Managing Myasthenia Gravis

This once grim disease is now fully treatable—and patients may even experience a complete resolution of some, if not all, symptoms.

BY BETH HOWARD

At first, doctors chalked up Keelie Brydson's drooping eyelid to lazy eye and outfitted her with a patch. It didn't help. The diagnosis also didn't explain the other symptoms that began to crop up around the time she started high school in her hometown of Pflugerville, TX. Her muscles got weak easily and her reactions slowed. "I was a volleyball player," she says, "but the ball would come to me before I could move."

Then age 14, Brydson experienced a lot of teasing from her classmates as she and her parents scuttled from doctor to doctor seeking help for her mysterious symptoms. Eventually, she received a diagnosis: myasthenia gravis.

FEAR OF THE FUTURE

An autoimmune neurologic disease that affects the body's voluntary muscles, myasthenia gravis can cause symptoms like Brydson's—drooping eyelids, weakness in the limbs, and chronic muscle fatigue. Blurred or double vision, slurred speech, trouble swallowing and chewing, and difficulty breathing are also common, according to the Myasthenia Gravis Foundation of America (**myasthenia.org**).

The degree of muscle weakness can vary greatly between individuals. In some people, it is limited to the eye muscles, a condition called ocular myasthenia; in others, muscle weakness is generalized and can be severe, affecting the muscles that control breathing. Muscle weakness tends to increase with activity and improve with rest, says Ted M. Burns, MD, professor of neurology at the University of Virginia School of Medicine in Charlottesville.

Brydson was devastated. "I'd never heard of myasthenia gravis," she says. "If you Google it, scary things pop up. Some doctors said it can affect lung function and you stop breathing. I was terrified."

Fortunately, Brydson, now 19, learned that while the condition is not curable, it is treatable, and most patients have a normal life expectancy. "There's plenty of reason for optimism," says Dr. Burns. Seventy-five years ago, two-thirds of patients diagnosed with myasthenia gravis died because no treatments existed, says Dr. Burns. "Now we have close to a dozen options. Some patients have proven difficult to treat, but our approach is that the disease is treatable. We would like to get everyone into remission without symptoms, or as near as possible."

THUMBS UP Keelie Brydson says she is in almost complete remission after a surgery to remove her thymus in 2013.

NERVE-SIGNAL MALFUNCTION

Myasthenia gravis is caused by a defect in the transmission of nerve impulses to muscles, explains Dr. Burns. Normally, nerve impulses travel down the nerves to the neuromuscular junction, where nerve signals meet muscle fibers. The nerve endings release a substance called acetylcholine, which travels to the muscle fiber, attaching to receptor sites. When enough acetylcholine binds to the receptors, they are activated and generate a muscle contraction.

In people with myasthenia gravis, antibodies produced by the immune system block or destroy the acetylcholine receptor sites, says Dr. Burns. The number of sites can be reduced by as much as 80 percent. Why some people are affected by myasthenia gravis and others aren't isn't fully understood.

THYMUS TROUBLE

The thymus gland, which is involved in the development of the immune system, is thought to play a role in the production of the antibodies that block acetylcholine receptors. Some patients with myasthenia gravis have an enlarged thymus or, less often, a tumor, called a thymoma, says Dr. Burns.

The disorder can affect people at any age, but it is more common in women under age 40 and men over age 60, according to the Myasthenia Gravis Foundation of America. There are approximately 36,000 to 60,000 cases in the United States, but because the condition is likely underdiagnosed, the prevalence may be higher.

DIAGNOSTIC TESTS

Diagnosis can be challenging because muscle weakness can be a sign of many other diseases. Brydson remembers that her workup took the better part of a day. "It was the longest office visit I ever had," she says.

Doctors may start with a blood test, since 80 to 90 percent of people with myasthenia gravis test positive for the acetylcholine receptor antibody (AChR). The remaining patients may test positive for other antibodies such as muscle-specific receptor tyrosine kinase (MuSK), low-density lipoprotein receptor-related protein (LRP4), and agrin (AGRN), which are related to the development and maintenance of the neuromuscular junction, says David P. Richman, MD, professor of neurology at the University of California, Davis. Currently, laboratory tests exist for MuSK and Lrp4, which help doctors identify the culprit in more patients.

