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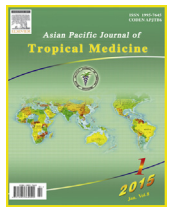

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Microsporidiosis in Iran: A systematic review and meta-analysis

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ABSTRACT

Objective: To examine all evidences about Microsporidia infection in vertebrate/invertebrate hosts and Iranian populations distributed in different regions of the country.

Methods: All published articles up to December 2015, including descriptive and cross-sectional studies related to the prevalence and genotyping of Microsporidia infection in Iran, was considered in this systematic review. The meta-analysis was done using the random-effects model and Stats Direct statistical software. MEGA 5.05 software and maximum likelihood algorithm with Kimura 2-parameter model were used for phylogenetic analysis.

Results: Of the 1152 investigated studies, 33 eligible studies reported a prevalence of Microsporidia infection in vertebrate and invertebrate hosts. According to this systematic review, the overall prevalence rate of Microsporidia infection in immunocompromised patients in Iran was 8.18%. Furthermore, the overall prevalence rate of Microsporidia infection in immunocompromised patients with chronic diarrhoea, patients with non-diarrhoea, gastroenteritis, and patients with CD4 (<200 cells/μL) was 15.4%, 4.1%, 0.5%, and 12.9% respectively. The highest prevalence rate of human and animal Microsporidia was estimated in Kerman (29%) and Khuzestan (26.5%). The overall prevalence rate of Microsporidia infection in honeybees using the random-effects model was 40%. Furthermore, the highest prevalence rate of nosemosis was described in East Azerbaijan (48.2%). The maximum number of Microsporidia isolates from immunocompromised patients and pigeons in Iran belonged to genotypes D (n = 16; 50%) and E (n = 6; 20.6%) of *Enterocytozoon bieneusi*.

Conclusions: This study may be the first systematic review and meta-analysis that provides a broad outlook on the prevalence of microsporidiosis in Iran. It is necessary to investigate Microsporidia infection in vertebrate and invertebrate hosts and environmental resources in Iran.

