitensis* infection; the *B. melitensis*Rev1 vaccine has not been fully evaluated for use in cattle[28]. In some South American countries, particularly Brazil and Colombia *B. suis* biovar 1 has become established in cattle leading to human infections[29]. The importance of screening of household members of acute brucellosis cases in endemic areas has recently been emphasized[30, 31].

Laboratory diagnosis

Diagnostic methods for brucellosis are primarily based on serology, with the LPS smooth chains producing the greatest immunological responses in various hosts. The major diagnostic problem is due to the similarity of the O-antigenic side chain of LPS of *Brucella* and other organisms like *Yersinia enterocolitica* O : 9, *Vibrio. cholerae, Esherichia. coli* 0 : 157, and *Francisella. tularensis*. Alternative antigens have been evaluated for their diagnostic potential, for a possible improvement in its specificity, however, these have largely been unsuccessful. (Blood culture is the gold standard in the diagnosis of bacterial infections including brucellosis, but this method is successful in only 40 – 70% of the cases. The Biphasic Ruiz-Castaneda system is the traditional method for the isolation of *Brucella* sps in clinical samples[32]. It has been largely replaced by the lysis centrifugation technique, where a higher rate of positive blood culture has been reported. An automated culture system has also improved the speed of detection[33]. Bone marrow cultures may provide higher sensitivity, yield faster culture times, and may also be superior to blood culture, when evaluating patients with previous antibiotic use. *Brucella* can also be cultured from pus, tissue, cerebrospinal fluid (CSF), and pleural / joint / ascetic fluid[34].

In the absence of culture facilitates the diagnosis of brucellosis relies on agglutination tests, such as, the Rose Bengal test, serum agglutination test, the antiglobulin or Coombs test, complement fixation test, and the recently introduced immunocapture test.The Rose Bengal test is used as a screening test and positive results are confirmed by the serum agglutination tests[35-37]. This agglutination test is based on the reactivity of antibodies against the smooth lipopolysaccharide. In the Rose Bengal Plate (RBPT) agglutination test the sensitivity is high (>99%) and false negative results are rarely observed[38]. To increase the specificity the test may be applied to a serial dilution (1:2 through 1:64) of the serum samples[39, 40]. The Standard Tube Agglutination Test (SAT) developed by Wright and colleagues remains the most popular and easy test to perform[41]. SAT can measure the total quantity of the agglutinating antibodies (IgG and IgM)[42]. The quantity of specific IgG is determined by treatment of the serum with 0.005M 2 mercaptoethanol (2ME), which inactivates the agglutinability of the IgM[43,44]. However, many patients have low levels of agglutinating IgG antibodies and the results can easily be misinterpreted[45]. SAT titers above 1:160 are considered diagnostic in conjunction with a compatible clinical presentation, however, in endemic areas the titer of 1:320 is taken as the cut off[46]. Coomb's test is the most suitable and sensitive test for confirmation in relapsing patients with persisting disease, but it is complex and demands technique. Enzyme linked immunosorbant assay (ELISA) has become increasingly popular, as well as a standardized assay for brucellosis. It measures IgG, IgM, and IgA, which allows a better interpretation of the clinical situation. The specificity of ELISA, however, seems to be less

than the agglutination tests. As the diagnosis of *Brucella* is based on the detection of antibodies against smooth LPS, the cut-off value needs to be adjusted, to optimize the specificity when used in endemic areas[47-49]. ELISA can also be applied in the diagnosis of CNS brucellosis with varying success and further research must be aimed at improving the diagnosis of this condition[50, 51]. The Fluorescence polarization assay (FPA) offers a valuable alternative to conventional serological tests[52,53]. This assay measures the size of a florescent tagged molecule such as an antigen ideally antigens selected for this technique should be small (20 Kda). The utilization of the O-side chain of LPS from *Brucella* spp has shown encouraging results[54]. The sensitivity of this test at the selected cut-off value is 96% for culture-confirmed brucellosis and the specificity is 98%[32].

