

Diagnosing NEUROMUSCULAR CONDITIONS in CHILDREN: A Process of Elimination

by **John Day, M.D., Ph.D., and Stephen Smith, M.D.**

Some physicians who treat neuromuscular diseases liken the process of diagnosing nerve and muscle conditions to solving crimes. In law enforcement investigations, detectives use fingerprints, DNA samples and other clues. Neuromuscular physicians also use clues — namely presenting symptoms, medical histories and physical examination results — to pinpoint the culprit behind their patients' symptoms.

There are more than 60 types of neuromuscular conditions. Neuromuscular diseases are either acquired or inherited. Acquired conditions typically result from injuries to or inflammation of the nerves and muscles. For this article, we'll concentrate on the inherited diseases Charcot-Marie-Tooth disease, muscular dystrophy, and spinal muscular atrophy and the acquired condition dermatomyositis. These neuromuscular conditions affect boys and girls of all ages and ethnic groups — often more than once in one family.

One of the goals of this article is to outline for pediatricians and primary-care physicians the clues indicating that a patient may have a neuromuscular disease. With this information, physicians can determine whether referring the patient to a neuromuscular specialist for further evaluation and treatment is necessary.

Finding a Diagnosis

Diagnosing neuromuscular conditions is complex. For that reason, patients with nerve and muscle diseases often travel a long road — possibly stopping at several physicians' offices — before they're referred to a neuromuscular specialist.

Testing numerous hypotheses is vital to diagnosing neuromuscular diseases. Testing hypotheses should begin almost immediately — even before the physical exam occurs. Physicians should be alert to how firm — or weak — patients' handshakes are, to whether patients have difficulty walking, and to whether they have trouble getting in and out of chairs. These observations can help determine whether a condition is a nerve or muscle disorder — the first step in making a diagnosis.

Neuromuscular physicians divide nerve and muscle diseases into four categories, based on location:

- Anterior horn cell (the motor-nerve cell in the spinal cord)
- Muscle
- Nerve
- Neuromuscular junction

The presence of twitching muscles suggests a problem with the anterior-horn cell or motor neuron. Poor gait and posture could indicate muscle atrophy, which results from anterior horn cell or nerve damage. Patients who dramatically fatigue during physical exertion may have a neuromuscular junction disorder, such as myasthenia gravis.

Acquired Conditions

Dermatomyositis

One of the most common acquired neuromuscular conditions is dermatomyositis. This autoimmune disease, one of a group of diseases called inflammatory myopathies, characteristically results in inflammation of the skin and muscle.

Etiology and Symptoms

The cause of dermatomyositis — which develops over weeks to months — is unknown, although the small blood vessels in the skin and muscles are involved.

A principal sign of the disorder is an erythematous surface rash on the face, elbows, knuckles and knees. Commonly, a purplish discoloration is present over the eyelids. The rash is often scaly and reddened in children with fair skin, and scaly and darkened in children with darker skin.

Along with the rash, muscle weakness in the hips and shoulders is present. Patients describe muscle aches and muscles which are tender to the touch. Children with dermatomyositis may eventually have difficulty rising from a sitting position, climbing stairs, lifting objects or reaching overhead. They may have trouble swallowing, complain of not feeling well, and be irritable and frequently tired. More rarely, a child's voice may change to a more nasal sound.

al motor or sensory nerve. The electrodes produce a small electric shock that can cause mild discomfort. The electrical impulse stimulates sensory and motor nerves and provides quantifiable information through which physicians can arrive at a diagnosis.

Although no treatments exist to prevent CMT disease from progressing, there are ways to reduce the physical symptoms that cause movement and coordination problems. Physical therapy can improve muscle flexibility with range-of-motion and balance exercises. Stretching the muscles can help reduce muscle-shortening (contractures), which often occurs with CMT disease.

Some patients wear lightweight braces to correct foot drop. Surgery is sometimes needed to correct severe foot deformities. Occupational therapy helps patients perform daily activities such as dressing, eating, opening doors and bottles, and writing. If patients have tremors, they should avoid caffeine and alcohol. In severe cases, beta blockers can help reduce tremors.

Muscular Dystrophy

Muscular dystrophy (MD) refers to a group of genetic diseases characterized by progressive weakness and degeneration of the skeletal (voluntary) muscles. The genetic flaws present in many forms of MD also affect the heart, smooth muscles, brain, eye, gastrointestinal tract, and reproductive and endocrine systems.

Etiology and Symptoms

Consequently, symptoms during the course of the disease — or even at onset — can be amazingly diverse, ranging from muscle weakness to involuntary stiffness. Swallowing difficulties, mental deficits, and vision and reproductive problems are also symptoms, depending upon the type of MD.

