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Case Report

Double trouble: A case of double seropositive myasthenia gravis

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ABSTRACT

Eighty percent of patients with myasthenia gravis have acetyl choline receptor antibody (AChRAb) and 6% have antibody to muscle specific tyrosine kinase (MuSK). MuSK myasthenia is characterised by prominent bulbar muscle involvement, rapid progression to myasthenic crisis, poor response to acetylcholinesterase inhibitors (ACEI), intravenous immunoglobulin, standard immunosuppressant therapies and thymectomy. Presence of both AChRAb and MuSK antibody in same patient is a rare occurrence-Double Sero Positive Myasthenia Gravis (DSP-MG). DSP-MG has a variable prognosis as some patients behave like AChRAb MG while rest behave like MuSK MG. Here we describe a patient with DSP-MG who presented with generalized myasthenia gravis who responded to ACEI.

1. Introduction

Around 20% of generalised myasthenia gravis (MG) are acetyl choline receptor antibody (AChRAb) negative. Around 20-40% of these seronegative myasthenia gravis (SNMG) patients have antibodies to muscle specific tyrosine kinase (MuSK).[1] Other antibodies rarely associated with MG are antibodies to low density lipoprotein receptor related protein 4 (LRP4), agrin, titin, cortactin, collagen Q, Kv1.4, Ryanodine receptor and rapsyn.[2] Presence of both AChRAb and MuSK antibody in same patient is a rare occurrence-Double Sero Positive Myasthenia Gravis (DSP-MG). Detection of MuSK antibody is important as prognosis is variable compared to classical MG.

2. Case Report

A 30-year-old psychologist from Kerala reported right sided weakness for the last 3 days. She had buckling of right knee once while coming back from the restroom. She also reported right upper limb weakness in the form of difficulty in brushing teeth. Her upper limb gets fatigued easily and had to use her left hand to complete her brushing. No history of slipping of chappals, dysphagia, dysarthria or diplopia. She used to get recurrent urinary tract infections for the last one year. She reported that whenever she takes antibiotics, she feels weak for some days. Also, she noticed that she feels weak during perimenstrual period. During these periods of weakness, she has noticed mild drooping of right eyelid. Prior to her presentation to our hospital, she had a course of ciprofloxacin for urinary infection. She has a history of congenital nonprogressive right eye elevation defect.

On examination she had fatigable ptosis of right eye, right eye elevation deficit (congenital), neck flexion

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Table 1: Repetitive nerve stimulation study at 3hz from right ulnar nerve

Trace	Amplitude mV					Decrement %				
	PRE EX	POST 0'	POST1'	POST3'	POST5'	PREX	POST0'	POST1'	POST3'	POST5'
1	21.2	20.1	19.3	19	19.5	0	0	0	0	0
2	20	17	18.7	18.8	18.6	-5.6	-11.3	-2.9	-4.8	-4.4
3	17.1	16.6	17	17.2	16.4	-19.3	-17.4	-11.7	-12.8	-15.8
4	14.9	16	15.2	15.9	15.2	-29.9	-20.3	-21.2	-19.8	-21.8
5	14.3	15.7	15.3	15.9	15.2	-32.5	-21.8	-20.9	-19.7	-22.6

Table 2: Comparison of AChR Ab positive MG and MuSK MG

Clinical Features	AChR-MG	MuSK-MG
Pattern of muscle weakness	Limb>bulbar, Neck extensor>neck flexor, Ptosis and external ocular muscle weakness often conspicuous	Bulbar>limb weakness, Neck flexor>neck extensor, Ptosis and external ocular muscle weakness usually mild
Muscle wasting	Loss of proximal limb and ocular muscles only in long-standing disease ('myasthenic myopathy')	Early wasting of facial and tongue muscles common
Thymus pathology	65% thymic hyperplasia; 15% thymoma	10% thymic hyperplasia
Risk of recurrent crisis	Low	High
Thymectomy	Effective in early (<65yrs)	No clear benefit, may cause worsening
Immunoglobulin subclass	IgG1, IgG3	IgG4
Treatment of crisis	IVIG or PLEX	PLEX preferred
Response to ACEI	Usually, positive response	Worsening of symptoms in 5-20%
Low Hertz Repetitive Nerve Stimulation	U pattern decrement	Steady decrement, R-CMAP may be present.

weakness, proximal and distal weakness of both upper limbs and proximal muscle weakness of both lower limbs. Upper limb weakness was slightly asymmetrical with more weakness on right side. There was no atrophy of tongue or other muscles. Deep tendon reflexes were normal. Sensory system was normal. Arm abduction time was 60 seconds and single breath count was 40. Ice pack test was equivocal. Neostigmine test was not done. Routine nerve conduction study was normal. Repetitive nerve stimulation at 3 Hz showed decremental response from facial, accessory and ulnar nerves (59%, 26%% and 32%) respectively Table 1. She was diagnosed as myasthenia gravis Class IIIa (Myasthenia gravis foundation of America clinical classification). CT chest was normal. Blood investigations including thyroid function tests and creatine phosphokinase were normal. Serum acetyl choline receptor antibody level was 3.39nmol/L (Normal <0.40nmol/L) by indirect ELISA method. Serum MuSK antibody level was 393 ng/ml (Normal 0-84ng/ml) by Sandwich ELISA method. She was treated with pyridostigmine 60 mg three times daily and her symptoms and signs fully reversed. She is asymptomatic at three months follow up on pyridostigmine.