Immunochromatographic *Brucella* IgM / IgG lateral flow assay (LFA), a simplified version of ELISA has a great potential as a rapid point-of-care assay. Studies have shown that this test has high sensitivity and specificity for *Brucella* IgM and IgG. This system uses a drop of blood obtained by a finger prick, which is used by the bedside and easy to interpret. It is a rapid and simple diagnostic test for confirmation of brucellosis in an endemic area[55-57]. In recent years new immunocapture agglutination for anti-*Brucella* (*Brucella* Capt BCAP) has been developed, to detect agglutinating and non-agglutinating antibodies with high sensitivity. It has been suggested as a possible substitute for Coombs test and a better marker for disease activity[58-62].

Compare ELISA and STA tests in diagnosis of Brucellosis, Indicated the STA (Standard Tube Agglutination) is a widely applied test, it cannot differentiate acute and chronic states of brucellosis, and suggested that IgG ELISA may be a suitable test for diagnosis and follow up of brucellosis[63, 64]. The Specific antibody level of hospitalized patients in Hamadan, Western Iran, showed the Wright test was higher than 1/160 in 49.31% of patients, while it was 43.46% in patients with antibody titer higher than 1/80 of 2ME test. This indicated some of those serology negative patients may involve with brucellosis and possibility of infection should be always considered in that serology negative patients since *B. abortus* antigen are applied in all serology tests. We can use Coombs test for clear understanding those cases with low antibody rises[65]. Direct

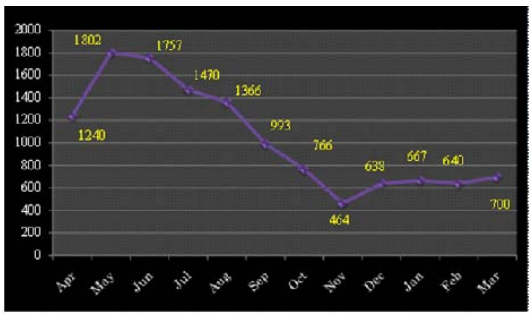

Fig. 7. Seasonal distribution of brucellosis cases (2009)

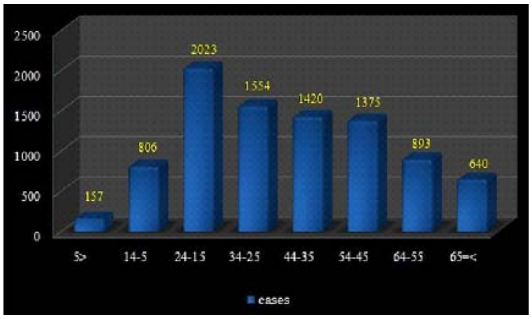

Fig. 8. Cases of brucellosis by age groups (2009)

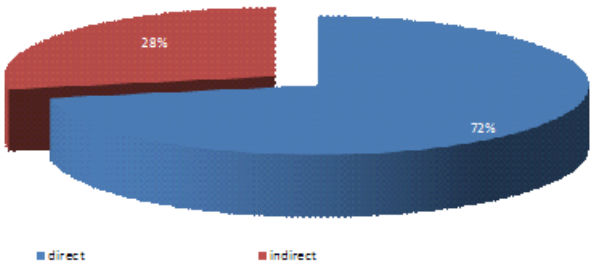

Fig. 9. Percent of cases of brucellosis through direct and indirect contact (2009)

urease test and acridine orange staining on bactec blood culture for rapid presumptive diagnosis of brucellosis in 102 seropositive patients indicates In the forty one blood cultures positive for *Brucella*, coccobacilli were seen in broth smears stained with acridine orange stain, and also were urease test positive, thus providing presumptive identification of *Brucella* growth. Urease test was negative and bacteria were not seen in the broth smears of the remaining 61 broths negative for *Brucella* growth. Because of simplicity, reliability and reproducibility, these tests can be routinely incorporated in the laboratory for diagnosis of brucellosis[66].

Complications

Brucellosis can affect almost any part of body, including r reproductive system, liver, heart and central nervous system. Chronic brucellosis may cause complications in just one organ or throughout body. Complications can be very diverse depending on the specific site of infection. Kidney, arthritis, meningitis, pancytopenia and diffuse maculopapular rash during the course of Brucella, neurobrucellosis, Brucellar epididymo-orchitis and congenital brucellosis are complication of Brucellosis in Iran[67]. Ghanei *et al*, reported a case of Brucellosis with involving Kidney , they concluded acute *Brucella* infection should be considered in the differential diagnosis of acute kidney failure when accompanied by symptoms such as arthritis, particularly in areas where brucellosis is endemic[68].