Neurologists also may conduct tests of reflexes, muscle strength, muscle tone,

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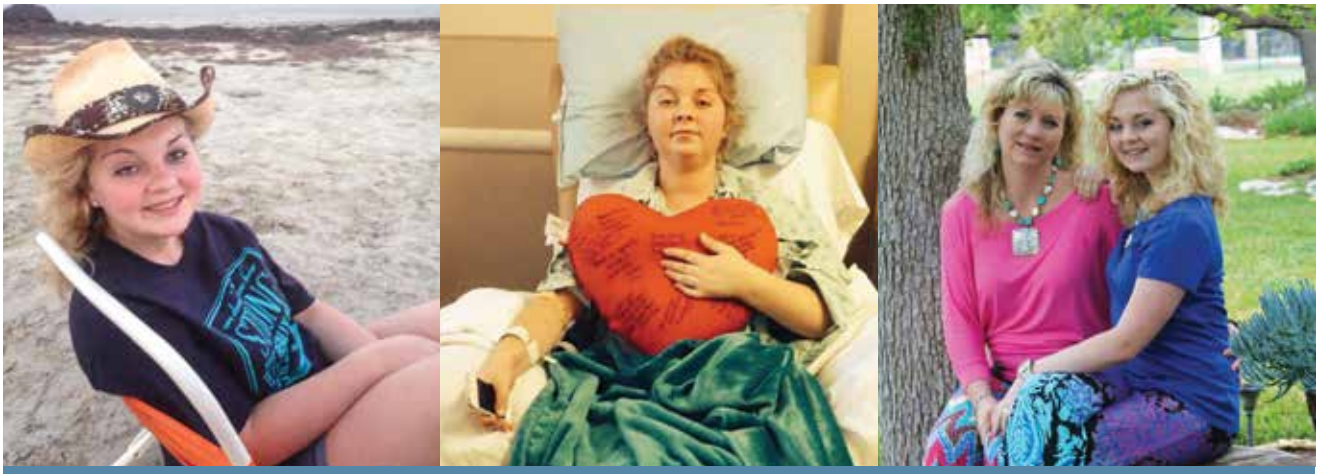

LIVING WITH MG Keelie Brydson in 2012, before surgery; in the hospital after her thymectomy; and with her mother, Melissa, after recovery.

sense of touch and sight, coordination, balance, gait, posture, and mental abilities, says Dr. Richman. They may also inject edrophonium chloride, a chemical that blocks an enzyme that breaks down acetylcholine, into an affected muscle. If the patient’s strength improves temporarily, it may be a sign that he or she has the disease. For patients like Brydson, who had a droopy eyelid, the doctor may place an ice pack on the eyelid for two minutes to see if the drooping improves.

To test nerve-muscle signaling, doctors may stimulate a nerve electronically six to 10 times to see if it worsens with repetition, says Dr. Richman. A more invasive test, a single-fiber electromyography, involves inserting a needle through the skin into a muscle to measure electrical activity between the brain and a single muscle fiber. Doctors may also order MRI or CT scans to look for abnormalities of the thymus. To determine breathing strength, doctors may conduct pulmonary function tests.

TREATMENT OPTIONS

ANTICHOLINESTERASES

The most common treatment for myasthenia gravis is a class of medications known as anticholinesterases, such as pyridostigmine bromide (Mestinon), says Gary S. Gronseth, MD, FAAN, professor and vice-chairman of the department of neurology at the University of Kansas Medical Center. They act quickly to relieve symptoms by preventing the breakdown of acetylcholine, the substance that signals muscles to contract. Sometimes these drugs are all that patients need to feel well.

IMMUNOTHERAPY

Most patients eventually will need treatment with prednisone, Dr. Gronseth says. Other immunotherapy drugs commonly added to prednisone include azathioprine (Imuran), mycophenolate mofetil (CellCept), tacrolimus (Prograf), methotrexate (Trexall, Rasuvo), cyclosporine (Sandimmune, Neoral), and cyclophosphamide (Cytoxan, Neosar). Immunotherapy helps prevent the body from making the antibodies responsible for myasthenia gravis, he explains.

MONOCLONAL ANTIBODIES

A new medical option for myasthenia gravis is the powerful monoclonal antibody rituximab (Rituxan), which is given by infusion. This medication may be more effective for patients who test positive for MuSK antibodies, Dr. Gronseth says. Another monoclonal antibody, eculizumab (Soliris), is also being investigated.