3. Discussion

MuSK myasthenia accounts for a significant portion of SNMG. MuSK-MG is a rare, frequently more severe subtype of MG with different pathogenesis, and peculiar clinical features.[3]Table 2. It constitutes about 6% of all MG patients. MuSK-MG usually has an acute onset affecting mainly the facial-bulbar muscles. Bulbar impairment has been demonstrated in up to 80% of MuSK-MG patients. They can have severe bulbar weakness with wasting and fasciculations of the tongue mimicking bulbar amyotrophic lateral sclerosis (ALS). Usually, axial muscle weakness involves neck extensor, which may present as head drop, and it can be the only presenting sign, without bulbar involvement. Some patients present like AChR Ab positive MG.[4] The symptoms usually progress rapidly and early respiratory crises are frequent. The disease may lead to generalized muscle weakness and muscle atrophy. The main bulbar involvement, the absence of significant thymus alterations, and the association with HLA class II DR14, DR16, and DQ5 alleles have been confirmed. Atypical onset, such as ocular involvement, lack of symptom fluctuations, acetylcholinesterase inhibitors failure, and negative results of electrophysiologic testing, if not specifically performed in the mainly involved muscle groups, makes MuSK-MG diagnosis challenging. Low frequency repetitive nerve stimulation shows a progressive decrement pattern unlike AChR Ab positive MG which shows a U pattern. Repetitive compound muscle action potential (R-CMAP) was detected in 48% of MuSK-MG cases. R-CMAP detection can represent a useful diagnostic clue for MuSK-MG and predicts poor tolerance

to ACEIs. MuSK-MG often manifest signs of cholinergic hyperactivity with standard doses of acetylcholinesterase inhibitors.[5] Worsening of symptoms with acetyl choline esterase inhibitors can occur in 5-20% cases. The use of 3,4-diaminopyridine in MuSK- MG patients has been described as mildly to moderately effective, with no remarkable side effects.

Not uncommonly, EMG examination demonstrates motor unit potentials with myopathic features and spontaneous activity, which may be interpreted as an inflammatory myopathy. Many MuSK-MG patients develop diffuse fasciculations, severe gastrointestinal discomfort and salivation, or worsening symptoms following edrophonium that can be a clue to the diagnosis.[6]These patients are less responsive to choline esterase inhibitors but respond to plasma exchange and other immunosuprressant medications. Among immunotherapies, prednisone, plasmapheresis, and RTX are the cornerstones of treatment for MuSK-MG.[7] The majority MuSK-MG patients can benefit from rituximab treatment regardless of age at onset.[8]

AChR and MuSK double positive myasthenia gravis has been rarely reported. Generally, it occurs in children and in adults after thymectomy or immunotherapy. In a few patients with bulbar or respiratory involvement, MuSK antibodies might be detected after clinical deterioration. In a study of 13 patients with DSP-MG, presentation was generalized in 9 patients, bulbar in 3 and ocular in 1. Four patients showed thymoma and one patient showed thymic hyperplasia. All 13 patients improved with Anticholinesterases.[9] In another study from China showed greater bulbar involvement, more severe myasthenia, higher incidence of myasthenic crisis, greater autoantibody abnormalities, need for immunosuppressant treatment and worse prognosis with less remission. There were no differences between DSP-MG and MuSK-MG patients.[10] The gender distribution, age of onset, pharmacological characteristics and electrophysiological examination of DP-MG patients were similar to those of MuSK-MG patients, but the severity of DP-MG patients was between that of AChR-MG and MuSK-MG patients.[11] Some guidelines advocate testing for MuSK antibody, only if AChR Ab and LRP4 ab are negative.[12] Rarely AChR Ab and MuSK Ab can be negative, but positive for LRP4 Ab and Agrin Ab.[13]We are suggesting testing for AChR Ab, MuSK Ab and LRP4 Ab in all patients with MG as there is significant overlap in symptoms with variable prognosis.

4. Conclusion

Acetyl choline receptor antibodies are absent in 20% of generalized myasthenia gravis. Up to 40% of seronegative myasthenia patients have anti MuSK antibodies. Presence of both AChR antibody and MuSK antibody in a patient is a rare occurrence. MuSK antibody assay may be done even if AChR antibody is positive as prognosis is variable in DSP-MG.

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None.

6. Conflict of Interest

None.

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