

Trials and Tribulations

The first controlled study of thymectomy for myasthenia gravis.

BY TOM VALEO

At the age of 20, Lindsay Knudsen was attending the University of Wisconsin-Oshkosh while holding down a part-time job. She also volunteered with a local community theater for fun. “I was busy, busy, busy,” she says.

Suddenly she started to feel exhausted all the time. Knudsen even began to have trouble chewing. “When I could eat only two or three bites of a hamburger, I knew something was wrong,” she recalls.

A trip to a neurologist revealed that she had myasthenia gravis (MG), a rare disease in which the immune system attacks receptors on the muscles that receive nerve impulses from the brain. As the receptors are destroyed, voluntary muscles throughout the body grow weaker. Sometimes only the muscles of the eye and eyelid are affected. But MG can affect any voluntary muscle, including those needed for swallowing and breathing.

Knudsen received a prescription for pyridostigmine bromide (Mestinon). The drug boosts levels of acetylcholine, a chemical needed to help nerve impulses reach the muscles. She felt better instantly. As her disease worsened, though, the drug alone was not enough. Even carrying groceries up the stairs of her apartment left her exhausted. A neurologist encouraged Knudsen to have her thymus gland surgically removed, a procedure known as thymectomy.

WHY THYMECTOMY?

Throughout childhood and adolescence, the thymus, nestled behind the breastbone, vigorously produces immune cells that help the body stave off disease. In adulthood the gland gradually shrinks, but people with MG sometimes develop a tumor or an overgrowth of thymus cells. Since the 1930s physicians have believed that the thymus encourages the immune system to attack nerve receptors on the muscles, and that removing it should help.



“I was diagnosed with myasthenia gravis on December 22, 2001, and I was on the operating table on April 23, 2002,” Knudsen says. “I was in a rapid decline.”

But does thymectomy really help?

Don Fleischhauer of Annapolis, MD, developed MG three years ago at the age of 72. His neurologist decided against thymectomy because Fleischhauer’s thymus didn’t appear to have a tumor or any other irregularity. Instead, the neurologist prescribed pyridostigmine bromide along with prednisone, a steroid that suppresses inflammation. Fleischhauer’s symptoms, which included speech and swallowing difficulties, improved on the medications, and after a few months he stopped taking pyridostigmine bromide. Today he takes only a small dose of prednisone.

“If I have to take prednisone for the

rest of my life, that wouldn’t be bad,” Fleischhauer says. “When I was taking a larger dose, my appetite increased and I gained a lot of weight, but at my current dose I don’t notice any side effects.”

Knudsen also started taking prednisone after her thymectomy, along with pyridostigmine bromide and other medications that suppress her immune system. And every three weeks she undergoes plasmapheresis, a treatment that removes from

her blood the antibodies suspected of attacking her acetylcholine receptors. “I call it my oil change,” she says.

After her surgery, Knudsen started to feel much better. She got a master’s degree in educational psychology and wrote her thesis on the social and psychological adjustments of people with MG. She even presented her findings to the American Psychological Association

At first, most patients wanted to be in the thymectomy group. Now, most of them don’t.

and the Myasthenia Gravis Foundation of America. Today, Knudsen is the chairperson of the Wisconsin chapter and serves on national committees.

THE CLINICAL TRIAL

But she isn't sure that the thymectomy had anything to do with her recovery. "I don't know if it helped, because I'm on so many medications," Knudsen says.

Neurologists can't prove that thymectomy is effective either. But now researchers are conducting the first controlled study to determine if the surgery actually helps control MG symptoms.

Thymectomy used to be the only immune-related treatment for the disease. Since the 1970s, however, prednisone has proved very effective at suppressing symptoms. Unfortunately, large doses of steroids cause serious side-effects, such as weight gain, insulin resistance, high blood pressure, osteoporosis, cataracts, glaucoma, and personality changes.

In 2000 a group of researchers began developing a study to test treatment with thymectomy plus prednisone against treatment with prednisone alone. The study, sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), has recruited nearly 60 patients and hopes to recruit 140 more. Half the patients in the study receive thymectomy and prednisone, while the other half receive prednisone alone. MG patients who have a tumor in their thymus gland are not eligible for the study.

"We need to know exactly what kind of additional benefit, if any, is conferred by thymectomy," says Gil Wolfe, M.D., a neurologist at the University of Texas Medical School in Dallas and one of the lead investigators.

At the start of the study, finding patients willing to forego thymectomy was difficult because most

patients wanted the operation. But prednisone and other medications have been so effective that fewer patients today are choosing surgery. Now the patients who decline to participate in the study because they *do not* want a thymectomy outnumber those who decline because they *do* want one by about three to one, according to Dr. Wolfe.

Dr. Wolfe still suggests thymectomy for some of his own patients, especially those who have a tumor or an overgrowth of cells in the thymus gland, but he makes these decisions only after careful assessment and discussion with the patient. Younger patients with an active thymus gland may be more likely to receive surgery than older patients, as are female patients, who are more susceptible to MG than males. Also, patients who have antibodies in their blood against acetylcholine receptors—strong evidence that the immune system is actively attacking them—are more likely to have their thymus removed.

"But the decision is made on an individual basis, and you have to tell patients you're not absolutely sure a thymectomy will benefit them," Dr. Wolfe says.

The study will judge the effectiveness of thymectomy by comparing disease status and how much prednisone patients need afterwards. If thymectomy patients do better, or need significantly

less prednisone to control their disease, then thymectomy will be deemed worthwhile, at least in cases similar to those in the trial.

"We think a 30 percent reduction in steroid use would be a significant benefit," says Henry J. Kaminski, M.D., of Case Western Reserve University, a primary co-investigator. "If thymectomy allows a 30 percent reduction in prednisone, that would make it worth the risk and discomfort of surgery."

When having their muscle strength evaluated, all study participants are instructed to wear a turtleneck sweater so the examining physician won't know if they've received a thymectomy. (Those patients will have a conspicuous incision over their breastbone.) If the scar were visible, physicians who favor thymectomy might be inclined, at least unconsciously, to perceive those patients as healthier. Dr. Wolfe does not expect the placebo effect to influence patients significantly because it diminishes over time. "A placebo effect from surgery persisting for three years would be highly unlikely," he says.

The study could produce ambiguous results. For example, if patients on prednisone experience a greater reduction in symptoms but don't go into remission as often as those who receive thymectomy, it would be hard to judge if the surgery is worthwhile or not.

In any event, Knudsen would be skeptical of results showing that thymectomy is of little value because each case is unique.

"Myasthenia gravis is called a snowflake disease because everyone has different symptoms, and everyone has a different treatment regimen," she says. "I don't think it's fair to take a weapon out of the arsenal because it didn't work for some patients. It may work for others." 

WANT TO JOIN THE MG TRIAL?

Go to clinicaltrials.gov/ct2/show/NCT00294658 or call Greg Minisman, M.A. (205-934-4905) or Gary Cutter, Ph.D. (205-934-4905).

For more information about myasthenia gravis, contact the Myasthenia Gravis Foundation of America (myasthenia.org) at 651-917-6256 or 800-541-5454.