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Case Report

Two sisters with anti-MuSK-positive myasthenia gravis

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1. Introduction

Myasthenia gravis (MG) is an autoimmune disorder caused by circulating antibodies against proteins of the neuromuscular junction. Although the disease is usually sporadic, 1–7% of MG patients have a close relative with MG [1]. Besides, other autoimmune diseases frequency is higher in first-degree relatives of MG patients.

Familial MG is in general associated with acetylcholine receptor antibodies (anti- AChR) whereas only few have been reported with anti-muscle specific kinase (anti-MuSK) antibodies [2–4].

Here, we present two sisters with anti-MuSK positive MG. We also examined the human leukocyte antigen (HLA) profile of the patients and their healthy relatives.

2. Case reports

2.1. Case 1

Fourteen-year-old female referred to our clinic because of dysphagia, hypophonia, and generalized weakness. The past medical history was unremarkable and there was not any consanguinity. The single fiber electromyography of frontalis muscle was compatible with neuromuscular dysfunction. Serum anti-AChR antibody was negative whereas anti- MuSK antibody titer was 2,15 nmol/L (Normal: < 0.05 mol/L, tested by RIA). Anti-thyroperoxidase and anti-thyroglobulin antibodies were negative, as were markers of systemic connective tissue disorder (RF, ANA, lupus anticoagulant, anti-dsDNA, ANCA, ENA).

Pyridostigmine up to 360 mg/day p.o. and prednisolone 1 mg/kg/day resulted in some improvement in symptoms, but a fluctuating course was observed with bulbar symptoms deteriorating every 2–3 months. These episodes did not respond to intravenous immunoglobulin (IVIg) 0.4 g/kg/day but benefited from plasma exchange. Rituximab (two times within 15 days, 500 mg) was given but stopped after 2 months due to frequent respiratory and urinary tract infections, and cyclosporine 100 mg/day was started and increased to 5–6 mg/kg/day. However, she had a myasthenic crisis in the sixth month of cyclosporine treatment. She was successfully treated with 5 sessions of plasma exchange and cyclosporine treatment was replaced with mycophenolate mofetil. She had no worsening or crisis for more than one year under mycophenolate mofetil treatment.

2.2. Case 2

The older sister of the proband, who had been living with the proband from her birth, presented with diplopia and bilateral ptosis at the age 20. Gaze palsy in the horizontal plane and right ptosis observed in the examination. Increased jitter was shown by single fiber electromyography of frontalis muscle. Anti-AChR and anti-titin antibodies were negative while anti-MuSK antibody titer was 2.12 nmol/L. Further investigations for thyroiditis, anti-thyroperoxidase and anti-thyroglobulin antibodies, symptoms or markers of systemic connective tissue disorder and vasculitis (RF, ANA, lupus anticoagulant, anti-dsDNA, ANCA, ENA) were negative. She had poor response to pyridostigmine. Methylprednisolone was started at the dose of 1 mg/kg/day, it was tapered and stopped when her symptoms improved. She remained symptom-free for 2 years after stopping methylprednisolone. Two years later she returned with dysphagia and hypophonia after a

Abbreviations: MG, myasthenia gravis; AchR, acethylcholine receptor; MuSK, muscle specific thyrosine kinase; RF, rheumatoid factor; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; ENA, extractable nuclear antigen antibodies; HLA, human leukocyte antigen; IVIg, intravenous immunoglobulin

