Journal of Neuroimmunology 298 (2016) 58–62

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Thymus involvement in myasthenia gravis: Epidemiological and clinical impacts of different self-tolerance breakdown mechanisms

Arnon Karni [a,*], Ali Asmail [a], Vivian E. Drory [c], Hadar Kolb [a], Anat Kesler [b]

[a] Neuroimmunology Clinic, Tel Aviv Sourasky Medical Center, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[b] Neuro-ophtalmology Unit of the Department of Ophthalmology, Tel Aviv Sourasky Medical Center, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[c] Neuromuscular Service of the Department of Neurology, Tel Aviv Sourasky Medical Center, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form 2 July 2016
Accepted 6 July 2016

Keywords:
Myasthenia gravis
Thymic hyperplasia
Thymoma

ABSTRACT

The reasons for the abrogation of self-immunological tolerance in patients with myasthenia gravis (MG) may be different between those with concomitant thymic hyperplasia or thymoma, and those with no evidence of thymic involvement. We conducted a retrospective observational case series study to investigate the epidemiology as well as the clinical, serologic, and electromyographic (EMG) characteristics of individuals diagnosed as having MG. We found that the average age at MG onset of patients with either thymic hyperplasia or thymoma was much younger (by ~20 years) than that of MG patients without thymic involvement. Thymic hyperplasia was more common in females than males. There were no differences in the rates of ocular MG vs. generalized MG among those three study groups. There were also no group differences in the rates of neuromuscular junction dysfunction, as observed on EMG or by the results of serology tests for acetyl choline receptor antibody. Interestingly, only patients without thymic involvement had other autoimmune diseases, and most of them were females. The patients with other coexisting autoimmune disease had a similar age at MG onset as the other patients with no thymic involvement. These results shed light on the impact of epidemiological and clinical factors that result from different mechanisms of self-immunological tolerance breakdown that occurs in MG.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease against post-synaptic components of the neuromuscular junction (NMJ) on the postsynaptic membrane of the striated skeletal muscle. The disease manifestation may include weakness of the ocular muscles that causes ptosis and/or diplopia, and of the muscle groups of the face, jaw, pharynx, larynx, neck, limbs and respiration. The weakness tends to fluctuate, and may be aggravated in response to triggers such as infections or therapy with medications, including certain antibiotics. MG is a prototypic autoimmune disease and, in the majority of the patients, it is mediated by antibodies (Ab) against the acetylcholine receptor (AChR) (Vincent & Newsom-Davis, 1985). MG is mediated in some patients by Ab against muscle-specific kinase (MuSK) that play a role in the clustering of AChRs, or by Ab against low-density lipoprotein receptor-related protein 4 (LRP4) that forms a complex with MuSK (Berrih-Aknin et al., 2014). Association of MG with agrin autoantibody and acetylcholinesterase autoantibodies were also been reported (Gasperi et al., 2014; Provenzano et al., 2010). However, the cause of the abrogation of self-tolerance to the neuromuscular junction epitopes that enables that evolvement of the disease is unclear. The thymus gland was long considered to hold the solutions for this enigma, since a high proportion of patients with MG demonstrate germinal center hyperplasia of the thymus or cortical epithelial cell thymoma (Levinson & Wheatley, 1996), and thymectomy is associated with clinical improvement, especially in young patients with thymus hyperplasia and recent disease onset (Olanow et al., 1987; Grob et al., 1987). Normally, the thymus functions in early life to prevent autoimmune disorders by its inherent role in clonal deletion by negative selection of auto-reactive T cells and by skewing the T cells' fate to become regulatory T cells in early life (Shevach, 2000; Sakaguchi et al., 1982). Thymic hyperplasia is associated with autoimmune disorders and, especially, with MG (Berrih-Aknin et al., 1987; Murakami et al., 1996).

Normally, the thymus consists of epithelial cells that form a frame that contains predominantly T lymphocytes, smaller populations of B lymphocytes and plasma cells, and scattered populations of other cells, such as neuroendocrine cells and myoid cells that express several muscle proteins, including AChR (Schluep et al., 1987). It is divided into a morphologically distinct cortex and medulla separated by a vascular cortico-medullary zone. In contrast, a hyperplastic thymus is populated with germinal centers of T and B lymphocytes in a manner that resembles those seen in lymph nodes or the spleen (Le Panse et al., 2010;

* Corresponding author at: Department of Neurology, Tel Aviv Sourasky Medical Center, 6 Weitzman St., Tel Aviv 6423906, Israel.
E-mail addresses: arnonk@tlvmc.gov.il (A. Karni), asmail.ali12@gmail.com (A. Asmail), vdrory@post.tau.ac.il (V.E. Drory), hadar.kolb@gmail.com (H. Kolb), anatk@tlvmc.gov.i (A. Kesler).

http://dx.doi.org/10.1016/j.jneuroim.2016.07.002
0165-5728/

Abdou et al., 1974). The lymphocytes of a hyperplastic thymus often produce detectable AChR Ab (Vincent et al., 1978), while, in contrast, thymoma cells do not (Newsom-Davis et al., 1987), and the production of those Ab is probably by a paraneoplastic mechanism since thymomas express the AChR epitope in many cases (Kirchner et al., 1988). Furthermore, there are lines of evidence to support the contention that there are fewer Foxp3 + T regulatory cells in a thymoma than in a normal or hyperplastic thymus (Scarpino et al., 2007). In addition, MG can emerge without associated thymic pathology due to multi-factorial genetic and environmental conditions (Thiruppathi et al., 2012a). Among the reasons for the abrogation of self-tolerance in these patients is the defected activity of peripheral T regulatory cells (Berrih-Aknin & Le Panse, 2014).

