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Original Article

Effects of thymectomy on multiple sclerosis with myasthenia gravis

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Abstract. Multiple sclerosis (MS) is the most common chronic autoimmune neuromuscular disease with prevalence rates that has increased in Iran especially in Isfahan population. In MS, there is a coordinated attack of innate and adaptive immune cell against central nervous system (CNS). Concurrence of autoimmune disorders is prevalent such as the concurrence of MS and myasthenia gravis (MG). MS could be associated with MG although they have different target organs. The aim of this study was to assess the effects of thymectomy as a proper treatment for both MS and MG. We studied patients who were referred to our MS clinic with the diagnosis of definite MS and MG made by a neurologist according to Isfahan MS Clinics, Isfahan, Iran (2010-2013). Age, sex, family and medical history, general neurologic symptoms and physical examination in all patients were recorded. We analyzed the clinical, laboratory, and brain magnetic resonance imaging (MRI) findings of the patients with MS and MG in an attempt to identify parameters involved in these diseases. We surveyed 12 patients (0.3%) out of 3920 patients who had both MS and MG. One of these patients had secondary progressive MS and the others had relapsing-remitting MS (RRMS). Five of them experienced thymectomy operation and about 4 (80%) of them completely improved after thymectomy, none of the symptoms of diseases were seen. Almost all of patients completely improved after thymus removal. We suggest thymectomy could be a valuable therapy for MS/ MG patients. However, more investigations should be done on this issue.

Keywords: Multiple sclerosis, myasthenia gravis, thymectomy

Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system (CNS) with prevalence rates that has increased in Iran especially in Isfahan population. It is the most common cause of non-traumatic disability in young adults [1]. The MS prevalence ratio of women to men has increased markedly during the last decades (2.3-3.5:1), which indicates a true increase in MS among women but not men [2, 3]. The cause of MS is not known but all evidence points to an interaction between environmental and genetic factors in the development of the disease.

The pathologic hallmark of MS consists of focal demyelinated plaques within the CNS, with variable degrees of inflammation, gliosis, and neurodegeneration. Active MS lesions show a reflective pathologic heterogeneity with four major patterns of immunopathology, suggesting that the targets of damage and mechanisms of demyelination in MS may be different in different disease subgroups [4]. Recent studies have suggested that the subarachnoid space and cortex may be initial sites and targets of the MS disease process, that inflammatory cortical demyelination is present early in MS, and that meningeal inflammation may drive cortical and white matter injury in some MS patients [5]. The mechanisms responsible for the formation of focal lesions in different patients and in different stages of the disease as well as those involved in the induction of diffuse brain damage are complex and heterogeneous [6]. This heterogeneity is reflected by different clinical manifestations of the disease, such as relapsing or progressive MS, and also explains at least in part the relation of MS to other inflammatory demyelinating diseases. Lymphocytes play a central role in the pathogenesis of MS. Both CD4+ and CD8+ T cells have been demonstrated in MS lesions, with CD4+ T cells predominating in acute lesions and CD8+ T cells being observed more frequently in chronic lesions [7]. Additionally, T cells are found in all four of the described histopathologic subtypes of MS [8, 9]. The success of several T-cell-targeted therapies in MS reinforces the importance of the role of the T cell in MS pathogenesis.

Concurrence of autoimmune disorders is prevalent, *i.e.*

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concurrence of MS and myasthenia gravis (MG). MS could be associated with MG, although they have different target organs [10].

The thymus is believed to play an important role in the pathogenesis of whose function is depressed in autoimmune diseases such as MS and MG [11]. Thymic abnormalities were first noticed at autopsies of patients with MG more than 100 years ago. An autoimmune disease like MG is mediated by antibodies against the acetylcholine receptor (AChR) of skeletal muscles [12]. Production of these antibodies in B cells is T cell dependent. T cells potentially specific for AChR are probably generated in the thymus via nontolerogenic thymopoiesis by an aberrant function of thymic epithelial cells. The pathogenetic step involves the activation of these potentially AChR-specific T cells; this activation is the trigger to develop the disease and a therapeutic target. The intra-thymic activation of AChR-specific T cells are probably limited to particular types of MG patients: those with early-onset MG in whom the thymus exhibits lymphofollicular hyperplasia (TLFH) and a few patients in whom MG is associated with a thymoma. The majority of thymomas and atrophic thymuses of patients with late-onset MG, an increasingly common condition, do not exhibit this T cell-activation process. Since the thymus is assumed to play an essential role in the pathogenesis of whose function is depressed in autoimmune diseases such as MS and MG, therefore thymectomy in humans might be act as treatment with less side effect compare to most drugs which use for very long period of life in MS/MG patients [13]. Accordingly, the aim of this study was to evaluate the effects of thymectomy on MS/MG patients in Isfahan city of Iran.

Methods

Based on a retrospective study, we studied 3920 patients who were referred to MS clinic with the diagnosis of definite MS and MG made by a neurologist according to Isfahan MS Clinics, Isfahan, Iran (2010-2013). Of these patients, concurrence of MS and MG was seen in 12 patients (0.3%). In this study, age, sex, family and medical history, general neurologic symptoms and physical examination in all patients were recorded. We analyzed the clinical, laboratory, and brain MRI findings of patients with MG and MS in an attempt to identify parameter involved and effect of thymectomy on those patients.

Statistical analyses

Data analyses were performed using SPSS software (Version 18). Results showed as mean ± standard deviation or percentages as appropriate.

