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Effect of ethnic origin and gender on the clinical manifestations of myasthenia gravis among the Jewish population in Israel

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ABSTRACT

Reports on patients with myasthenia gravis (MG) of different ethnic origins demonstrated differences in weakness distribution and serological results. We studied MG characteristics in a cohort of Ashkenazi (ASH) and non-Ashkenazi (NASH) Jewish origin according to their ethnic origins and gender. The frequency of age of MG onset was distributed in a bi-modal fashion in the female patients and increased gradually over time, with a peak around 70 years of age in the male patients. Ocular MG was more frequent in males and ASH patients. Unlike previous reports, our male patients had a higher proportion of positive serum anti-acetyl choline receptor (AChR) than female patients, with no ethnic-based differences in the rates of anti-AChR or anti-muscle specific kinase. Comorbidity with another autoimmune disease was more frequent among female patients with late-onset MG and NASH patients (mainly Israel-born). Male MG patients tended to have more malignant comorbidities than female MG patients. These results demonstrate the effect of ethnicity on clinical aspects of MG within the Jewish population in Israel, and reveal novel effects of gender-associated comorbidities in patients with MG.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease that affects the post-synaptic components of the neuromuscular junction of striated skeletal muscles. The disease is mediated by antibodies (Ab) against the acetylcholine receptor (AChR) in most patients (Vincent and Newsom-Davis, 1985) and occasionally by either Ab against muscle-specific kinase (MuSK) that play a role in AChR clustering or Ab against low-density lipoprotein receptor-related protein 4 (LRP4) that forms a complex with MuSK (Berrih-Aknin et al., 2014). Antibodies against agrin may also play a role in MG and these antibodies as well as those against cortactin often occur in combination with other autoantibodies (Gasperi et al., 2014; Gallardo et al., 2014). The disease manifestations may include ocular muscle weakness that causes ptosis and/or diplopia, as well as weakness 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 (e.g., certain antibiotics). The distribution and the extent of the weakness dictate the severity of the clinical condition. Some patients have ocular weakness as the only symptom of the disease along its entire course (ocular MG, OMG), while the majority of the patients also have weakness of other muscles (generalized MG, GMG) (Drachman, 1994). MG that appears in young adulthood (early-onset MG, EOMG), with a peak age at onset between 45 and 55 years, is characterized by female predominance, and MG that appears after the age of 60 years, with a peak age at onset between 70 and 85 years (late-onset MG, LOMG), is characterized by male predominance.

Females were often reported to have a bimodal distribution in age at onset (Aarli, 2008; Alkhawajah and Oger, 2013; Zhang et al., 2007; Peragallo et al., 2016), and one report demonstrated that this also occurs in males (Hellmann et al., 2013). Patients with EOMG reportedly have a higher titer of anti-AChR, higher rates of thymic hyperplasia and lower rates of thymoma than patients with LOMG (Drachman, 1994; Murai et al., 2011; Perlo et al., 1975; Marx et al., 2013). In addition, females with EOMG were shown to have high rates of comorbidity with other autoimmune diseases (Klein et al., 2013).

Differences in MG characteristics according to ethnic or racial origin have been described in certain populations. For example, a high proportion of patients from eastern Asia have juvenile-onset MG (Carr

Abbreviations: OMG, ocular myasthenia gravis; SP, seropositive; SN, seronegative; AChR, acetyl choline receptor; MuSK, muscle-specific kinase; RSEMG, repetitive stimulation electromyography; SFEMG, single-fiber electromyography

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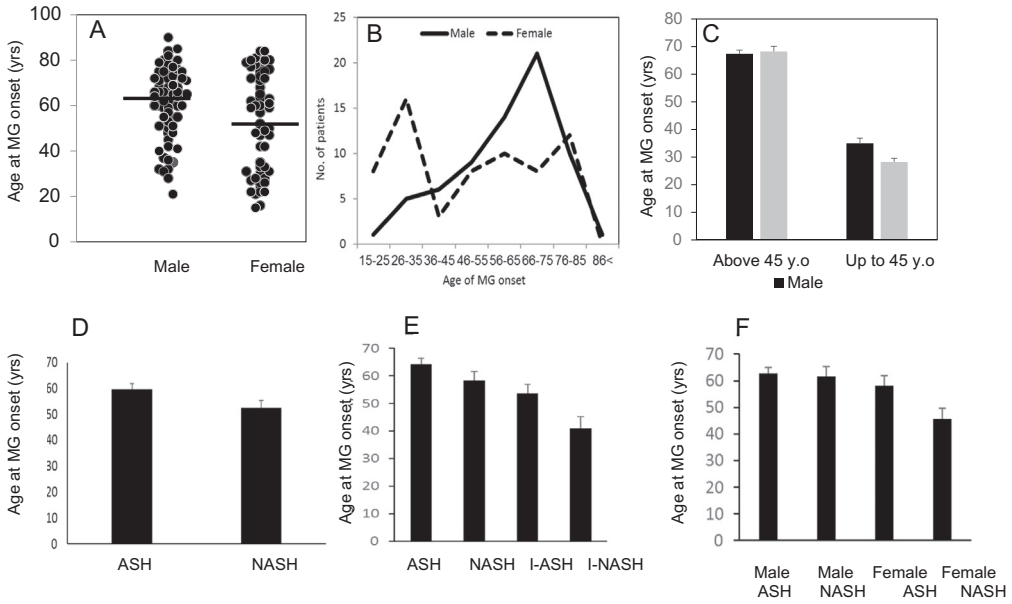

