Dermatology Practical & Conceptual

Prevalence of Multiple Sclerosis in Vitiligo Patients and Their First-Degree Relatives: Two Diseases with Similarities in Pathogenesis and Treatment

Mohammadreza Kavyani[1,2], Vahideh Lajevardi[1,2], Maryam Ghiasi[1,2], Maryam Daneshpazhooh[1,2], Sama Heidari[1,2], Amir Teimourpour[1,2], Kamran Balighi[1,2]

1 Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran

2 Autoimmune Bullous Diseases Research Center, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Corresponding Author: Kamran Balighi, Razi hospital, Vahdat Eslami Square, Tehran, Iran. Email: Kamran.balighi@yahoo.com

ABSTRACT

Introduction: Vitiligo is a common pigmentation disorder manifested by white macules and patches. It is accompanied by some autoimmune and neurological diseases. Recently, it has been suggested that multiple sclerosis (MS) is more common in vitiligo patients and that they have a higher risk of developing MS during their lifetime.

Objectives: In this study, we aimed to determine the prevalence of MS in patients with vitiligo and their first-degree relatives and compare it with the prevalence in the population.

Methods: In this cross-sectional study, data were consecutively collected from patients referred to Razi Hospital from March 2020 to December 2021.

Results: Seven hundred and nine patients with vitiligo participated in this study, and 15 reported a history of MS (2.12%, 95% confidence interval [CI] 1.06%-3.17%). This rate was significantly higher than the prevalence of MS in the average population of Tehran ($P < 0.001$). Of the 2886 first-degree relatives of the patients, 10 had MS (0.35%, 95%CI 0.13&-0.56%), which was higher than the prevalence of MS, yet not statistically significant.

Conclusions: A significant association between vitiligo and MS was observed, which should be of clinical and therapeutic importance. However, the prevalence of MS in first-degree relatives of vitiligo patients was higher than the average rate, yet not statistically significant.

Introduction

Vitiligo is the most common chronic acquired pigmentation disorder with an autoimmune basis. It manifests as white macules and patches due to progressive loss of melanocytes in various areas [1,2]. The latest estimate of the worldwide prevalence of vitiligo varies from 0.004% to 2.28% [3]. The disease can occur at any age and in any gender, but women are more commonly treated [4].

Vitiligo has been reported to be associated with other autoimmune diseases such as autoimmune thyroid disease, alopecia areata, Addison disease, autoimmune gastritis, pernicious anemia, psoriasis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and type I diabetes mellitus. In addition, changes in the nervous system have been observed to some degree in vitiligo, such as dystrophic changes and increasing basement membrane thickness of Schwann cells in cutaneous nerves [5,6].

Some studies have shown the co-occurrence of vitiligo and multiple sclerosis (MS) [6,7]. While the main pathophysiological pathways of both diseases are different, they would have similarities in some aspects, including increased interferon-gamma, IL17, oxidative stress, and IL2RA genes [6]. In addition, genes containing HLADRB1 and HLADQB1 might be responsible for the co-occurrence of vitiligo and MS in some individuals [6,8].

Some studies have investigated the association of these two, most of which were conducted in Western countries.

Objectives

Due to the different ethnic, genetic, and environmental factors in different regions, it seems necessary to investigate this association in other areas. In the current study, we aim to report the frequency of MS in vitiligo patients and their first-degree relatives referred to Razi Hospital in Tehran, Iran.

Methods

This study was a cross-sectional study approved by Tehran University of Medical Sciences. The population of the study included vitiligo patients who were clinically reviewed by dermatologists at Razi Hospital, Tehran, Iran, between March 2020 and December 2021. Sampling was performed consecutively in the general outpatient clinic and the phototherapy department of Razi Hospital. Informed consent was obtained from all participants, data were then collected manually using a questionnaire.