Prevalence of neurobrocellosis in patients with brucellosis in Hamedan (west of Iran) was 1.45% mainly with meningitis (acute and subacute) manifestation[69]. Hossein Hatami *et al*, *studied* epidemiological, clinical, and laboratory features of brucellar meningitis. They found that the average age was 26.9. 64% were female and 36% were male. There were 25% cornered cases in the spring, 21% in summer, 33% in autumn and 21% in winter. Patient complaints in order of frequency were: headache (95%), vomiting (77%), fatigue (39%), myalgia (15%), movement disorders (15%), arthralgia (13%), sleepiness (13%), and aphasia (3%). The main clinical findings were: nuchal rigidity (74%), splenomegaly (49%), fever (41%), Kernig's (41%), and Brudzinski's signs (39%). Lukopenia (WBC<4.5×109/L; 18%), leukocytosis (WBC>9.5×109/L; 20%), and anemia (hemoglobin level<13 g/dL in men and 12 g/dL in women) were detected in 16% of patients. The Wright agglutination test, with a titer of 1:80 to 1:1280 was present in the serum of all patients, CSF Wright test or Coombs test was positive in half of the patients. Blood, bone marrow and CSF cultures were positive in 6 out of 10 patients. They concluded the epidemiological aspects of brucellar meningitis are similar to systemic brucellosis and, in most studies; there is no significant difference between them. The sex distribution of patients was different from most studies. Seasonal distribution of the disease did not follow seasonal distribution of systemic brucellosis[70]. Pancytopenia and diffuse maculopapular rash during the course of Brucella infection was reported[71].

Ghaffarpour *et al.,* in 2006 evaluated clinical, epidemiological and paraclinical aspects of brucellosis with and without neurological manifestations. They detected that the constitutional manifestations of the disease were more common in patients with neurobrucellosis exception headache, which was more (73% vs. 33%) and arthralgia which was more frequently in cases with brucellosis than neurobrucellosis (53% vs. 13%). Less common neurological presentations, in decreasing order of frequency were ophthalmoplegia, papilledema and seizures (each in 26.7% of cases), spastic weakness of limbs (20%), hearing loss (13.3%) and spinal epidural abscess (6.7%). Two of our patients with neurobrucellosis had negative serum and CSF agglutinin test, in whom diagnosis was made by blood and CSF cultures in patients with neurobrucellosis, MRI of brain and spinal cord showed abnormalities in 5/15(33.3%) of cases[70,72-73]. However, the disease should be ruled out in all patients who develop unexplained neurological symptoms[74].

In a study in north of Iran an unusual complication of disease, epididymoorchitis occurred in 11.1% of male patients with brucellosis, the mean age of the patients was 35.5+/-15.9 years. 26 (49.1%) subjects had orchitis. Scrotal pain and swelling, fever, sweating, and arthralgia or arthritis occurred in 53 (100%), 43 (84.3%), 40 (78.4%) and 25 (47.1%) cases, respectively. All of the patients had standard tube agglutination titers e" 1:160 and those of 2ME > 1:80. The most notable ultrasonographic finding was an enlarged and

heterogeneous epididymis, predominantly the body and tail. Testicular involvement consisted of a diffusely hypoechoic testis or focal intratesticular areas,with 86.4% of patients had unilateral testicular involvement. All of cases had testicular involvement, and in 40.1% this was accompanied by epididymal involvement. Abscess formation was also observed in five patients (16.7%)[75].

Esmailpour reported between April 1998 and March 2006, patients with Brucella endocarditis involved the aortic valve (66.6%), the mitral valve (22.2%) and the aortic valve plus the mitral valve (11.1%)[76]. Soudbakhsh A, *et al.,* reported a rare case of brucellosis presenting with pleural and pericardial effusions in a 35 year-old male rancher[77]. Azizi *et al.,* reported a Brucella infection of the thyroid gland[78].Chest wall involvement as a manifestation of Brucellosis was seen, in endemic areas can be misdiagnosed with tuberculosis[79]. in the endemic areas, brucellosis should be considered in the differential diagnosis of patients who present with any type of rheumatologic manifestations[80].

