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Original Article

Multiple sclerosis among patients with previous diagnosis of leishmaniasis

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Abstract. Leishmaniasis is a protozoan parasitic disease which is caused by leishmania genus and is transmitted by sand flies. Multiple sclerosis (MS), however, is a chronic inflammatory disease of central nervous system (CNS). Since co-existence of these two diseases in an individual is rare, we aimed to evaluate prevalence of leishmaniasis among MS patients. At first, total Isfahan MS (TIMS) records of 5123 MS patients who registered in Isfahan multiple sclerosis society (IMMS) from April 2003 till July 2014 were searched in order to find cases suffering from leishmaniasis. Secondly, a comparison between the prevalence of leishmaniasis among the general population and the rate of leishmaniasis in population of MS patients was done. Among 5123 MS patients, we could find two cases (both female) with leishmaniasis and the type of leishmaniasis in both of them were cutaneous and also they had developed MS after diagnosis of cutaneous leishmaniasis (CL). Further analysis showed that CL patients have a lower risk of MS, suggesting a protective effect of CL against MS. Our data suggests that although leishmaniasis and MS may have similarities in some aspects of their pathogenesis, leishmaniasis patients have a lower risk of MS than general population.

Keywords: Multiple sclerosis, leishmaniasis, cutaneous leishmaniasis

Introduction

Leishmaniasis is a complex protozoan parasitic disease which is caused by leishmania genus and transmitted by bites of sandflies. Approximately 12 million people are affected by leishmania worldwide and 350 million people are at risk of development of leishmaniasis during their lives and also approximately 1.5-2 million new cases are added each year. Leishmaniasis is a group of diseases with different symptoms which can be divided into three types, including: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis (MCL). CL is one of the endemic diseases of Iran which is characterized with skin ulcers and is also caused mostly by leishmania major and leishmania tropica. According to the previous reports, CL is endemic in over 80 countries, but it should be considered that more than 90% of cases belong to just 8 countries including Iran, Peru, Brazil, Afghanistan, Algeria, Saudi Arabia, and Syria. In recent years, CL has emerged as a great health problem in Iran with prevalence rate of 1.8 to 37.9% in different regions throughout the country [1, 2]. On the other hand, multiple sclerosis (MS) is an autoimmune disease of central nervous system (CNS) that affects about 2.5 million individuals worldwide and has been known as the most common debilitating neurological disease in young adults. The prevalence of MS in Isfahan, central province of Iran, has been determined by Etemadifar, et al. as 73.3 per 100,000 [3]. Based on the prevalence of these two disorders, their co-existence in an individual is rare, therefore in this study we aimed to report the epidemic aspects of MS among CL patients in Isfahan province of Iran.

Materials and Methods

This retrospective population-based study was carried out in Isfahan, which is located in central part of Iran with a population of 4815863 according to the 2011 census. Inspection of cases with diagnosis of both MS and leishmaniasis was performed at Isfahan MS Society (IMSS), which is the only referral center for MS patients that provide health care, treatments and insurance support for these patients. To this date, 5123 MS patients have been registered in IMSS and were diagnosed according to the 2005 revisions of McDonald's criteria by qualified neurologists. Since during registration in IMSS the clinical history and demographic characteristics for each patient including expanded disability status scale (EDSS), age of

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TABLE 1
CLINICAL AND PARACLINICAL FEATURES OF TWO PATIENTS WITH DIAGNOSIS OF BOTH MULTIPLE SCLEROSIS AND LEISHMANIASIS

	Age	Sex	MS Type	Age at onset	Current medication	EDSS	Marital status	Location
Case 1	43	F	RR	32	Betaferon	2	Married	Isfehan
Case 2	32	F	RR	27	Fingolimod	2.5	Married	Isfehan

Abbreviations: MS: multiple sclerosis, EDSS: expanded disability status scale, RR: relapsing remitting.

TABLE 2
COMPARISON OF FREQUENCIES OF MULTIPLE SCLEROSIS IN LOW AND HIGH PREVALENT LEISHMANIASIS POPULATION BY X^2 TEST STATISTICS

	Leishmaniasis			
	Low prevalence (1.8%)		High prevalence (37.9%)	
	Present	Absent	Present	Absent
Multiple sclerosis				
Present	4724056 (99.9%)	86683 (100.0%)	2985530 (99.8%)	1825210 (99.9%)
Absent	5121 (0.1%)	2 (0.0%)	5121 (0.2%)	2 (0.0%)

onset, current medication, type of MS, first manifestation are exactly collected, thus in this study we decided to determine eligible cases using the IMSS records. At first we reviewed total Isfahan MS (TIMS) records in order to find cases with diagnosis of leishmaniasis, considering the incidence at any stage of their life span. Secondly, the issue that whether the co-occurrence of leishmaniasis and MS was only incidental or not was discussed and as a result a comparison between the prevalence of leishmaniasis among the general population and the rate of leishmaniasis in population of MS patients was performed. Protocol for this retrospective study was approved by ethnical institutional committee of Isfahan University of Medical Sciences.

For statistical analysis, SPSS software for Windows operating system (version 20.0) was used and data were reported as mean (±SD**)** and percentage of numbers. A $p<0.05$ was considered as significant.