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1. Introduction

Microsporidia are opportunistic pathogens and parasites that infect a wide range of vertebrate and invertebrate hosts [1,2]. These obligate intracellular eukaryotes consist of more than 170 genera and 1300 species [3,4]. The life cycle of Microsporidia species that infect all major animal groups is direct and simple [2]. *Enterocytozoon bieneusi* (*E. bieneusi*) is a zoonotic pathogen and animals contribute considerably to infections found in watersheds. Owing to the unpredictably high level of infections in calves, cats, dogs, and wild mammals (beavers, foxes, otters, raccoons, and muskrats), watersheds have been considered a reservoir of human infections [5,6]. *Nosema apis* (*N. apis*) and *Nosema ceranae* (*N. ceranae*) are the two causes of nosemosis in honeybees, which reduce both the honey yield and the population of honeybees [7,8]. Microsporidia as a single-celled parasite, may cause infection in immune-competent population (travellers, persons wearing contact lenses, children, elderly, and undernourished people) and immunocompromised patients (HIV positive, organ transplant recipients, cancer patients undergoing chemotherapy) [2,9]. The prevalence rate of human microsporidiosis range is between 0% and 50%, but its prevalence in HIV positive patients lies between 1.5% and 50% depending on the geographical region [10,11]. The most prevalent signs of microsporidiosis are fever, weight loss, as well as chronic and self-limiting diarrhoea in immunocompromised and healthy people, respectively [12]. At least 15 species are recognized to be pathogenic for human including among others *E. bieneusi*, *Encephalitozoon cuniculi* (*E. cuniculi*), *Encephalitozoon intestinalis* (*E. intestinalis*) and *Encephalitozoon hellem* (*E. hellem*) [13]. *E. bieneusi* can cause infections like cholangitis, cholecystitis, malabsorption, bronchitis, rhinitis, pneumonia [14]. Disseminated microsporidiosis is caused by a number of *Encephalitozoon* species (*E. cuniculi*, *E. hellem*, and *E. intestinalis*), *Pleistophora* and *Trachipleistophora* [10]. The other species of human Microsporidia include *Vittaforma cornea*, *Nosema ocularum*, *Brachiola algerae* which lead to keratoconjunctivitis [10]. *Nosema* infections have significant effects on honeybees including dysentery, shortened life periods of honeybees, and decrease in colony size [15,16]. The most effective drugs for treating microsporidiosis in humans are albendazole and fumagillin for keratoconjunctivitis. In contrast to *E. bieneusi*, albendazole is more effective against *Encephalitozoon* species, such as *E. intestinalis* [17,18]. The diverse modes of transmission are as follows: faecal–oral or oral–oral route, inhalation or ingestion of Microsporidia spores in contaminated water or food [5]. In addition, human to human transmission is proved in some studies [5]. Risk factors related to microsporidiosis include the status of the immune system (immunosuppression), swimming in a polluted pool, eating raw meat, being stung by a bee or wasp, dealing with recreational water sources and animals (zoonotic role) [5]. The numbers of Microsporidia genotypes, based on the internal transcribed spacer (ITS) nucleotide sequence of the ribosomal RNA gene, have augmented. Formerly, over 93 *E. bieneusi* genotypes had been published in GenBank. Some genotypes are host-specific, while others may infect a range of host species. Also, genetic characterization of Microsporidia species leads to a better understanding of the route(s) of transmission and the causes involved in the transmission cycle [19,20]. Microsporidial infections in human are detected by serology, light microscopy using specific staining techniques, electron microscopy, and PCR methods [10]. To this end, this study carried out a systematic review with meta-analysis of Microsporidia studies in vertebrate and invertebrate hosts and Iranian populations distributed in different regions of the country. The present study may be the first meta-analysis that provides overall results based on available molecular and staining methods. According to this systematic review article, not only can we create awareness regarding parasite prevalence in various regions of Iran, but we will also be able to implement better preventive and treatment strategies.

2. Materials and methods

2.1. Search strategy

Pubmed, Science Direct, Scopus, Proquest, and Google scholar were used for searching English articles. SID, Magiran, Iran Medex, and Iran Doc were used for looking up articles in Persian. Both English and Persian language articles have been included in this study. After the search of the above databases, manual searches were conducted. All published articles up to December 2015 were chosen. Keywords used for searches were Microsporidiosis, Microsporidia, *Microsporidium*, Microspora, *Nosema*, *E. bieneusi*, *Encephalitozoon* spp., Iran, Human, Immunocompromised patients, Animal, Epidemiology, and Prevalence.

2.2. Study selection

The inclusion criteria were: all published articles up to December 2015, including descriptive, cross-sectional, case–control and epidemiology studies, and articles published in English and Persian. The studies with the reported overall prevalence rates for Microsporidia and Microsporidiosis were selected. Exclusion criteria were: articles that used other diagnostic methods, except staining and molecular techniques, articles written in a language other than English and Persian, unscientific publication about Microsporidia infection (abstracts, national conference proceedings) and duplicate studies with overlapping data. The suitability of all studies was considered by three different authors. Any disagreement was resolved by discussion between the authors. After the articles were selected and the decision was confirmed, the authors recorded the following information in a standard data extraction form. A flow diagram of the study design process has been shown in Figure 1.

2.3. Data extraction and analysis

After precise extraction of information, the results were categorized in a table composed of parts of province, year of publication, total individuals or participants, positive cases, gender, age, diagnostic methods, and genus of the parasite involved. Fact estimates and 95% confidence intervals (*CI*) of prevalence of all involved studies were assessed. The total prevalence and group-specific prevalence were considered by age groups (>20, <20 years), gender (male and female). A forest plot was used to show the heterogeneity among the studies. It showed proportions of individual studies and total prevalence. The statistical techniques, I^2 and Cochrane Q tests (*P*-

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