We followed-up patients through telephone interviews to verify the accuracy of their information and to complete the questionnaire. Patients who did not answer the questions on MS in the questionnaire and did not respond to phone calls were excluded from the study. The questionnaire contained demographic information of the subjects, including gender, age, duration of the disease, site of the disease (face, trunk, limbs, and genitals), age at onset of the disease, number of first-degree relatives of patients (including siblings and parents), and history of MS in patients themselves and their first-degree relatives. Patients were divided into the early-onset group (≤ 12 years old) and the late-onset group (> 12 years old) according to the age of onset [1,9]. We obtained the history of MS based on self-reports and had no evidence to verify their disease.

Statistical Analysis

We used the chi-square test to compare the prevalence of MS in the population of the study with the prevalence of MS in the average population, based on the Iranian MS Society (IMSS) records, as reported by Amini et al [10]. To assess the association between MS and other variables, we used chi-square, Mann-Whitney, and Fisher Exact tests, as appropriate. P values were 2-sided, and P values of less than 0.05 were considered statistically significant. All tests were performed using R software, version 4.1.2.

Results

In this study, 709 vitiligo patients were studied over 21 months between March 2020 and December 2021. 328 (46.26%) were female and 381 (53.74%) were male. The mean age of patients was 35.06, with a range of 2-87 years (Table 1).

Among the vitiligo patients, 15 (2.12%, 95% CI:1.06%-3.17%) reported a history of MS (12 male patients and 3 female ones). Of the 2886 first-degree relatives of patients with vitiligo, 10 (0.35%, 95% CI:0.13%-0.56%) had MS (Table 2).

The most commonly affected areas with depigmented lesions were the limbs (86%) and face (74%) (Table 3). We found no significant association between the history of MS and age (P = 0.363), gender (P = 0.072), duration of disease (P = 0.320), and location of depigmented lesions (P > 0.05) in patients with vitiligo (Figures 1 and 2).

Table 1. Characteristics of patients

Age (years)	
Mean	35.06
Range	2–87
Gender	
Male, N (%)	381 (53.74)
Female, N (%)	328 (46.26)

Table 2. Frequency of multiple sclerosis in patients and their first-degree relatives

Patients	N (%)
Male	12 (1.69)
Female	3 (0.42)
Total	15 (2.12)
Patients first-degree relatives	**N (%)**
	10 (0.35)

Table 3. Frequency of multiple sclerosis by depigmented lesion location

Multiple Sclerosis, N (%)		P
No	Yes	
Face		
513 (74.03)	9 (60)	0.239
Limb		
601 (86.72)	14 (93.33)	0.706
Trunk		
408 (58.87)	8 (53.33)	0.868
Genital		
283 (40.84)	5 (33.33)	0.749

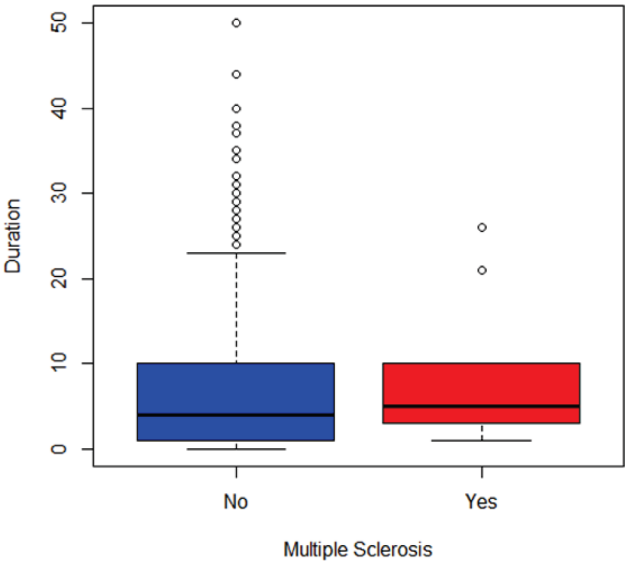

Figure 1. History of multiple sclerosis and duration (years) of vitiligo (P value = 0.320).