Results

During investigation throughout TIMS records, we could find two MS patients with accompanying prior CL diagnosis. Both of our cases were female and their mean (±SD) age was 37.5±5.5. Furthermore, the mean age at the onset of MS was 29.5±6.25. These patients had developed MS within mean (±SD) duration of 8±1 years after being diagnosed with MS. Demographic characteristics and clinical features of these two cases are summarized in Table 1. Although both of them were put on betaferon treatment, after appearance of severe complication in case No. 2, betaferon treatment was replaced by fingolimod. Isfahan has been suggested as a high prevalent region of Iran with respect to leishmaniasis and since the prevalence of this infection has been reported as 1.8% to 37.9% in different provinces of Iran, we could estimate prevalence of leishmaniasis at as high as upper estimation for the country. However, we compared by χ2-statistics the prevalence of MS in the general population with the frequency of MS among an estimated population who develop leishmaniasis based on both lower and higher estimations of prevalence of leishmaniasis in the country. Both of our cases had developed leishmaniasis before the diagnosis of MS giving a frequency of 2/5123. With respect to the lower leishmaniasis prevalence estimate of Iran, patients with diagnosis of leishmaniasis may have lower risk of MS in comparison with general population ($p = 0.00$, OR = 0.02, and 95%CI = 0.005-0.085). In a similar way, analysis based on higher leishmaniasis prevalence estimate in the country, patients with leishmaniasis may have a lower susceptibility for development of MS than healthy population ($p = 0.00$, OR = 0.01, and 95%CI = 0.000-0.003). The statistical details including p-value, OR, and CI for each analysis are shown in Table 2.

Discussion

In this retrospective study, we summarized clinical and demographic features of two MS patients who suffered from CL during their life. Both patients had been diagnosed with MS after development of CL. Our data suggests a lower risk of development of MS following CL.

Association between MS and leishmaniasis has not drawn much attention until now, and to the best of our knowledge this study is the first one which investigated prevalence of leishmaniasis among MS patients, although possible linkage of other autoimmune diseases with VL has been reported in previous studies [4, 5]. In addition, some experimental studies suggested autoimmune laboratory features as a common manifestation during VL infection [6].

Among different immune cells involved in the pathogenesis of leishmaniasis, Th1 and Th2 cells and their cytokines have one of the most important roles, as induction of each of them causes different phenomena, including production of IFN-Y by Th1 cells which leads to resistance to protozoa and susceptibility to parasitic infections by Th2 cells producing IL-10 and TGF-beta,

although most of the previous studies showed presence of a mixture of Th1 and Th2 cells and cytokines in CL patients [7-9]. Similarly, role of different subsets of T cells in MS has been vastly investigated, and it has been elucidated that Th2 cytokines such as IL-4, IL-5, and IL-10 cause anti-inflammatory status and improvement of symptoms, while Th1 cytokines such INF-Y cross-inhibit Th2 cytokine production and cause inflammation which leads to disease progression [10, 11]. Taken together, these data suggest that in patients with progressive CL, Th1 cells and cytokines are dominant, so MS patients are similar with CL patients with respect to the Th1/Th2 balance, although it should be considered that in remitting CL patients' Th1/Th2 shifts to Th2 cells which may lead to reduction of inflammation in MS patients and also decrease the risk of MS among them.

IL-17 is another inflammatory cytokine which is produced by Th-17 cells and induces production of other pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α by macrophages and neutrophils and has a role in defense against protozoa and bacterial infection; though it also participates in pathogenesis of autoimmune diseases, as elevated levels of it has been shown in sera of MS patients, so it might link pathogenesis of MS with leishmaniasis [12-14].

Furthermore, investigations on CD8+ T cells have been shown that they contribute to pathogenesis of both viral and intracellular parasitic infections by two different mechanisms that include increasing cytokine production and killing virally infected cell directly in viral infection, and production of IFN-Y by CD8+ cells in parasitic infections. Taken together, it has been shown that increased level of CD8+ cells in sera of patients can be associated with progression and pathogenesis of other infections and also autoimmune diseases [15-17].

In a study that was conducted by Pourfallah et al., it has been shown that levels of iron in sera of CL patients are significantly lower than controls [18]. On the other hand, there are many evidences indicating the role of iron in pathogenesis of MS, as higher levels of iron in both sera and cerebrospinal fluid (CSF) of MS patients, and also effects of higher levels of iron on magnetic resonance imaging (MRI) of MS patients have been shown [19, 20]. Consequently, it might be possible that lower levels of iron in CL patients have a role in low rate of co-morbidity of MS with CL.

Susceptibility to CL is mostly affected by environmental factors such as exposure to sand flies and prevalence of reservoirs and vectors, and as both of our cases developed MS after being diagnosed with CL, this hypothesis that MS affecting the susceptibility to CL is far-fetched.

In summary, we found that leishmaniasis patients have a lower risk of MS suggesting a possible protective effects of CL against autoimmune diseases such MS, although it should be considered that this study is an epidemiological investigation that does not include CL patients whose condition improved before the diagnosis of MS which may lead to underestimation of the rate of CL among MS patients, ergo more experimental evidences are needed to demonstrate this association between them.

Conflict of Interest

The authors declare no conflicts of interest.

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