The major forms of MD include myotonic, Becker, and Duchenne. Duchenne MD is the most common form in children and is an X-linked recessive disorder mostly affecting boys. Weakness in Duchenne first appears when a boy is 2 to 6 years old.

Boys with Duchenne MD show generalized weakness that affects hip, shoulder and trunk muscles first. The patients' calves are often enlarged. This type of MD progresses slowly, but eventually will affect all voluntary muscles. The disease progresses to death (often by the age of 20) due to heart failure or compromised respiration.

Becker MD is genetically similar to Duchenne MD but less severe. Its symptoms and rate of progression are typically milder than Duchenne MD, so Becker patients can have a normal life span with only mild progressive weakness.

Myotonic MD is an autosomal dominant disease that varies markedly in boys and girls. It usually progresses very slowly, sometimes over more than 50 years. Unlike other muscular dystrophies, myotonic MD is accompanied by an inability to relax affected muscles.

Myotonic MD usually shows first in the face, feet, hands and neck. It may eventually affect all skeletal muscles as well as the throat and breathing muscles. About half of the people with myotonic MD will show symptoms by age 20. Patients may present with drooping eyelids, difficulty swallowing, a weakened grip or myotonia.

Diagnosis and Treatment

Early diagnosis of MD helps identify and manage the profound features of the disease, expands treatment options and improves outcomes. To improve diagnosis of all forms of MD, primary-care physicians need to be alert to these facts:

- *MD is a genetic disorder, but often there's no family history of the disease.* If progressive muscle disease is known to occur in the family, MD is a logical assumption. Because inheritance is complex, however, MD frequently appears without having been evident in earlier generations. In such instances, the disorder must be distinguished from inflammatory or toxic myopathies to ensure proper treatment.
- *The hallmark of MD is weakness.* Although MD can result in muscle pain, stiffness, tenderness or fatigue, the hallmark of these diseases is progressive weakness. MD is a possibility in patients of any age who have progressive weakness.
- *Superimposed muscle disease can unmask previously undiagnosed MD.* Patients with underlying MD can first become symptomatic, for example, because of superimposed viral myositis. Because of their underlying muscle disease, MD patients have persistent symptoms and serological abnormalities even after the superimposed insult resolves.
- *Serum creatine kinase (CK) can identify many, but not all, people with MD.* A marked elevation of serum CK is a reliable hallmark of Duchenne MD. Although other forms of MD also show elevated CK levels, that trait is not invariable.
- *EMG is a sensitive clinical indicator of people with myotonic dystrophy.* EMG is useful in distinguishing neurogenic and myopathic causes of weakness. EMG can be helpful in diagnosing myotonic dystrophy, which causes spontaneous trains of electrical activity in muscle fibers, but this finding is not always present in myotonic dystrophy, and it does occur in many other disorders.
- *Genetic testing can diagnose MD without the need for a muscle biopsy.* We can now use a genetic blood test to investigate a clinically suggested diagnosis of MD. If the diagnosis is genetically confirmed, a muscle biopsy may provide little additional useful information and can be avoided. Informed genetic counseling is essential before and after any genetic testing.

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There is no specific treatment for any of the forms of MD. Physical therapy to prevent contractures, orthoses, and corrective orthopaedic surgery may improve the quality of life in some cases.

Spinal Muscular Atrophy

There are three main types of spinal muscular atrophy (SMA), which is caused by progressive degeneration of motor neurons in the spinal cord. The inherited condition affects infants and young children, producing severe (type I), moderate (type II), and mild (type III) phenotypes.

Childhood-onset SMAs may run in families, and more than one case is likely to occur in siblings or cousins of the same generation. Parents carry the gene but have no symptoms. Since SMA is a recessive disorder, on average one of every four children will have the disease if both parents are carriers. The gene for SMA has been identified, and accurate genetic diagnostic blood tests exist. The condition causes weakness and wasting of the voluntary muscles.

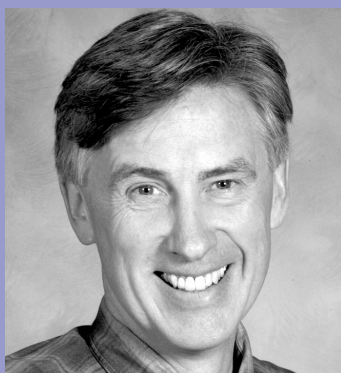
Etiology and Symptoms

SMA type I, also called Werdnig-Hoffmann disease, is evident before birth or within the first few months of life. Its symptoms include floppy limbs and trunk, feeble movements of the arms and legs, swallowing and feeding difficulties, and impaired breathing. Affected children never sit or stand and usually die before the age of 2. Symptoms of SMA type II usually begin between 3 and 15 months of age. Children may have respiratory problems, floppy limbs, decreased or absent deep tendon reflexes, and twitching arm, leg or tongue muscles. Such children may learn to sit but will never be able to stand or walk. Life expectancy varies. Symptoms of SMA type III, also known as Kugelberg-Welander disease, appear between 2 and 17 years of age. They include abnormal walking patterns, difficulty running, climbing steps or rising from a chair, and slight tremors of the fingers.