Of 690 patients, 144 (21%) had early-onset and 546 (79%) had late-onset vitiligo disease. The prevalence of MS was higher in the late-onset group (3.76-fold increase), but not statistically significant (P = 0.33) (Table 4). The prevalence in women in the early-onset group was higher than in men; however, in the late-onset group, the men had a higher frequency. No significant differences in age were found between men and women.

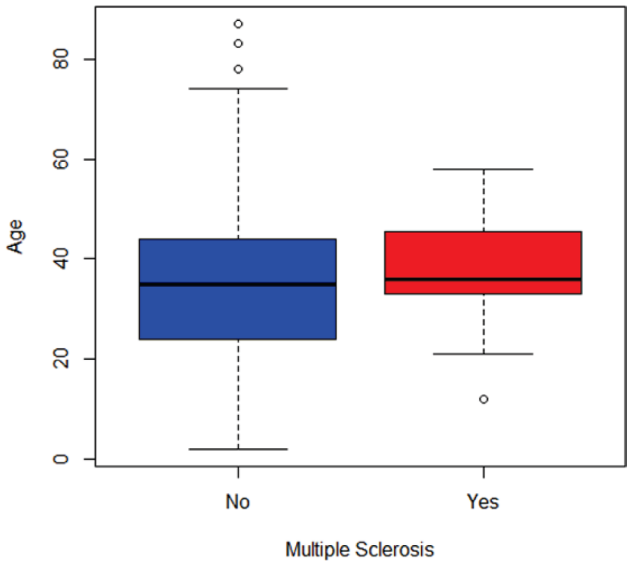

Figure 2. History of multiple sclerosis and age (years) of patients (P value = 0.363).

Table 4. Frequency of multiple sclerosis in early-onset and late-onset groups

N (%)	P-value
Early-onset	0.33
1 (0.69)	
Late-onset	
14 (2.56)	

Conclusions

Considering the convergence theory, previous publications have pursued the immunologic, genetic, biochemical, and neuronal hypotheses as etiologic factors of vitiligo [11].

Years ago, a link between neural and melanocytic systems was claimed. This theory was inspired by some observations, such as the dermatome-like distribution of lesions in some segmental vitiligo patients, various degrees of degeneration of dermal nerves in some patients with active vitiligo, and the origin of melanocytes and nervous system cells from the neural crest [12-14]. Some studies have suggested that neurogenic mediators such as neuropeptides and neurotransmitters play an important role in the development of cutaneous neurogenic inflammation and melanocyte destruction or inhibition of melanin synthesis. These mediators are derived from cutaneous nerve endings and regulated by descending anti-inflammatory neural pathways [12-15].

Based on a widely held belief, suffering from one autoimmune disease increases the possibility of occurring other autoimmune diseases in individuals and within families through gene polymorphism [16,17]. A combination of genetic, environmental, and random influences will presumably make synergy and a weak tolerance of the patient own tissues to

immunity, resulting in an autoimmune attack [18]. Patients with vitiligo have a higher prevalence of autoimmune diseases such as autoimmune thyroid disease, type I diabetes mellitus, pernicious anemia, RA, SLE, Addison disease, and Guillain-Barre syndrome [4]. It appears that infiltration of T-cells, including CD4+ and CD8+ T cells, plays an important role in the pathogenesis of vitiligo and MS. Besides, interferon-gamma, interferon-gamma-induced chemokines, and IL17 are also potent cytokines in the pathway of autoimmunity [18]. Another cytokine that has recently been mentioned as a common component in the pathological pathways of MS and vitiligo is IL15. IL15 plays a pro-inflammatory role, inducing demyelination and increasing IL17 production by Th cells. On the other hand, in patients with relapsing-remitting MS, the percentage of IL15 producing γδ-T cells is significantly more frequent than in normal individuals, and IL15 is upregulated during relapses [19]. In addition, IL15 is one of the most important factors in the maintenance of skin-resident memory T-cells which are implicated in the pathogenesis of vitiligo [20]. It is also strongly suggested that cellular stress (including the generation of misfolded proteins, the formation of ROS, and environmental exposures such as UV light and chemicals) is involved in the pathway of vitiligo and MS, and as previously noted, inflammation can be a consequence of cellular stress [18].