In endemic areas clinicians should consider brucellosis in any unusual presentation involving multiple organ systems, even if serology is inconclusive. In endemic areas low STAT and 2-ME titers should be considered as an indication of brucellosis and in these cases additional testing is recommended to rule out brucellosis[1]. Main manifestation of brucellosis in childhood in iran is arthritis such as monoarthritis (with involvement of the knee, hip, ankle and Sacroilitis,) and polyarthritis. Therefore all physicians who work in endemic areas should consider the possibility of brucellosis in all children who present with arthritis and arthralgia[12, 13, 81].

Treatment

Treatment for brucellosis aims to relieve symptoms, prevent a relapse of the disease and avoid complications. We'll need to take antibiotics for at least six weeks, and our symptoms may not go away completely for several months. The disease can also return and may become chronic. Traditional therapy is using doxycycline for 45 days plus streptomycin for 14 days. In a randomized clinical trial the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks versus streptomycin for 2 weeks plus doxycycline for 45 days in the treatment of human brucellosis was compared. The efficacy with the gentamicin/doxycycline regimen was 95.12% and that with the streptomycin/ doxycycline regimen was 89% [82].

Hasanjani Roushan *et al* indicated, Streptomycin for 14 days and doxycycline plus Rifampicillin for four months is a better regimen for therapy of brucellar spondylitis[83].

In Ahvaz (southwestern Iran), Alavi *et al.,* indicated the co-trimoxazole plus doxycycline (CD) regimen has a better therapeutic effect than doxycycline plus rifampicin regimen[84]. Doxycycline plus rifampin (DR) in the treatment of brucellosis is still the first choice regimen and CR or CD may be used as alternatives for treatment of brucellosis in adults[85]. Fortunately, since brucella genus is susceptible to common antibiotics that used for brucellosis therapy, in the world and in Iran were not any reports about drug resistance brucella spp.

Prevention

Prevention of human brucellosis is dependent on control of the disease in domestic livestock mainly by mass vaccination[86]. In many countries, the use of *B.abortus* strain vaccine in cattle and *B.melitensis* strain Rev1vaccine in goats and sheep has resulted in the elimination or near-elimination of brucellosis in these animals. A plan for the control of bovine brucellosis has already been developed in India[87]. Brucellosis transmitted from small ruminants poses a significant health risk factor; efforts are urgently required to control brucellosis in goats and sheep also. Since the treatment of animal brucellosis is very expensive, one should encourage the mass vaccination of livestock. Animal owners should be taught about the importance of vaccination of their animals. In spite of the clinical efficacy and cost effectiveness of vaccination, the lack of awareness have led to the persistence of brucellosis in most areas especially Iran. Vaccination now has only a small role in the prevention of human disease, although in the past, various preparations have been used, including the live attenuated *B. abortus* strains 19-BA and 104M (used mainly in the former Soviet Union and China), the phenolinsoluble peptidoglycan vaccine (formerly available in France), and the polysaccharideproteinvaccine (used in Russia). All had limited efficacy and in the cases of live vaccines, were associated with potentially serious reactogenicity. Subunit vaccines against brucellosis are still of interest[20,

[25]. The live vaccines have provoked unacceptable reactions in individuals sensitized by previous exposure to *Brucella* or if inadvertently administered by subcutaneous rather than percutaneous injection. This has led to screening and slaughtering of infected animals causing economic burden. The lack of human vaccines and effective control measures make it necessary for the doctors and other health care workers to take protective measures. Protective clothing / barriers while handling still births / products of conception and cultures can reduce occupation-related brucellosis[88]. finally to reduce the risk of getting brucellosis, take precautions including: Avoid unpasteurized dairy foods, Cook meat thoroughly, Wear gloves (Veterinarians, farmers, hunters and slaughterhouse workers), Take safety precautions in high-risk workplaces, vaccinate domestic animals, and public health education about the disease and its risk factors, good administrative arrangement and ensuring the maximum cooperation of the community, particularly between health and veterinary authorities.

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