In this retrospective observational case series study, we investigated the epidemiology as well as the clinical, serologic and electromyographic (EMG) characteristics of individuals diagnosed as having MG who have coexisting thymic pathology, and compared those parameters with those of MG patients free of thymic involvement.

2. Methods

2.1. Study design and participants

We retrospectively reviewed all the files of patients diagnosed as having MG who attended the Neuro-immunology Clinic at the Tel Aviv Medical Center, Tel Aviv, Israel, from January 1, 2006 until December 31, 2014. The MG diagnosis was determined by history, physical examination, single-fiber EMG (SFEMG), repetitive stimulation EMG (RSEMG), edrophonium testing and serology of AChR Ab (cut-off: 0.5 nM) or MuSK Ab (cut-off: 0.05 nM). In addition to compatible history and physical examination findings, the diagnosis of MG was established when at least one of the three following types of tests was supportive for MG: serology, SFEMG and/or RSEMG, and edrophonium assessments, as well as when other possible diagnoses were ruled out.

The study included 131 patients diagnosed as having MG and who were evaluated for thymus involvement. All patients had either a computerized tomography (CT) scan of the chest or a magnetic resonance imaging (MRI) scan of the chest, and those with radiological evidence of thymus enlargement or a suspected thymoma underwent thymectomy.

The patients were categorized into three groups: (1) patients without evidence of thymus involvement by chest CT or MRI and no evidence of thymic pathology after thymectomy, (2) patients with thymic hyperplasia and (3) patients with thymoma. All study participants underwent serology tests for AChR Ab, and those who were negative were also tested for MusK Ab. All 131 patients underwent SFEMG and RTEMG, and 30 patients also underwent edrophonium testing of them 4 patients were seronegative and negative for SFEMG and RSEMG.

2.2. Data analyses

The study was approved by the local Helsinki Committee. The significance of differences between groups was examined by Student's *t*-test for parametric parameters and by the Chi-Square test or Fisher Exact test for non-parametric parameters. Data are presented as mean ± standard deviation for age at the time of disease onset or as the number of patients for the other studied variables. Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Rates of thymic hyperplasia and thymoma in relation to age at MG onset and gender

One-hundred and thirty-one MG patients (65 females and 66 males) were included in the study. Of them, 97 patients had no evidence of thymus involvement on chest CT or MRI and 34 had thymic pathology: 25 patients had thymic hyperplasia (19.1%) and 9 patients had thymomas (6.9%). Most of the patients with thymic pathology had a relatively young age at disease onset. Table 1 displays the age at MG onset and the gender distribution of the study participants who had hyperplasia, thymomas or no involvement of the thymus. The average ± S.D. of age of MG onset was 61.5 ± 17.6 years in the patients without evidence of thymus involvement, 42.6 ± 17.3 years for the group with thymic hyperplasia and 38.7 ± 13.7 years for the patients with thymoma. ($p < 0.001$, for each of the latter groups vs. those without thymus involvement, Fig. 1). Among the 97 patients without evidence of thymus involvement 21 (21.6%) had age of disease onset of 50 years or younger and 76 (78.4%) had age of disease onset of >50 years. While in the 25 patients with thymic hyperplasia: 19 (76%) had age of disease onset of 50 years or younger and 6 (24%) had age of >50years ($p < 0.001$). In the patients with thymoma: 7 (77.8%) had age of disease onset of 50 years or less and 2 (22.2%) had age of disease onset of >50 years ($p = 0.001$, vs. no thymus involvement) (Table 1a). Therefore, among all 47 patients with disease onset of 50 years or younger: 21 (44.7%) were without evidence

Table 1
Gender and age at myasthenia gravis onset according to thymus involvement.

Table 1

	No thymus involvement $n = 97$	Hyperplasia $n = 25$	Thymoma $n = 9$	*P*
Age at onset, years	61.5 ± 17.6	42.6 ± 17.3	38.7 ± 13.7	<0.001[a]
Age at onset ≤50 years, *n*	21 (21.6%)	19 (76.0%)	7 (77.8%)	<0.001[b]
Females:males	42:55	19:6	4:5	0.004[a]

[a] *P* value for no thymus vs. hyperplasia.
[b] *P* value for both no thymus vs. hyperplasia and no thymus vs. thymoma.

Table 1b

	Females	Males	*P*
Age at onset of MG patients, years	50.9 ± 21.6	61.6 ± 15.2	0.001
Age at onset of patients with no thymus involvement, years	58.1 ± 21.6	64.0 ± 13.6	0.105
Age at onset of patients with thymic hyperplasia, years	39.2 ± 15.3	53.5 ± 14.5	0.171
Age at onset of patients with thymoma, years	31.0 ± 13.9	44.8 ± 14.5	0.077

Values are ± standard deviation unless otherwise indicated.