On the other hand, according to a systematic review by Marrie et al, no particular increased risk was found between MS and other autoimmune diseases, except for inflammatory bowel disease, uveitis, and pemphigoid. These diseases may be more common in MS due to a shared genetic susceptibility and environmental influences (Table 5) [21].

Vitamin D regulates melanogenesis and immune functions. The occurrence of vitiligo, like many other autoimmune conditions, including rheumatoid arthritis, diabetes mellitus, and multiple sclerosis, may be due to low vitamin D status [22,23]. Some studies have shown that a polymorphism in the vitamin D receptor (VDR) gene increases the risk of many autoimmune diseases such as Hashimoto thyroiditis, IBD, Graves disease, RA, SLE, PBC, autoimmune hepatitis, Addison disease, vitiligo, celiac disease, T1DM, and MS [17].

In the current study, 709 vitiligo patients were observed, 15 of whom (2.12%, 95% CI:1.06%-3.17%) had MS, which, according to Amini et al, was significantly higher than the mean of the Tehran MS population (0.184%) ($P < 0.001$) [10]. Our results support the hypothesis that patients with vitiligo have a higher tendency to get MS in their lifetime. However, to generalize this conclusion to the general vitiligo population, further studies need to be conducted on a larger scale. Since most of the previous studies were conducted in Western countries, it is better to conduct this research in other communities in the future. There are some studies that confirm our findings. According to Hadi et al, patients with vitiligo had a higher MS frequency than the average population (4.48-fold increase, $P < 0.001$) [7]. In some studies, vitiligo was also reported as a common comorbid disease in patients with MS [16]. However, in many studies, researchers found no significant association between vitiligo and MS [2,5,9,21,24]. A systematic review and meta-analysis conducted by Shen and colleagues found no association between MS and vitiligo [6].

Table 5. The prevalence of autoimmune comorbidities in patients with multiple sclerosis according to a review conducted by Marrie et al [21]

Autoimmune comorbid diseases	Prevalence, range (%)
Gastrointestinal	
Autoimmune hepatitis	0.06–0.2
Celiac disease	0–11.1
Inflammatory bowel disease	0.36–4.66 [a]
Primary biliary cirrhosis	0–0.12
Endocrine	
Adrenocortical insufficiency	0–0.31
Diabetes	0–9.4
Autoimmune thyroid disease	2.08–10 [a]
Eye	
uveitis	0.41–1.95 [a]
Hair and skin	
Alopecia areata	<1
Pemphigoid	0.08 [a]
Pemphigus	0.02–0.62
Psoriasis	0.39–7.74 [a]
Vitiligo	0–0.70
Connective tissue disorders	
Ankylosing spondylitis	0.12–1.98 [a]
Dermatomyositis	0.03
Polymyositis	3.33
Polymyalgia rheumatica	0.12–0.15
Rheumatoid arthritis	0.30–3.64 [a]
Sjogren syndrome	0–16.7
Systemic lupus erythematosus	0.14–2.90 [a]
Systemic sclerosis	0.06–0.85
Wegener granulomatosis	0.02–0.03
Autoimmune hematologic disorders	
Pernicious anemia	0–2.44 [a]
Autoimmune hemolytic anemia	0.02–1.11
Idiopathic thrombocytopenic purpura	0.11–0.13
Others	
Myasthenia gravis	0–0.56 [a]
Guillain-Barre syndrome	0.11–1.66 [a]

[a] Comorbidities that had more significant prevalence compared with the normal population in at least one study.

