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The Challenges of Treating Coexisting Autoimmune Disorders

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Introduction

Myasthenia gravis (MG) is an autoimmune disorder characterized by the production of antibodies against peptides localized at the neuromuscular junction (NMJ).

The muscle-specific tyrosine kinase (MuSK), is involved in the synaptic differentiation with a fundamental role in the development of the NMJ. MuSK Myasthenia gravis (MMG) is a particular entity , described in 2001 after the recognition of the antibodies (MuSK-Ab) by Hoch et al. with a clinical presentation characterized by respiratory, facial and neck weakness. Classic MG has positive AChR-Ab in 80-95% of the cases. Seronegative MG is comprised of 10-15% of these cases, 40-60% of which will have positive MuSK antibodies.

Coexisting autoimmune disorders with MG were described in up to 20% of cases by Margolis and Graves in 1945. Current data links these entities in up to 29%.

Multiple Sclerosis (MS) and MG coexisting have a frequency of 0.3%, and the clinical presentation of MMG has overlapping features with MS, including demographics. The thought behind the mechanism of these diseases is the immune dysregulation, over activity of the T cells and auto-reactivity of the B cells with autoantibody production and upregulation of cytokines mediating a common autoimmune pathway.

We present the case of a young woman with known diagnosis of MS with and new isolated bulbar symptomatology.

Case Presentation

This is a 32-year-old African American woman with an established diagnosis of Multiple Sclerosis since 2010, on Methylfumarate treatment.

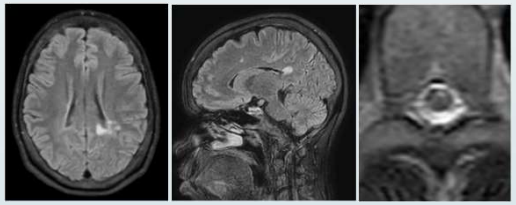
In 2016, she presented with a six-month history of fluctuating dysphagia, dysarthria, diplopia and what she described as a “frozen face”. On exam she have profound dysarthria, hypophonia and nasal speech, facial diplegia, tongue atrophy, ophthalmoplegia and bilateral ptosis There was no limb weakness. She had no limb fatigability.

There were no cerebellar or sensory abnormalities and her gait was normal.

Initial workup included:

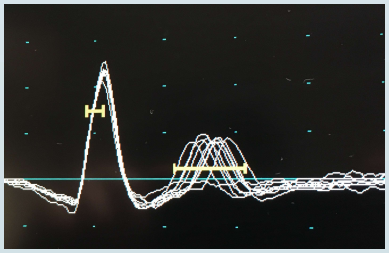
Ach-Ab -Blocking -Binding -Modulating	18 nmol/L 0.03 nmol/L 12 nmol/L	**RNP**	negative
OCB	**2.2 Bands**	**SS-A/B**	negative
IgG Index	**0.75 mg/dl**	**SS-B**	negative
IgG serum	1200 mg/dl	**RF**	negative
Aq4-Ab	negative	**CRP**	negative
HBV	negative	**ESR**	negative
HCV	negative	**Lyme**	negative
ANA	negative	**VDRL-RPR**	negative
Ds-DNA	negative	**ACE**	negative
Anti-Sm	negative	**Anti-proteinase**	negative
Anti-SCL	negative	**HIV**	negative
p-ANCA/ c-ANCA	negative	**Anti-myeloperoxidase**	negative

MRI Brain and T-spine w/o contrast: Presence of multiple T2 hyperintense periventricular and yuxtacortical white matter lesions, as well as T2 hyperintense lesions at the ventral cord at T9 level.



-An **Edrophonium test** was administered with dramatic improvement in her facial weakness and nasal speech.

-**SFEMG Frontalis muscle:** Abnormal Jitter.



Results

Given her clinical description, response to the Edrophonium Test and SFEMG findings, she was treated as bulbar myasthenia gravis. She completed 5-days of plasmapheresis and was started on Pyridostigmine 30mg three times daily. There was minimal improvement in symptomatology and therefore prednisone 40mg daily and Azathioprine were added to her treatment regimen.

MuSK-Ab: 1:2560 was reported positive 1 week later, confirming diagnosis of ***Muscle Specific Tyrosine Kinase Myasthenia Gravis.***

In the outpatient setting, she was noted to remain symptomatic despite compliance with her prescribed treatment.

Given her poor response we began to explore options for dual management of MS and MMG, specially given the theoretical common final pathways of these two diseases. Rituximab was initiated for this purpose. Methylfumarate, azathioprine and pyridostigimine were discontinued.

She had a dramatic improvement in her facial and bulbar symptoms. It has been 20 months since she presented, and she remains asymptomatic.

Admission

Edrophonium Test

PLEX Day 1/5

4m after Rituximab

Conclusion

MuSK is a postsynaptic transmembrane glycoprotein. It is involved in the synaptic differentiation stimulated by the proteoglycan Agrin, causing the adhesion of LRP4 with subsequent clustering of the Ach-R. It is essential to the development, function and stability of the NMJ.

The vast majority of the identified MuSK-Ab to date are IgG4, generated by Th2 cells, not associated with complement activation. These antibodies block the interaction between MuSK and LRP4-Collagen Q, disrupting the Ach-R signal cascade, decreasing the Ach-R density causing synaptic dysfunction.

The common pathogenesis between MS and MMG implies an immune dysregulation; both disorders are T cell mediated, with increased number and activity of Th2 and Th17 cells with dysfunctional and upregulated associated cytokines. Autoreactive B cells with antibody production have been associated as well.

The clinical presentation of MMG has overlapping features with MS, and both include similar demographics. Relapsing remitting MS and MG can both present with exacerbations, and this may further obscure the diagnosis.

It is important to consider overlapping autoimmune disorders, particularly if new symptoms develop given their potential association. Consideration should be given to the mechanism of these coexisting diseases to find a targeted treatment option.

While there are prior reports of coexisting MS and seronegative MG, ours is one of the few cases reporting MG with positive Musk-Ab with MS.

Furthermore, this is one of the few cases with successful dual treatment of MS and MMG with rituximab therapy.

References

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