RESEARCH PAPER

Establishment of brucellosis relapse and complications registry: a study protocol

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Keywords

Brucellosis • Relapse • Complication • Registry • Developing countries

Summary

Brucellosis is an endemic bacterial zoonotic disease in developing countries; that is a serious public health problem in Iran. Brucellosis is a life-threatening multi-system disease in human with different clinical manifestations, complications and relapse. The incidence of brucellosis in Hamadan province, west of Iran is high. In addition, there is few reliable and population-based studies regarding relapse and complications of brucellosis in developing countries, therefore establishment of the registry system in areas with adequate occurrence of cases is needed to better understand the predictors of brucellosis relapse and complications and management of the disease. Detecting occurrence of relapse and complications over time and by geographical area provide information for further investigations and identification of health system deficiencies in the management of patients.

IMPACTS

- There is limited data on brucellosis patients with history of relapse or complications in endemic countries of brucellosis.
- Diseases registries like Brucellosis Relapse and Complications Registry can be used to perform epidemiological studies to identify the main risk factors as well as clinical research.
- Registration the occurrence of relapse and complication among brucellosis patients provides information for better management of patients.

Introduction

Brucellosis is a zoonotic bacterial disease, which can cause of significant economic losses due to the livestock abortion, and also because of its burden and complications in human, especially in developing countries, considered as a big concern for public health and international trade [1].

True incidence of brucellosis in livestock may be 10-20 times higher than the reported figures [2]. Brucellosis in humans can cause a wide range of clinical manifestations (fever, chillness, myalgia, arthralgia, night sweating, fatigue, weight loss, etc) with various organ involvements. Brucellosis can present in acute, subacute and chronic forms and it causes serious complications such as endocarditis or neurobrucellosis. The disease has the ability to relapse, and in 5 to 15% of cases, even with treatment, relapse is seen. Mortality is reported less than 1% of patients with brucellosis (Harrison 2019 and Mandell 2020) [2, 3].

Nearly half of the countries with the highest incidence rate for human brucellosis including Iran are located in the Middle East region [4]. Despite the preventive efforts by the health authorities, Iran is still one of the endemic countries for the disease. Results of the meta-analysis study showed that the highest incidences of brucellosis are occurred in west and northwest parts of Iran [5].

Hamadan province is located in the west of Iran. This province is known as one of the hubs of animal husbandry in the country, so that the production of livestock during 2016 in Hamadan was 598,000 tons, the province is ranked the first in the Western part and 9th throughout the country in terms of animal husbandry and livestock [6]. Hamadan has always been one of the provinces with high incidence of brucellosis in the country [7] with 7,318 brucellosis cases from 2009 to 2015 [8].

Despite the introduce and use of standard therapeutic options for brucellosis [9] a proportion of patients are encountered with failure in treatment, relapses and complications [10]. Results of a local study in Hamadan province declared that the rate of relapse among brucellosis patients was 6.45% [8]. The evidence regarding risk factors for relapse are rare. Host characteristics like advanced age, immunity status, severity of infection, and treatment delays are mentioned as the potential risk factors of relapse [8, 10].

Until now no data have been published on the epidemiology of relapse and complications of brucellosis in Iran with a valid and reliable data. A

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published similar study in west of Iran has used data from national notification brucellosis surveillance system to address baseline characteristics of brucellosis patients with potential complications [8]. Therefore, robust longitudinal data are needed to better understand the predictors of brucellosis relapse and complications and management of disease. This study aims to describe the protocol of Brucellosis Relapse and Complications Registry in Hamadan province, west of Iran

The objectives of the registry

Identification of the potential risk factors for relapse and complications of brucellosis is essential to provide a comprehensive understanding of the nature of the disease. Considering the limited conducted studies regarding brucellosis relapse and complications as an endemic country for brucellosis and paucity of information, the need to achieve a valid and reliable data with considerable sample size is necessary. The registry will provide enough motivation for researchers to do multiple researches across the fields of medical, nursing and public health.

