Review

The seroprevalence rate and population genetic structure of human cystic echinococcosis in the Middle East: A systematic review and meta-analysis

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ABSTRACT

Cystic echinococcosis (CE) represents an increasing public health concern in many parts of the world, including the Middle East. The present study is the first systematic review and meta-analysis to assess the seroprevalence rate and population genetic structure of human CE in the eastern Mediterranean region. To estimate the population genetic structure, *Echinococcus* sequences of the cytochrome oxidase subunit 1 (*cox*1) gene isolated from countries from this geographical area were retrieved from the GenBank database. An electronic search for articles from 1990 until 2015 was performed using databases PubMed, ScienceDirect, and Scopus. A total of 53 articles reporting on CE seroprevalence and genotyping data met our eligibility criteria and were included in a meta-analysis. The overall CE seroprevalence rates in the general population and in individuals at high risk of infection were estimated using the random-effect model at 7.4% (95% CI = 4.8–10.6) and 10.7% (95% CI = 7.6–14.3), respectively. Risk factors including age group ($P < 0.001$), dog ownership ($P = 0.03$), residence area ($P < 0.001$), and educational level ($P = 0.04$) showed a statistically significant association with CE seroprevalence. A pairwise fixation index (*F*st), used as an estimation of gene flow, suggested a moderate level of genetic differentiation between members of the *E. granulosus* sensu stricto (G1-G3) complex from Iranian and Turkish metapopulations (*F*st = 0.171). The finding of common haplotypes may represent an ancestral transfer of alleles among populations probably during the early stages of animal domestication. The high CE seroprevalence rates found highlight the necessity of implementing appropriate public education for preventive and control strategies, particularly in individuals at high risk of infection; furthermore, our genetic findings reveal novel molecular data concerning microevolutionary events of *Echinococcus* isolates among Middle East countries.

1. Introduction

Cystic echinococcosis (CE) is one of the most important zoonotic parasitic diseases that is caused by the larval stages of the taeniid tapeworm *Echinococcus granulosus* complex, affecting humans and a variety of ungulates worldwide [1–4]. CE is transmitted between the definitive host (usually dogs or other canids) and intermediate hosts (herbivorous and omnivorous mammals) (Fig. 1). Humans act as a dead-end host, acquiring the infection after accidental ingestion of *Echinococcus* eggs, which are shed in the feces of infected canids [5–7]. Adult tapeworms develop in the small intestine of definitive hosts, while metacestodes (also called hydatid cysts) infect the internal organs, especially the liver and lungs, of the intermediate hosts [8,9]. This multi-host disease is one of the most important public health infection diseases in Middle East [7,8]. Echinococcosis is one of the leading problems not only in humans but also in traps that causes a huge
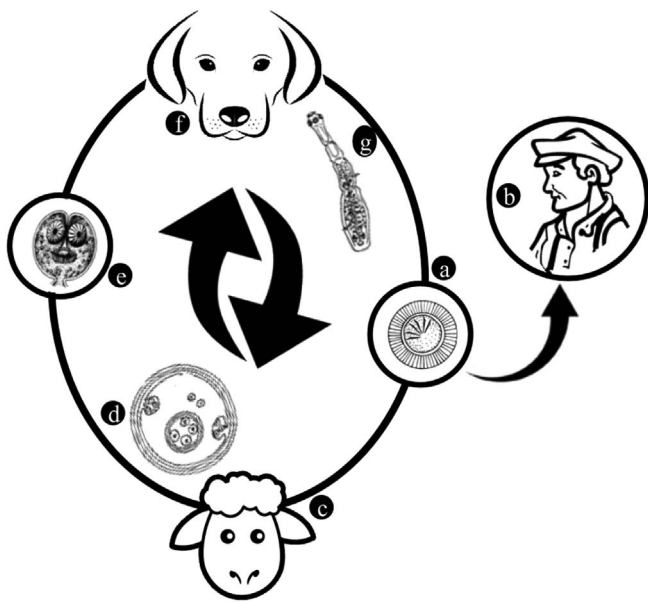
Fig. 1. The life cycle of *E. granulosus* the causative agent of cystic echinococcosis. **a:** The eggs are released from gravid proglottids and passed in the feces (infective stage for intermediate hosts), **b:** Humans can become infected accidentally (as intermediate host), **c:** Intermediate host (such as sheep, goat, swine, cattle and horses), **d:** Cystic echinococcosis, **e:** *Echinococcus* protoscolex, **f:** Dogs and other canidae (as definitive hosts), **g:** The adult worm of *E. granulosus* resides in small intestine of the definitive hosts.

economic burden for governments [8,9].

