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The Pediatric Primary Care Management of Myasthenia Gravis

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ABSTRACT

Myasthenia gravis (MG), an autoimmune neuromuscular disorder, is characterized by variable skeletal muscle weakness that temporarily improves as the person rests. Early diagnosis by the nurse practitioner is critical for decreasing the rate of disease progression. This article addresses the background, pathophysiology, clinical presentation, diagnostic evaluation, treatments, and psychosocial impact on children with MG. It will prepare nurse practitioners to recognize the common signs and symptoms of ocular and generalized MG and provide management based on the current recommendations and research.

Keywords: autoimmune disease, myasthenia gravis, neuromuscular junction, pediatric primary care, pediatrics

R.G. is a 15-year-old previously healthy boy who presented to the pediatrician for evaluation of double vision and a droopy eyelid. The patient wears contacts and recounts no significant past medical history. The pediatrician reported no other findings and referred him to ophthalmology. R.G. was diagnosed with myasthenia gravis (MG) after subspecialty referrals, consultations, tests, and maternal research. This article explores juvenile myasthenia gravis or pediatric MG. Although a rare pediatric condition, the ability to identify MG could prevent underdiagnosis and promote early treatment.

BACKGROUND

MG is an uncommon and underdiagnosed autoimmune disease of childhood. In the United States, 1.7 to 30.0 per 1,000,000 people have MG.[1] In children under 18 years old, 1 to 5 per 1,000,000 are affected, with a 3 times higher incidence in females.[1,2] MG is an autoimmune disorder of the neuromuscular junction (NMJ). Autoantibodies are created and produce a neuromuscular blockade.[3] The presence of human leukocyte antigen types DR2, DR3, B8, and DR1 can predispose to MG. Various combinations of these human leukocyte antigen types correlate with different clinical presentations.[4]

PATHOPHYSIOLOGY

A T cell and antibody-mediated disease, MG is caused by autoantibodies created against proteins at the postsynaptic neuromuscular synapse.[5] Acetylcholine receptors (AChRs) and muscle-specific tyrosine kinase (MuSK) are postsynaptic transmembrane proteins found in the NMJ of skeletal muscles. MuSK is activated by agrin when bound to low-density lipoprotein receptor-related protein 4 (LRP4).[6] This agrin/MuSK complex triggers the clustering of AChRs. Neuromuscular transmission is dependent on AChR clustering. In most cases of MG, the autoantibodies against AChR, MuSK, or LRP4 hinder neuromuscular transmission.[7]

The positivity rate for AChR antibodies in MG is 72% for generalized symptoms and is 41% in ocular symptoms.[1] Antibodies against the AChR composed mainly of immunoglobulin (Ig) G1 and IgG3 along with MuSK antibodies composed mainly of IgG4 are important in the immunologic pathogenic antibodies.[6] The proposed mechanism for NMJ disruption in these patients involves anti-AChR antibodies interfering with neuromuscular transmission. Antigenic modulation accelerates the destruction of cell surface antigens and functionally blocks AChRs.[1,8] This sequence of events prevents acetylcholine (ACh) from binding to the receptor

and inducing an end plate potential.[1] Adequate release of ACh during presynaptic events remains intact. The inability of the postsynaptic membrane to sufficiently bind ACh results in the weakness and fatigability of skeletal muscles.[5]

Recently, anti-MuSK and anti-LRP4 antibodies were discovered to play a role in the pathogenesis of MG. Ten percent of patients without detectable anti-AChR antibodies have anti-MuSK antibodies.[5] Anti-MuSK antibodies disrupt neuromuscular transmission by decreasing the number of MuSK receptors on the postsynaptic cleft. The decrease in receptors alters AChR clustering and leads to generalized muscle weakness.[1] Anti-LRP4 antibodies repress the agrin/MuSK complex and hinder the role of MuSK, leading to the same cascade of problems observed with anti-MuSK antibody patients.[8]

The pathogenic autoantibodies arise from the humoral response created by the interaction between B cells and helper T cells.[7] Autoreactive T cells are present and circulate after a lack of adverse physiologic selection.[9] The pathophysiology within the thymus gland in MG is not entirely understood[6]; however, autoreactive T cells specific for AChR have been detected in thymomas and circulation.[8]

CLINICAL PRESENTATION

Nurse practitioners (NPs) may encounter patients with symptoms as early as the first year of life through adulthood.[1] There is no prepubertal gender bias; however, postpubescent children diagnosed with MG are 3 times more likely to be female. Pubertal status has been shown to influence the presentation of ocular or generalized subtypes.[6] The hallmark clinical feature of both subtypes is fluctuating weakness of specific skeletal muscles. Weakness is aggravated by the persistent use of the muscles and alleviated when the child rests.[1] Stress, heat, and infection exacerbate the muscular fatigability and weakness.[10] The fluctuating nature of the weakness is key to differentiating MG from other diseases.

Ocular MG

Ocular MG (OMG) is more common in children of Asian descent.[1] It is important to note that pupils are not affected by OMG, and although patients may present with pseudocranial nerve palsies and different types of strabismus, the pupils remain normally reactive to light. The affected muscles of OMG are the levator palpebrae superioris, orbicularis oculi, and the vertical and horizontal rectus muscles. Patients present with weakness of the lid, double vision, or strabismus in OMG.[1] Ocular clinical features may present unilaterally or bilaterally asymmetrically.[11] To be characterized as purely OMG, the patient must remain free of generalized symptoms a minimum of 2 years after symptomatic onset.[4] Although the development of widespread MG in children initially presenting with ocular symptoms is reported to range from 8% to 33%,[1] screening for overall fluctuating weakness is essential.

Generalized MG

Children who are postpubertal have a higher incidence of generalized MG (GMG).[1] Although ptosis and diplopia are still among the classic presenting features, GMG exhibits further nonophthalmic skeletal muscle weakness. When bulbar and limb musculature is affected, there is difficulty speaking, discomfort swallowing, and/or proximal muscle difficulties.[12] Untreated MG has the potential to advance to respiratory distress.[13] Recognizing early MG can prevent the need for intubation or mechanical ventilation.

DIAGNOSTIC EVALUATION

The history shows variability in symptoms, particularly worsening weakness in the evening, after repeated activities, or during stressful situations. Exploration of the associated symptoms to the initial muscle groups should be exhausted. Upper airway symptoms such as difficulties breathing, swallowing, or choking need immediate attention. Supplementary Figure 1 (available online at http://www.npjournal.org) contains the specific history questions and focused physical pointers.

Physical Examination

Patients with MG require repetitive and sustained movements to provoke variable muscle weakness.[10] The eyes and extraocular muscles are the first to be assessed because the ocular muscles are typically the first affected. The NP must evaluate for unilateral or bilateral ptosis and failure of the eyes to demonstrate coordinated movements.[6] A lid fatigability test is a