Methodology of the registry

Study design

Brucellosis Relapse and Complications Registry is an observational and prospective study enrolling relapse and complicated cases of brucellosis. Approval from the Ethical Committee of Hamadan University of Medical Sciences was obtained (Ref. No. 16.35.1.4218). Enrollment and registration of eligible brucellosis relapse and complication cases were started from September 2015. The recruitment process in primary phase was ended in December 2019. All patients must provide written informed consent to participate in the registry.

Case definition

A case of brucellosis is define as "a patient with clinical manifestations compatible with brucellosis (fever, chillness, myalgia, weakness, night sweating, arthralgia) and Standard Tube Agglutination Test (STA) ≥ 1:80, and 2-mercaptoethanol (2ME) agglutination ≥ 40 or a positive blood culture for Brucella" [11].

Case classification

- *Confirmed case*: a clinically compatible illness with definitive laboratory evidence of Brucella infection.
- *Probable case*: a clinically compatible illness with at least one of the following: Epidemiologically linked to a confirmed human or animal brucellosis case or presumptive laboratory evidence, but without definitive laboratory evidence, of Brucella infection.
- *Suspected case*: lab results only without clinical information.
- *Relapse*: is defined as the recurrence of characteristic signs and symptoms (with positive culture or serology of brucellosis) occurring at some time after the completion of a course of treatment. Patients with relapse characteristically have objective signs of infection, such as fever, and persistently elevated titers of IgG antibodies in their serum. Most relapses occur within six months after therapy is discontinued, and relapse is not usually due to the emergence of antibiotic resistant strains, although this has been seen after monotherapy with rifampicin or streptomycin [12].
- *Complicated case* defines as a patient with symptoms of brucellosis who has at least one involved organ and has a positive serology or culture simultaneously.

Eligibility criteria

The new cases of brucellosis without any complications as well as non-native patients will be excluded from study.

Data collection procedure

The data collection procedure obviously showed in Figure 1. As shown, identified cases of relapse brucellosis or patients with complications related to brucellosis by physicians in rural or urban health centers, private clinics and hospitals in Hamadan province, using a referral form is referred to a trained infectious specialist present at Sina Hospital in official hours and Imam Khomeini Clinic in other times for final diagnosis and examination of documents.

After confirmation and meets the eligibility criteria by focal-point, completed the questionnaire for patients and finally data is entered in the software by the trained expert.

Recorded data is refined and reviewed monthly to fixing defects and avoid duplication of records. Repetitive case will be recorded as a new item in the software if they have relapse criteria or complications. Patients are actively re-examined every three months by mentioned trained infectious specialist and record the results. The incomplete questionnaires will be followed up by the relevant expert to correct the deficiencies.

