Myasthenia Gravis: Do the Subtypes Matter?

Acquired myasthenia gravis (MG) is a group of neuromuscular junction (NMJ) disorders caused by autoantibodies against components of postsynaptic muscle endplate. Autoantibodies target the acetylcholine receptor (AChR), muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (LRP4) and agrin. Clinically, MG is characterised by fluctuant muscle weakness.[1]

MG is classified into subtypes based on serum antibodies and clinical features. Identification of the specific subtype dictates the therapeutic approach and also prognosis.[1,2] Clinical subtypes include ocular MG, early-onset generalised MG and late-onset MG. The subtypes by antibodies include MG with AChR antibodies, MG with anti-MuSK antibodies, MG with anti-LRP4 antibodies, seronegative myasthenia and myasthenia with coexisting autoimmune diseases.[1,2] The other subtype is adult-onset MG with thymoma with titin and ryanodine receptor antibodies.[3] The relative prevalence of subtypes by antibodies is: MG with AChR antibodies 80%, MG with MuSK antibodies 4%, MG with LRP4 antibodies 2% and seronegative myasthenia.[1]

In this issue of Annals of India Academy of Neurology, Samal and colleagues compared the demographic and clinical characteristics, treatment response, and outcome of MG with MuSK antibodies, MG with AChR antibodies and seronegative MG.[4] They did not find any difference among all the three subtypes in all the parameters studied including long-term prognosis and quality of life. The authors concluded that clinical features and response to therapy in addition to antibody status must be considered before planning a therapy. These observations are at variance from the published studies. The major limitations of the study are retrospective nature of the study, small sample size in the MuSK positive and seronegative groups and different treatment protocols.

There are distinct differences between late-onset MG with AChR antibodies and MG with MuSK antibodies. MuSK antibodies are mainly IgG4, unlike the IgG1 and IgG3 anti-AChR antibodies, and are not complement activating.[5] MG with MuSK antibodies is seen predominantly in females, commonly has atypical clinical features such as the selective facial, bulbar, neck, and respiratory muscle weakness and marked muscle atrophy, occasionally with relative sparing of ocular muscles.[6,7] Respiratory crises are more common. Weakness can involve muscles that are not usually symptomatic in MG such as paraspinal and upper oesophageal muscles.[8] Anticholinesterase agents are less effective and induce frequent side effects.[9] Thymus histology is usually normal.[9] MG with MuSK antibodies has lower response with immunosuppressive treatment, and rituximab has a favourable response.[1] Thymectomy may not be associated with clinical improvement in MG with MuSK antibodies.[10,11]

Accumulating evidence suggests that clinical MG subtypes might respond differently to treatments. However, treatment is far from antibody specific. The future research approach should be towards an individually adapted treatment based on biomarker (autoantibody) assessment and monitoring.[1]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

J. M. K. Murthy

Department of Neurology, CARE Institute of Neurosciences, CARE Hospital, Banjara Hills, Hyderabad, Telangana, India

Address for correspondence: Dr. J. M. K. Murthy, Clinical Director and Chair, Department of Neurology, CARE Institute of Neurosciences, CARE Hospital, Banjara Hills, Hyderabad - 500 034, Telangana, India.
E-mail: jmkmurthy49@gmail.com

References

1. Gilhus NE, Verschuuren JJ, Myasthenia gravis: Subgroup classification and therapeutic strategies. Lancet Neurol 2015;14:1023-36.
2. Dalkas MC. Immunotherapy in myasthenia gravies in the era of biologics. Nat Rev Neurol 2019;15:113-24.
3. Romi F. Thymoma in myasthenia gravis: From diagnosis to treatment. Autoimmune Dis 2011;2011:474512.
4. Samal P, Goyal V, Singh MB, Padma Srivastva MV, MuSK (muscle specific kinase) positive myasthenia: Grave prognosis or undue prejudice? Neurol India 2020.
5. McConville J, Farrugia ME, Beeson D, Kishore U, Metcalfe R, Newsom-Davis J, *et al*. Myasthenia detection and characterization of MuSK antibodies in seronegative gravis. Ann Neurol 2004;55:580-4.
6. Evoli A, Tonali PA, Padua L, Monaco ML, Scuderi F, Batocchi AP, *et al*. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain 2003;126:2304-11.
7. Sanders DB, El-Salem K, Massey JM, McConville J, Vincent A. Clinical aspects of MuSK antibody positive seronegative MG. Neurology 2003;60:1978-80.
8. Sanders DB, Juel VC. MuSK-antibody positive myasthenia gravis: Questions from the clinic. J Neuroimmunol 2008;201-2:85-9.
9. Hatanaka Y, Hemmi S, Morgan MB, Scheufele ML, Claussen GC, Wolfe GI, *et al*. Non-responsiveness to anticholinesterase agents in patients with MuSK-antibody-positive MG. Neurology 2005;65:1508-9.
10. Leite MI, Ströbel P, Jones M, Micklem K, Moritz R, Gold R, *et al*. Fewer thymic changes in MuSK antibody-positive than in MuSK antibody-negative MG. Ann Neurol 2005;57:444-8.
11. Clifford KM, Hobson-Webb LD, Burns TM, Burns TM, Barnett C, Silvestri NJ, *et al*. Thymectomy may not be associated with clinical improvement in MuSK myasthenia gravis. Muscle Nerve 2019;59:405-10.

Received: 09.11.2019 **Accepted:** 09.11.2019
Published: 21.01.2020

DOI: 10.4103/aian.AIAN_595_19