Although human CE is usually asymptomatic, a substantial number of infections cause morbidity and occasional mortality with considerable economic losses in both humans and livestock [10–14]. The disease has a worldwide distribution affecting primarily rural regions where livestock rearing is the main industry [6,15]. The common signs of CE in symptomatic cases are cough, fever, chest pain, dyspnea, abdominal masses, ascites, hepatomegaly, and splenomegaly [16,17]. Cystic lesions most frequently located in the liver followed by the lung and, less frequently, in other organs, characterize CE. The disease can be fatal if inappropriate treatment is provided. In general, surgery is the treatment of choice, followed by chemotherapy being mainly used as the recommended supplementary treatment approach [18–22].

The diagnosis of CE is primarily based on imagery and serological diagnostic methods. Both serology and ultrasound (US) are used in most of the studies. Serological assays have been recommended as first-line screening tests in endemic regions [4,23,24]. However, it should be noted that these methods might have overall reduced sensitivities when used directly in endemic communities compared with those obtained in advanced symptomatic cases. These data suggest that the prevalence of CE may be higher than shown by the results reported in endemic areas [6]. Serological techniques may deliver false-negative results due to circulating immune complexes, whereas false-positive data may be associated with cross-reactivity with other parasitic infections [25,26]. Serological methods for the detection of CE antibodies include ELISA, IHA, IFA, Indirect-ELISA, EIA, WB, Casoni test, etc. [27]. As a quantitative, inexpensive, and sensitive method, ELISA is the most commonly used serological method for CE detection in the reviewed studies.

According to the World Health Organization (WHO), human CE represents a worldwide health problem and is considered a neglected disease exerting a significant impact on the economy and social welfare of people in many countries [11,28]. The infection is endemic in the Middle East, central Asia, South America, and northern and eastern Africa [29–32].

In determining the spatial genetic structuring of *Echinococcus*, computation of gene flow index (also known as gene migration) among different endemic foci can provide valuable data concerning the

epidemiological drift of the parasite, allele frequencies, and speciation events. Furthermore, exploring genetic traits of *E. granulosus* populations may have a direct impact in control programs of the disease, particularly in aspects related with the efficacy of anti-helminthic treatments and their relationship with drug susceptibility/resistance [3]. In order to overcome knowledge gaps on human CE in the Middle East, we conducted a meta-analysis study to ascertain the current situation of CE seroprevalence and risk factors associated with the disease. In addition, a microevolutionary study of *Echinococcus* populations has been carried out among the studied CE patients. In this systematic review and meta-analysis study, we provide some insights into seroprevalence of CE in different countries of Middle East from 1990 to 2015 where no coordinated mass screenings have been performed in the past.

2. Materials and methods

2.1. Search strategy

Three publicly available databases, PubMed, ScienceDirect, and Scopus, were searched for publications in English (full texts and abstracts) associated with human CE infection, from 1990 to 2015. The search terms, used alone or in combination, were "echinococcosis", "cystic echinococcosis", "human echinococcosis", "hydatidosis", "hydatid cyst", "*Echinococcus granulosus*", "*E. granulosus*", "seroprevalence", "seroepidemiology", "prevalence", "serology", "genotyping", "genotype" and each of the Middle East countries (Bahrain, Cyprus, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates and Yemen).

2.2. Study selection

The eligibility of articles was evaluated against the inclusion criteria by two independent reviewers who are expert in CE field. Cross-sectional studies that estimated the seroprevalence of human cystic echinococcosis by any given immunological assay (e.g. ELISA, Western blot, indirect hemagglutination, or latex agglutination) in Middle East countries were selected, and independently evaluated for eligibility. The excluded articles were repetitive manuscripts, veterinary studies, non-serological studies, and studies with insufficient data.

2.3. Data extraction

Relevant sociodemographic, diagnostic, and molecular data were gathered from the selected studies and tabulated in a spreadsheet. Variables considered included first author, year of publication, country, sample size, number of seropositive cases, number of male and female participants and their test results, age distribution, serological diagnostic methods, sequenced gene and genotype assigned.

The individuals enrolled in the study were divided into two groups: (i) the general population and (ii) CE suspected and at risk individuals. The group of CE suspected and at risk, individuals included patients with suspected hydatid cyst, residents in endemic rural areas, nomadic population, and veterinary surgeons.

To evaluate the population genetic structure, the registered sequence numbers of *Echinococcus* cytochrome *c* oxidase subunit 1 (*Cox*1) gene in the GenBank database were retrieved and compared to measure the pairwise fixation index (*Fst*; F statistics) as a degree of gene flow. *F*st index was estimated by DnaSP software version 5.10.

2.4. Statistical analyses

Point estimates and their 95% confidence intervals (CI) of seroprevalence rates of all the included studies were calculated. The group-specific seroprevalence was calculated according to population groups (general; and CE suspected and at risk individuals), age group