SOUTHWESTERN NEWS

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NEW CAUSE IDENTIFIED FOR INCURABLE MUSCLE CONDITION

DALLAS – May 20, 2003 – Researchers from UT Southwestern Medical Center at Dallas and the Mayo Clinic have discovered a novel genetic mutation that leads to a debilitating muscle condition known as myasthenia.

Myasthenia, a severe form of muscle weakness, usually results from an autoimmune attack against the nerve-muscle junction in which the nerve's communication to the muscle is broken down. In a study appearing this week in the online early edition of *Proceedings of the National Academy of Sciences*, researchers unveil a new cause discovered in a single patient: a genetic mutation leading to a shutdown in muscle responsiveness to the nerve's electrical impulses.

"This was a surprise in that it's a totally different mechanism for a well-researched disease," said Dr. Stephen Cannon, chairman of neurology at UT Southwestern, who studied the consequences of the genetic mutation. "Until this study, every single case of myasthenia ever examined had been attributed to a reduction in what's called the safety factor of neurotransmission – or how reliably the nerve talks to the muscle."

The discovery may open new avenues of investigation into the disease and, possibly, new therapeutic approaches, said Dr. Cannon.

The patient in whom the genetic mutation was discovered is a 20-year-old woman diagnosed with congenital myasthenic syndrome – a subset of illness under the disease known as myasthenia gravis. Myasthenia gravis, which literally means grave muscle weakness, affects about 37,000 Americans. People who have this disease often cannot walk long distances or hold up their arms, and some have difficulty breathing. Muscles that control eye and eyelid movements, facial expression, chewing, talking and swallowing are often, but not always, involved.

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Myasthenia gravis occurs in all ethnic groups and both genders. It most commonly affects young adult women between the ages of 20 and 40 and older men in their 50s and 60s, but it can occur at any age. The late Sir Lawrence Olivier suffered from the illness, which has no cure, but is manageable with treatment.

In people with normal nerve-muscle interaction, every nerve impulse elicits a muscle response. The initial response is a localized electrical current, which in turn triggers sodium channels within the muscle to generate electrical impulses that travel the entire length of the muscle.

All previously known cases of myasthenia resulted from a reduction in the safety factor of nerve-muscle interaction, most often due to a person's own autoimmune antibodies attacking the acetylcholine receptor. In some cases, the reduction resulted from mutations in the receptor itself or the cellular components that make or degrade the acetylcholine neurotransmitter.

Dr. Andrew Engel, director of the Neuromuscular Research Laboratory at the Mayo Clinic and senior author of the study, discovered that the myasthenic patient in this study exhibited normal function at the neuromuscular junction, but once the signal traveled to the muscle, it failed to excite, or spread over, the length of the muscle. Genetic analysis revealed a new mutation in the muscle's sodium channel. Dr. Cannon's team identified a defect in the gates that open and close the channel, allowing it to conduct the current. In the case of this patient, the gate to the sodium channel was inactivated, or stuck in a closed position.

Akira Tsujino of the Mayo Clinic and Chantal Maertens of Harvard Medical School were first authors on the paper.

The study was funded by the National Institutes of Health and the Muscular Dystrophy Association.

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