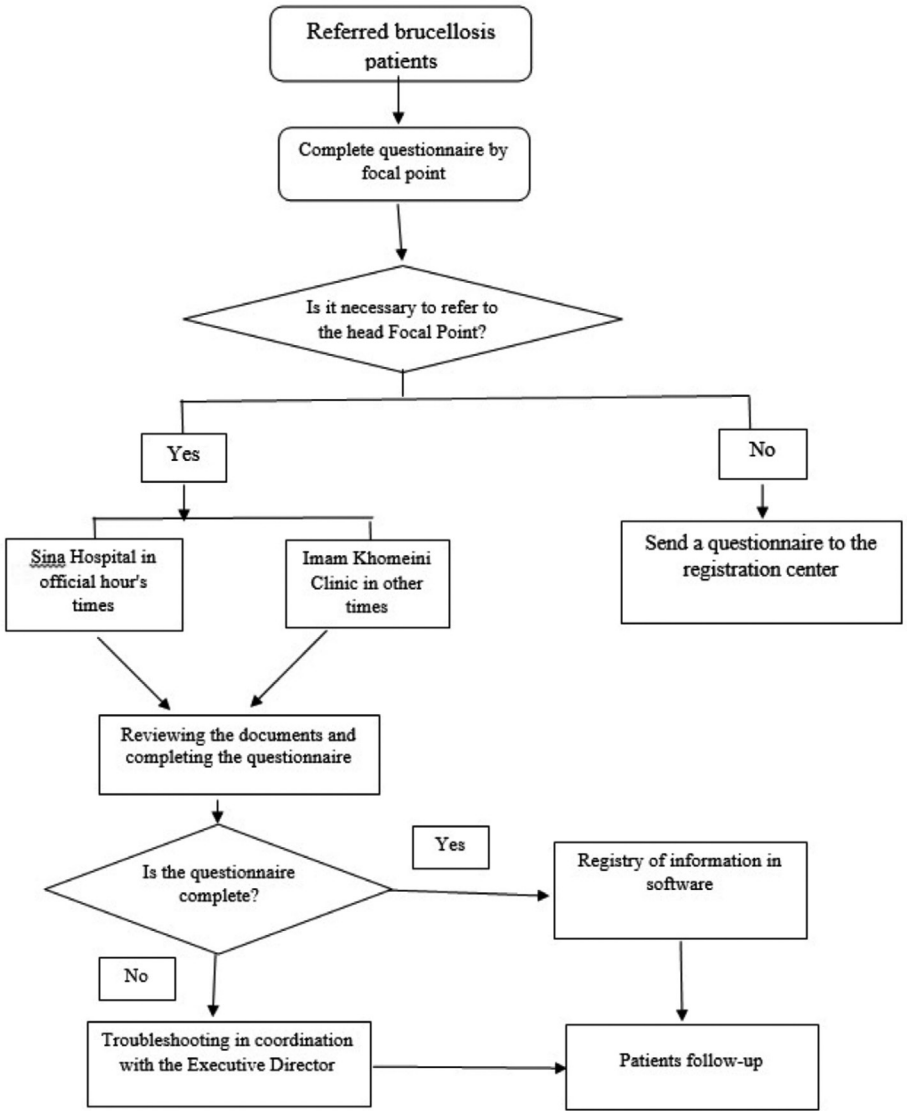
Measurement tool

A researcher- developed questionnaire is used to collect data. To ensure the validity of questionnaire, it was designed by three of researchers. Subsequently, the questionnaire is reviewed and validated by a multidisciplinary panel of experts including: principal investigator, microbiologist, health professional, epidemiologist and four infectious disease specialists. For comparability of results, we used ICD-10 codes for coding of relapse and complications. To ensure uniformity in the register by the executive director, a dictionary was provided for the questionnaire.

This questionnaire including:

1. demographic characteristics (age, sex, pregnancy status, residency, place of residency, job);

Fig. 1. Flowchart of brucellosis relapse and complications registry.



2. information regarding disease (history of disease, date of infection, treatment status);
3. risk factors of disease (Contact with domesticated animals, history of unpasteurized dairy consumption),
4. clinical symptoms (e.g. fever, chillness, weakness, fatigue, sweating, sleep disorders, weight loss, anorexia, headache, generalized body pain, lumbar pain, back pain, joint pain, abdominal pain, testicular pain, constipation, diarrhea, cough, behavioral disorders);
5. clinical signs (e.g. joint swelling, splenomegaly, vertebral tenderness, orchitis, rash, lymphadenopathy, hepatomegaly, nuchal rigidity, heart murmur);
6. complications of brucellosis including:
   - osteoarticular complications - e.g. sacroiliitis, spondylitis, peripheral arthritis, osteomyelitis, bursitis, and tenosynovitis,
   - gastrointestinal complications - e.g. nausea, vomiting, and abdominal discomfort. Rare cases of ileitis, colitis and spontaneous bacterial peritonitis have been reported,
   - hepatobiliary complications - e.g. Hepatic abscesses and chronic suppurative lesions, acute and chronic cholecystitis,
   - respiratory tract complications - e.g. hilar and paratracheal lymphadenopathy, interstitial pneumonitis, bronchopneumonia, lung nodules, pleural effusions, and empyema,
   - genitourinary complications - e.g. orchitis and epididymitis, pelvic abscesses and salpingitis,
   - pregnancy - e.g. brucellosis during the course of pregnancy carries the risk of spontaneous abortion or intrauterine transmission to the infant,
   - cardiovascular complications - e.g. infective endocarditis,
   - neurological complications - e.g. neurobrucellosis, cerebral vasculitis, mycotic aneurysms, brain and epidural abscesses, infarcts, hemorrhage, and cerebellar ataxia,

Tab. I. Steps of assessing the quality of data.