Fig. 1. A) The age of MG onset tended to be younger in female MG patients than in male MG patients. B) The distribution of age at MG onset had a bi-modal pattern in female patients, with the first period between age 15–40 years and the second period between age 45–86 years. Males had a unimodal appearance with increasing frequency with age (between ages 21–90 years), peaking at around 70 years. C) Younger age at MG onset among females vs. males is mainly among patients with early MG onset (up to 45 years old). D) Non-Ashkenazi (NASH) patients had a younger age at MG onset compared to ASH patients. E) Immigrant NASH patients were younger than immigrant ASH patients, and Israeli-born NASH patients were younger than Israeli-born Ashkenazi (I-ASH) patients. F) Female NASH patients tended to be younger than female ASH patients.

et al., 2010), and African-American patients with MG in Alabama (USA) have a higher proportion of OMG compared to GMG, lower rates of positive anti-AChR and higher rates of positive anti-MuSK compared with Caucasian MG patients (Oh et al., 2009). One study showed that the age of MG onset in Caucasians was higher than that of non-Caucasians (Peragallo et al., 2016), and another showed that female gender was more common among Hispanic, Asian, and African-American ethnicities compared to those of Caucasian ethnicity (Abukhalil et al., 2015). In certain populations, as in China, MG may appear in infancy and juvenile ages (Carr et al., 2010). One Japanese study reported that OMG is more common in LOMG (Suzuki et al., 2011), while another study reported higher bulbar weakness in patients older than 50 years (Donaldson et al., 1990).

The Jewish population in Israel is divided into two major ethnic groups: one is Ashkenazi (ASH) Jews, whose origins are in Central and Eastern Europe and considered a homogenous origin, and the other is non-Ashkenazi (NASH) Jews, whose origins are mainly in the Middle East/Asia and North Africa whose origins are diverse and due to the small sub-groups of the Middle Eastern/Asian and North-African NASH patients we did the comparison between ASH and NASH patients group as was also reported before (Karni et al., 2003). We have previously reported on the distribution of muscular weakness among the MG patients attending our clinic (Karni et al., 2016a) as well as according to thymus pathology (Karni et al., 2016b). We now report the effect of gender and ethnic origin on the clinical manifestations of MG patients among the Jewish population in Israel.

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), serology of anti-AChR Ab or anti-MuSK Ab (all done in the same laboratory), and edrophonium testing (when indicated). 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 study included 126 patients diagnosed as having MG. Sixty-five of them were males and 61 were females, 77 were of ASH origin (50 immigrants and 27 Israeli-born) and 46 were of NASH origin (29 immigrants and 17 Israeli-born). Three Jewish patients were of mixed ASH and NASH origin. We studied the effects of ethnic origin and gender on the clinical manifestations of MG and associated diseases in accordance with early or late age at MG onset. The age of the patients at EOMG onset was between 15 and 59 years and the age of the patients at LOMG onset was between 60 and 86 years.

The study was approved by the local Helsinki Committee.

2.2. Statistical analyses

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 (S.D.) for age at the time of disease onset and as the number of patients for the other studied variables. Values of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Age at MG onset according to gender and ethnic origin

One-hundred and twenty-six MG patients (61 females and 65 males) were included in the study. The age at MG onset was significantly lower in the female group (51.9 ± 22.1 years) compared to the male group (61.6 ± 15.8 years, $P = 0.007$) (Fig. 1A). These differences are attributable to the frequencies of cases with early age of onset among female vs. male and to a younger age of onset among females with early MG onset than males with MG. The distribution in age at onset among females was bi-modal and even tri-modal. The first period, which was between the ages of 15–45 years, had a peak around the age of 30 years,