Among 2886 first-degree relatives of patients, 10 individuals (0.35%, 95% CI:0.13%-0.56%) had MS. Although this was higher than the prevalence of MS in the average population of Tehran [10], this difference was not statistically significant (P = 0.0802). Thus, it seems that the history of vitiligo in patients does not increase the risk of MS in their first-degree relatives. According to a study by al Khateeb et al, no association was observed with the frequency of MS in first-degree relatives of vitiligo patients [2].

In recent studies, MS is about three times more common in women than in men [25-27]. Interestingly, MS is about four times more common in men in our study (P < 0.001). It is also inconsistent with previous studies showing that comorbid autoimmune diseases are more common in women [7]. Although it can be suggested that male gender is a risk factor for MS in patients with vitiligo, the limited number of cases of MS prevents us from generalizing the results.

In this study, a comparison was made between patients who had both MS and vitiligo and those who had vitiligo only, and there were no associations between the history of MS and age, age of onset, duration of vitiligo, and location of the depigmented lesions. However, according to Elbuluk et al, older age, older age at onset, and longer duration of vitiligo are associated with the development of comorbid autoinflammatory diseases in patients with vitiligo [1]. According to Mokhtarpour et al, patients in the early-onset group are less likely to develop autoimmune diseases [28].

We also evaluated demographic data. Previous literature suggests that men and women are equally affected by vitiligo, with women more likely to seek treatment, probably because of the greater social impact on them [29,30]. This contrasts with our findings that men were slightly more likely to be affected, possibly because of cultural issues.

It should be mentioned that women were more likely to be affected in the early-onset group (≤ 12 years old) and men were more frequently affected in the late-onset group (> 12 years old), which is consistent with previous studies [28]. Thus, women are more likely to develop vitiligo earlier than men.

Considering the high burden of MS and its increasing prevalence worldwide, (especially in Iran), we suggest screening vitiligo patients and their first-degree relatives for early signs of MS, to detect the disease at an early stage and treat it efficiently. Conversely, we also recommend screening patients with MS to detect early signs of vitiligo as soon as possible. Because of some similarities in the pathological pathways of both diseases, such as the role of IL15, some current or future treatments of one may have beneficial effects on the other, such as targeting IL15 signaling with anti-CD 122 [20].

According to a review by Nociti et al, patients with isolated MS have a more severe course of the disease and subsequently more disability compared to MS patients with at least one autoimmune comorbidity [31]. On the other hand, according to another study, concurrent autoimmune comorbidities in MS result in lower quality of life, brain parenchymal fraction, cortical and total gray matter, and magnetization transfer ratio. Also, it is associated with a higher rate of relapses, mortality, and more physical and cognitive impairments [32]. These comorbidities can affect many aspects of an MS patient, including diagnosis (delay in diagnosis which results in higher rates of disability and relapse) and prognosis (higher mortality and lower quality of life). Moreover, the management of clinical and socioeconomic burdens will be more complex [31,33].

To optimize MS care, physicians should consider the impact of treatment models on initiating or outcomes of some comorbidities. Alemtuzumab, an anti-CD52 antibody approved d for the treatment of active relapsing-remitting multiple sclerosis (RRMS), can trigger some comorbid autoimmune diseases in almost 30% of treated patients [32]. It is been reported some MS patients develop vitiligo months after treatment with alemtuzumab [8,34]. Also, according to the study published in 2009 by Kocer et al, in which a patient presented with vitiligo after treatment of her relapsing-remitting MS with interferon (IFN) β-1a. The IFN β-1a was terminated and the vitiligo lesions improved within three months [35].

In this study, the location of the depigmented areas was not precisely determined, and these areas included only the face, trunk, limbs, and genitals, and it was not specified in detail. We had no control group, and the cases were not matched for age and gender with the average population. The insufficient sample size due to the pandemic COVID-19 was another limitation of this examination.

In conclusion, the association between vitiligo and MS appears to be significant, and some treatments may target both in the future.

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