Stage	Comparability	Completeness
Questionnaire design	Using ICD-10 codes for coding of relapse and complications	Focus group discussion with infectious specialists
Questionnaire completion	Increase Kappa agreement between interviewers by holding workshop and sharing standard procedures	Holding briefings and workshops, choosing focal-point for each county, drawing patients registry software

- peripheral nerve complications include neuropathy/ radiculopathy, Guillain-Barré syndrome, and a poliomyelitis-like syndrom,
- cutaneous complications - e.g. rashes, nodules, papules, erythema nodosum, petechiae, and purpura,
- ophthalmic complications - e.g. uveitis. It can present as chronic iridocyclitis, nummular keratitis, multifocal choroiditis or optic neuritis;

7. para laboratory and imaging findings [Wright, 2ME, Coomb's Wright, Blood culture, Bone marrow aspiration culture, ESR (mm/h), CRP (qualitative), WBC (mm^3) and Hb (g/dl) , Whole body bone scan with TC 99, MRI of vertebra , Testis sonography, Abdominal sonography)].

Quality assessment

Quality assurance

In order to ensure the quality of the data, several steps were considered. Table I shows these steps.

Quality control

During the registration process, all completed questionnaires will be reviewed by the program manager. In the case of a defect, a questionnaire will be sent to the relevant physician for correction, and the repeated questionnaires will be deleted.

To ensure proper diagnosis, the program manager will randomly review some of the referral patients' questions.

In order to ensure that data entry is adapted to the software and the questionnaire, randomly each week, a number of patients' questionnaires registered by the registration expert will be reviewed by the executive director of the program.

Coverage of registration of eligible cases will be estimated using completeness percent. Moreover, frequency distribution of registered cases among a variety of characteristics includes sex, age groups and residency areas will be estimated.

In regard of representativeness of the study population, given that the Sina Hospital is referral hospital, and because of the presence of infectious specialists in Imam Khomeini Clinic simultaneously, it seems that the registered patients in this system represent all patients with relapse and complications of brucellosis in Hamadan province.

Ethical considerations

The study protocol has been approved by Ethics Committee of Hamadan University of Medical Sciences was obtained (Ref. No: 16.35.1.4218). Entry to the study will be voluntary. Prior to registration, about the confidentiality of information, planning the registry, the purpose of the project, the non-interference of the registration process with the treatment process will be explained for patients.

Discussion

Registries are powerful instruments to support health care and research, and usually made on data collected from events or outcomes interested for specialists in daily healthcare and cannot be achieved in another way [13].

Brucellosis Relapse and Complications Registry is the first registry regarding brucellosis relapse and complications in Iran. The aim of this registry is providing better understanding of the nature of the disease and effectiveness of treatments by identification of potential risk factors for relapse and complications of brucellosis. As we know brucellosis a rare disease in advanced countries with eradication programs [14]. For example in France, from 2004 to 2013 according human brucellosis surveillance a total of 250 brucellosis cases was notified (0.3 cases per million) [15]. But in Iran, the situation is different, so that in Hamadan province (2.4% of the country's population) the number of 7,318 brucellosis cases was notified in a seven year period [8].

Vast majority of studies in the field of brucellosis in developed countries is restricted to case reports or case series studies, because the number of patients in these countries is not considerable, in other words, brucellosis is not the problem of those countries. In limited studies conducted in the country [8 16], the results are based national modifiable surveillance system data, which are not collected for research purposes and are based on the passive surveillance. The generalizability results of other studies because of their low sample size or restricted study area are also low [2, 3, 17]. Given the same situation in other endemic brucellosis countries, establishment of relapse and complications of brucellosis registry is essential in endemic areas.

Conclusions

Developing Brucellosis Relapse and Complications Registry in endemic countries with adequate occurrence of relapse and complications is essential. Outputs of these registries can be used to perform epidemiological studies to identify the main risk factors as well as clinical research. Detecting occurrence of relapse and complication over time and by geographical area provide information for further investigations and identification of health system deficiencies in the management of patients.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

FK, MM, MA and MK developed the original idea and the protocol, abstracted, and prepared the manuscript. All authors participated in the study design and read and approved the final manuscript.

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