What's Hot off the Press in Neuromuscular Junction Disorders?

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Introduction

We would like to welcome MGFA members to a new column that will appear quarterly. Our goal is to highlight some of the latest developments in research related to neuromuscular junction disorders. Every column should include new developments in myasthenia gravis (MG), but we will be covering other disease states as well. For this inaugural column, we will lead off with congenital myasthenic syndromes. We will try to keep things to the point, in language that is understandable. Feedback will be appreciated. Happy reading!

Congenital Myasthenic Syndromes

Congenital myasthenic syndromes (often abbreviated as CMS) represent a wide variety of inherited disorders that compromise in one way or another transmission from the nerve to the muscle.[1] As we think most of you realize, this transmission must negotiate the neuromuscular junction. Most people who have CMS present in the first two years of life, with symptoms varying from problems feeding and breathing, droopy eyelids, reduced eye movement, poor muscle tone, muscle weakness and fatigue. Most forms of CMS arise only if abnormal genes are inherited from both the mother and father. We call this autosomal recessive inheritance. An abnormal gene coming from only one parent will usually not cause any problem. Many of the CMS disorders are caused by gene mutations for proteins that are part of the structural building blocks of the muscle membrane, including the acetylcholine receptor, the protein that is the immune target in most patients with MG. Recently, mutations in two proteins that are not structural but serve as enzymes, glutamine-fructose-6-phosphate transaminase (GFPT1) and dolichyl-phosphate N-acetylglucosaminephosphotransferase 1 (DPAGT1),[2] have been discovered in patients presenting with forms of CMS that impact the limb muscles far more greatly than the ocular muscles. This pattern is often referred to as limb-girdle myasthenia and is seen in several forms of CMS.

Selcen and her coauthors[3] from the Mayo Clinic group led by Dr. Andrew Engel that has defined many forms of CMS over the last 20 years, recently described the clinical features of 11 subjects with GFPT1 mutations. Problems in these individuals began anywhere from the time of birth to 19 years. Fortunately, all but one of these 11 individuals could walk. The weakness observed was in keeping with a limb-girdle pattern. Unlike some patients with CMS and most patients with MG, the authors did observe weakness below the elbows and below the knees involving foot and hand function. For those people who presented in early childhood, there were problems breathing, weak crying, problems eating and marked loss of muscle tone. As far as treatment, ten of the 11 patients had partial responses to pyridostigmine (Mestinon), a drug many of you take for MG. Other drugs such as 3,4-diaminopyridine (used often in Lambert-Eaton myasthenic syndrome), ephedrine and albuterol could also be helpful.

The loss of the GFPT1 enzyme activity caused by the gene mutations is believed to impact the proper structure of several proteins on or associated with the muscle membrane, thereby impairing proper transmission from the nerve to the muscle. What this research article should do is alert neurologists and other physicians to a clinical pattern of limb-girdle myasthenia that responds favorably to pyridostigmine. In addition, both GFPT1 and DPAGT1 mutations produce characteristic features on muscle biopsy that may also raise a clinician's suspicion for these disorders. Of course, these individuals will not harbor the antibodies in the blood that are typical for MG.

A common form of CMS is the slow channel syndrome, caused by mutations in the genes for the acetylcholine receptor.[4] This is the one form of CMS that can be inherited from a single abnormal gene coming from just one parent. So the inheritance pattern is quite different than the disorders we spoke about earlier, and is termed autosomal dominant. Many individuals with slow channel syndrome respond well to fluoxetine (more commonly known as Prozac) and quinidine (a drug used for heart rhythm problems). They get worse with pyridostigmine. Peyer and colleagues[5] recently described a patient

with slow channel syndrome who could not tolerate fluoxetine and was treated successfully with quinine, a medication that has a similar structure to quinidine. So this report suggests another treatment alternative for this group of individuals. Unfortunately, quinine, an old drug that is still sometimes used for malaria, is no longer easy to get your hands on in the United States, due to the FDA's concern about the effects it may have on blood cells and kidney function.

Myasthenia Gravis

Now, let's turn to MG. There have been several recent articles describing people with MG who often struggled with other treatments but had impressive responses to rituximab. Favorable responses have been seen in different types of MG, particularly in MuSK MG. In MuSK MG, an initial series of infusions of this manufactured antibody over a period of about 2 months can lead to a positive treatment response lasting years.[6] In a brief report, Catzola and coauthors from Italy[7] analyzed the effects of rituximab on regulatory T cells, white blood cells that are known to play a crucial role in preventing the host from attacking itself. There is good evidence that this class of white blood cells do not function properly in individuals with MG. The authors studied two patients with MG who were refractory to standard therapy. One had antibodies to the acetylcholine receptor and the other to MuSK. The MuSK MG patient had a dramatic response to rituximab; an increase in the regulatory T cells was also observed. The same clinical improvement and regulatory T cell boost were not observed in the other patient. Although limited by a single patient in each group, this report confirms prior observations that rituximab seems to work particularly well in MuSK MG and suggests that the drug's impact on these regulatory T cells may be largely responsible for the improvement. In this case, good disease control lasted for over 2 years after an initial series of the rituximab in the first month of treatment and a single dose 3 months later. Other medications were stopped and prednisone could be lowered. We think that the growing number of favorable reports for rituximab in MG begs for a formal drug trial. Efforts, in fact, are underway to conduct such a study through the NeuroNEXT clinical trials network funded by the NIH and all of our tax dollars.

Finally, steroid-sparing immunosuppressant agents are commonly used in MG. Black box warnings that alert doctors and patients to serious side effect for this class of medications typically include a risk for cancer, mainly lymphoma. But the data behind such warnings has largely been derived from individuals who have received these drugs to prevent rejection of transplanted organs such as kidneys and hearts. Actual studies in patients with neurologic disorders are few and far between. Pedersen and colleagues[8] recently performed a careful study on the risk of cancer in Danish MG patients treated with azathioprine (Imuran). Using several national databases in Denmark, they identified 89 patients treated with azathioprine who developed cancer and 873 controls (MG patients who also received azathioprine but did not develop cancer). They found a slightly higher rate of cancer with long-term use of azathioprine, defined as duration of treatment for 5 years or more. The increase in the rate of cancer over the control group was less than 25%, so considerably less than even a two-fold increase. The patients who developed cancer tended to be older men. The total number of cancer cases was too small to estimate the increased risk of specific types of cancer, but lymphoma was more common for those patients receiving longer treatments and higher doses. Larger studies will be necessary to clarify what the risk is for specific cancer types. But for now, it does appear the increased risk of cancer with azathioprine -- one of the oldest and most commonly used steroid-sparing agents in MG -- is fairly modest.

See you next time.

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