RAPID-ACTING IMMUNOTHERAPIES

Therapies such as intravenous immunoglobulin (IVIG) and plasmapheresis, which start working rapidly but also wear off quickly, are prescribed in certain situations—for example, when patients are waiting for slower-acting medications to kick in or to augment immunotherapy drugs when symptoms aren’t completely under control. They may also be used to build strength prior to surgery or to manage a crisis, such as when respiratory muscles are so weak that a patient is at risk of not being able to breathe, says Dr. Gronseth.

With IVIG, normal antibodies from donated blood are infused into the patient’s bloodstream to alter the immune system and relieve symptoms temporarily. With plasmapheresis (or plasma exchange), another temporary fix, doctors remove blood from the patient’s body intravenously. The plasma that contains the harmful antibodies is then separated out,

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and the antibody-free blood is returned to the patient, explains Dr. Gronseth.

When prednisone and pyridostigmine failed to help Brydson, she started receiving plasmapheresis treatments every two weeks. She experienced substantial relief from chronic weakness by her third treatment, and in subsequent treatments. "I was stronger for two weeks, almost normal again," she says. "The drawback was that I would crash at the end of the two weeks and I'd feel worse than ever."

THYMECTOMY

In some cases, Dr. Gronseth says, doctors will recommend a surgical procedure called a thymectomy, which involves removing the thymus gland. This procedure has been used for many decades, mostly in patients with thymomas and in those under age 60 with moderate to severe generalized myasthenia. Until recently, though, there was no clear evidence that it was better for patients than leaving the gland in place.

That changed when researchers published a randomized controlled trial, the gold standard of medical research, in the *New England Journal of Medicine* in 2016 showing that the procedure combined with prednisone is more effective than prednisone alone in patients without thymomas. "After three years, 70 percent of patients getting surgery plus prednisone had virtually no symptoms, versus 50 percent of the patients just getting prednisone," says Dr. Gronseth. "It's not a cure, but it's a pretty big benefit. Patients get better and they end up needing less prednisone."

SURGERY

The traditional surgical approach for thymectomy involves making an incision through the sternum (breastbone) to open the chest and remove the thymus, which lies behind it. The procedure allows doctors to see into the chest and ensure that all the thymus tissue is removed. But it also involves several days in the hospital plus weeks or months of

recovery, and leaves a scar, says Dr. Gronseth.

A less invasive approach involves making small incisions on the side of the chest; a scope outfitted with a tiny camera and surgical instruments allows the surgeon to visualize and remove the thymus. "There's not as much scarring and a shorter hospital stay, but we are not as certain about the effectiveness of these less invasive options," Dr. Gronseth says. However the surgery is performed, it can take several years to realize the full benefit, he adds.

CUSTOM TREATMENT

Treatment for myasthenia gravis is highly individualized, depending on the patient's age, the severity of the disease, and the pace of progression. In addition, doctors consider the personal characteristics of a patient's disease.

"Over the past decade or so, we have discovered that it is important to keep in mind the subtype of myasthenia gravis—the antibody profile, thymic pathology, and age of onset—when discussing treatment options, as this may affect choice and response to treatments," says Julie Rowin, MD, FAAN, a neurologist in Chicago.

In particular, clinicians now have a better understanding of a type of myasthenia gravis called MuSK-associated myasthenia gravis, in which patients have MuSK antibodies. "These patients not only have different symptoms, but they have different responses to medications than other subtypes," Dr. Rowin says. For example, acetylcholinesterase inhibitors and thymectomy are less likely to be effective in this subgroup, she says. These patients are more likely to benefit from the monoclonal antibody rituximab, and they tend to do better with plasmapheresis than with IVIG.

OPTING FOR SURGERY

After repeated courses of plasmapheresis, Brydson, who is now studying biomedical sciences at Texas A&M University, was ready to have her thymus removed. "That was my saving grace," she says. Recovering from surgery was challenging, but she has had no second thoughts. "It's been several years since my thymectomy, and I am close to remission," she says. "I haven't experienced any major symptoms since then."

Luckily, Brydson's experience is not unique. "For nearly a century, myasthenia gravis patients and their physicians have had the mindset of bravely living with myasthenia gravis," says Dr. Richman. "With our current treatments, on the order of 80 percent of patients can experience a remission—complete resolution of all, or nearly all, symptoms. The new mindset should be, 'Aim to live a normal life.'" NN