Results

We surveyed 12 (0.3%) patients who had both MS and MG. The characteristics of the patients are shown in Table 1. One patient had secondary progressive MS and the others had relapsing-remitting MS. The mean age of the patients was 36±16 years, respectively. Most of the patients (83%, n=10) were women and the rests were men (17%, n=2). Family history of MS was found in only one of the patients with MS. The mean age at onset of MS was between 13-50 years. MS was the first disease in 8 (66.7%) patients and the rest had MG as the first disease. The mean period of disease was 8±3 years. Thymus hyperplasia was found in 2 patients with MS. None of those patients had hypothyroidism. In addition, magnetic resonance imaging (MRI) of the patients showed major evidence of periventricular plaques in all 12 patients. Other associated neurological disorders are shown in Table 2.

TABLE 1
SUMMARY OF CHARACTERISTICS OF PATIENTS WITH MULTIPLE SCLEROSIS (MS) AND MYASTHENIA GRAVIS (MG)

Characteristics	No. of patients	%
Gender (F/M)	10:2	83.33:16.66
Age (mean)	36±16	–
First disease	8 (MS)	66.7
	4 (MG)	33.3
Attack (last 2 years)	1	8.33
Duration of disease (mean)	8 3±3 year	–
NMO	0	0
AChR-Ab	8	66.7
RI abnormality (plaques)	5	100
Thymectomy (F/M)	5	100
Improved after thymectomy	4	80

TABLE 2
NEUROLOGIC FINDINGS IN MULTIPLE SCLEROSIS (MS) AND MYASTHENIA GRAVIS (MG) PATIENTS

Variable	MS (%)	MG (%)
Spasm	6.66	0
Paresthesia	33.33	4.76
Limbs weakness	33.33	23.80
Dysphonia	0	14.28
Dysphagis	0	9.52
Blured eye	20	0
Petosis	0	23.80
Diplopia	6.66	23.80

The surgical approach for thymectomy was used in 5 patients (41.6 %) who were all female. Of these patients, 4 (80%) were completely improved after thymectomy (Table 1). Only 2 of patients with MS had thymus hyperplasia which completely improved after thymectomy, and the rest had normal thymus. Among patients, 8 (66.6%) had circulating AChR-abs that 5 of them had MS and the rest had MG. Symptom's results showed in Table 2.

Discussion

One of the most important forms of the CNS autoimmune inflammatory diseases is MS. T cells have been at the center of research in MS immunology for a long time, and different interventions targeting them have been considered. T-cell-mediated damage may be relevant to the progressive forms of MS [14, 15]. The presence of numerous changes in T lymphocyte activity found in MS patients points to the involvement of the thymus in

multiple sclerosis. It has been proved that the thymus maintains its immunocompetence even in adulthood and that it has a role in the pathogenesis in several autoimmune diseases [16]. In exacerbations of MS there is a decrease in T suppressor lymphocytes while histological and lymphocyte subset changes have been demonstrated in the thymus of MS patients [17]. The lymphocyte response to mitogens is also suppressed in MS. Moreover, occurrence of CNS demyelinating disease in patients with myasthenia gravis is going to be increased. An increased incidence of MS has been reported in patients with MG [18].

MG involves neuromuscular junction which is mediated by AChR antibodies and are found in at least 80% of patients with MG. In comparison, in this study 66.6% of patients (MS, n=5; MG, n=3) had circulating AChR-Abs. These results in consistence with other studies showed that AChR antibodies are most patients with MG but not in all of them [12, 19, 20].

According to our results, in half of the patients with MS, thymectomy had better improvement as compared to MG patients (25%). There was no any correlation between the positive AChR-Ab and/or hyperplasia and better improvement after thymectomy in the patients. It is likely that thymectomy could decrease the activity of T-helper lymphocytes or, alternatively, it might enhance the activity of T-suppressor lymphocytes, whose function is depressed in MS. Our results showed that the effect of thymectomy were seen in RRMS, and also this study demonstrated thymectomy had improved symptoms of MG in these patients. Our results are in contrast to other study which has shown in patients who were treated with thymectomy, there was no evidence of benefit after 3 years [21]. Moreover, comparable with our study, other group of researchers [22] revealed that patients with MS showed significant improvement in total functional groups (Kurtzke scale) and pyramidal functions 1 and 2 years following thymectomy. Additionally, thymectomy was performed on 249 patients with myasthenia gravis between 1957 and 1981. During a follow-up period that ranged from 2 months to 24 years, the remission rate for the entire group was 51 percent, and an additional 36 percent had improvement [23]. One reason could be that the thymic disorganization may be due to a progressive degeneration of both epithelial cells and thymocytes. These suggest a direct involvement of the epithelial thymic cells and thymocytes in MS pathogenesis and may possibly hint the intriguing therapeutic concept of thymectomy in the management of multiple sclerosis.

In parallel with our results after thymectomy, other research demonstrated that in MG patients with an atrophic thymus, thymectomy has an effect on the number of circulating T cells, and in particular, on those T cells expressing 3A1 and OKT4 antigens. This effect may be in part mediated by changes in plasma adrenal corticosteroid levels after thymectomy or may be due to a factor produced by atrophic thymuses in MG [24]. Collectivelly, it suggests that the morphological and functional study of the thymus biopsy specimen should supply the appropriate criteria of suitability for surgical treatment. Finally, we conclude that patients with myasthenia gravis or MS with MG could benefit from thymectomy, and that the improvement persists over an extended period.

Conflict of Interest

The authors declare no conflicts of interest.

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