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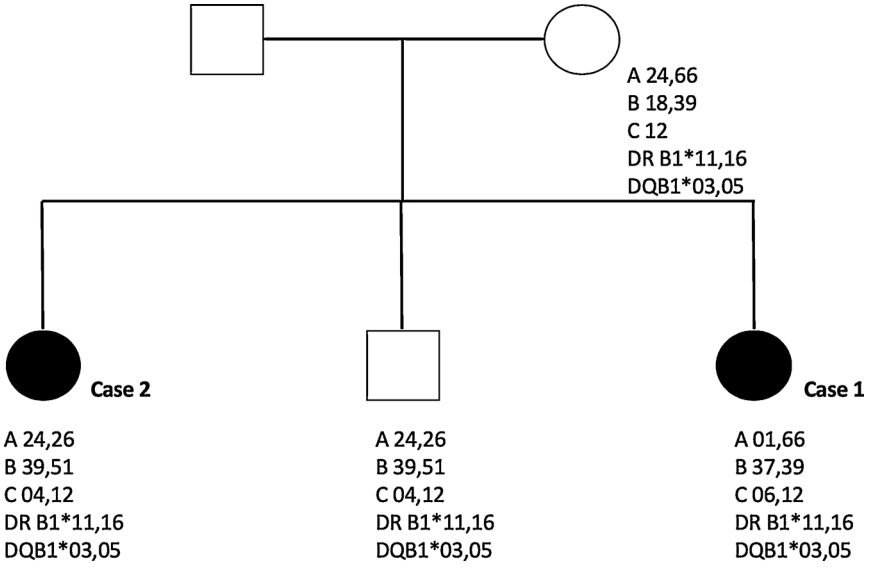

Fig. 1. The pedigree and the HLA profile of the family.

viral respiratory infection. Her neurological examination revealed facial paresis, palatal weakness and hypophonia, but no limb weakness. Intermittent intravenous immunoglobulin (IVIg) was initiated with 2 g/kg loading dose the dose followed by 0.4 g/kg/week. As the clinical improvement was not sufficient, cyclosporine was started at dose of 100 mg/day at the goal of 5 mg/kg/day. She has not experienced any worsening under cyclosporine for 2 years.

The HLA allele profile was examined in these patients, their healthy mother (39 years-old) and brother (22 years-old). Together with our two patients all are positive for HLA-DRB1*11, HLA-DRB1*16, HLA-DQB1*03, HLA-DQB1*05 (Fig. 1).

3. Discussion

Autoimmune MG is a non-inherited disease with multifactorial causes. Epidemiological studies emphasized the role of genetic factors underlying susceptibility to autoimmune MG. The human leukocyte antigen (HLA) has been described as the main genetic factor predisposing to MG. Studies examining absolute and relative distribution of HLA polymorphisms in MG patients with anti-MuSK antibody and healthy controls demonstrated strong association with HLA DQB1*05 [5] and conflicting results about DR alleles. A recent meta-analysis by Hong et al. showed an increased risk of anti-MuSK-positive MG in individuals with HLA DQB1*05, DRB1*14 and DRB1*16 [6]. Moreover, the authors suggest the higher frequency of HLA DQB1*05 in Balkan-Mediterranean population could explain higher prevalence of anti-MuSK-positive MG in Mediterranean countries. The meta-analysis also suggests that HLA DQB1*03 and DRB1*03 could be protective alleles due to their low frequency in anti-MuSK positive MG [6].

Familial autoimmune MG frequency is reported in 1–7% of MG patients, the majority being anti-AChR antibody positive [1]. We found only three autoimmune MG families with anti-MuSK antibody positivity in the English language literature [2–4]. Two siblings with anti-MuSK positivity were previously reported from Turkey [3]. Additionally, Lavrnic et al reported a mother with anti-AchR antibody positive MG and her daughter diagnosed with anti-MuSK positive MG [4]. Although previous studies suggested HLA as a genetic factor predisposing to MG, no particular HLA group was found in familial autoimmune MG patients with anti-MuSK positivity. Previous study of Alahgholi-Hajibehza et al. showed HLA-DRB1*16, -DRB1*14 and -DQB1*05 associated with anti-MuSK positive MG in Turkish population [5]. According to this Turkish cohort and the meta-analysis by Hong et al, HLA DQB1*05 and DRB1*16 could be favoring factors [4,6]. We could not find any particular HLA antigens expressed in our two patients and not their healthy relatives; a possible effect of male sex might be considered in their unaffected brother who also carries the same HLA group. Interestingly, HLA DQB1*03 which was previously reported as a protective allele is also positive in our MG patients and their healthy relatives [6]. Thus, non-HLA genes are also likely to play a role in the pathogenesis of familial MG.

4. Conclusion

Familial occurrence in anti-MuSK positive patients is rare. The HLA type has been suggested as the main genetic factor predisposing to MG. We report two sisters with anti-MuSK positive MG. The occurrence of HLA DQB1*05 and DRB1*16 could be a favoring factor in these patients.

Conflict of interest

None.

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