Treatment

Treatment of all forms of SMA is symptomatic and supportive. It includes treating pneumonia, curvature of the spine, and respiratory infections, if present. Physical therapy, orthotic supports and rehabilitation therapies also are useful. Genetic counseling is imperative. Some problems with fatigue can be lessened by use of food supplements or medications that enhance neuromuscular transmission. The prognosis for individuals with SMA varies depending on the severity of the symptoms.

Authors' Profiles



John Day, M.D., Ph.D., is a neurologist and a professor of neurology and human genetics at the University of Minnesota. At the University, he's also director of the Paul and Sheila Wellstone Muscular Dystrophy Center and medical director of the Neuromuscular Biopsy Laboratory.

At Gillette Children's Specialty Healthcare, Day sees pediatric and adolescent patients with muscular dystrophy, spinal muscular atrophy, and other neuromuscular conditions.

He received his medical degree from the University of Minnesota in 1977 and a doctorate in neurosciences from Albert Einstein College of Medicine in New York in 1982. Day completed training in internal medicine at Montefiore Hospital in New York and in neurology at the University of California–San Francisco, where he also completed a fellowship in clinical neurophysiology. He has more than 15 years' experience treating pediatric neuromuscular disease.



Stephen Smith, M.D., is a pediatric neurologist at Gillette Children's Specialty Healthcare and medical director of Gillette's neuromuscular program. He sees patients with muscular dystrophy, spinal muscular atrophy, and other neuromuscular conditions. He has a special interest in neuromuscular pathology and heads

a neuromuscular laboratory at Hennepin County Medical Center in Minneapolis. He has more than 25 years' experience treating pediatric neuromuscular disease.

At the University of Minnesota, Smith completed his medical degree, a residency and a pediatric neurology fellowship. He also completed an internship and residency at the University Hospitals of Cleveland.

Gillette Participates in Clinical Trial

Gillette Children's Specialty Healthcare is one of five U.S. medical centers taking part in a study of children with spinal muscular atrophy (SMA). Funded by the National Institutes of Health, the \$1.1 million study attempts, first, to accurately measure muscle strength in children with SMA and, second, to record changes — even small ones — that may occur after muscle-strengthening treatment.

The study, which was launched in 2000, has several phases:

- Phase I – Determining whether muscle strength and other attributes of children with SMA can be measured (phase complete)
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- Phase III – Testing whether creatine, a nutritional supplement, affects lung capacity, muscle strength or muscle function (phase complete)
- Phase IV – Testing the drug, riluzole — which is used to treat adults with ALS — on infants with type I SMA (planned)

Stephen Smith is a co-investigator in the study. Other members of the Gillette study team are:

- Ralph Faville, M.D. and Mark Gormley Jr., M.D.
- Jean Stout, P.T. and Joyce Trost, P.T.
- Maureen Cronin, R.N.
- Andrea Postier, research coordinator

For additional information, contact Andrea Postier at 651-325-2314.

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For more information, visit our Web site at www.gillettechildrens.org, or call Susan Ellerbusch, program manager of Gillette's Center for Pediatric Rehabilitation, at 651-229-3915 or 800-719-4040. Registration deadline is April 16.

Fourteenth Annual Conference

Clinical Gait Analysis

May 13 – 15, 2004
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This three-day course features simultaneous basic and advanced courses. The basic course teaches introductory skills for analyzing gait and planning associated treatments. The advanced course is tailored to clinicians who have more experience in gait analysis. It examines in greater depth the complexities of gait interpretation in children who have disabilities. Both courses focus on interpreting gait data and planning associated treatment for ambulatory children with cerebral palsy.

For registration information, contact Amy Schall at 651-229-1721 or go to www.gillettechildrens.org.

Registration deadline is April 23.

If you're interested in obtaining **back issues of A Pediatric Perspective**, log on to Gillette's Web site at <http://www.gillettechildrens.org/default.cfm/PID=1.7.8.1>. Issues from 1998 to the present are available.

Diagnosis and Treatment

To diagnose dermatomyositis, order blood levels of muscle enzymes and an electromyogram (EMG). For a definitive diagnosis, arrange for a muscle biopsy. The disease typically responds well to oral steroids but is sometimes resistant and may require treatment with azathioprine or methotrexate (immunosuppressive drugs). Treatment with intravenous immunoglobulin has also been proven to be safe and effective. Physical therapy helps to preserve muscle function and joint mobility and helps control muscle pain.

Genetic Conditions

Genetic neuromuscular conditions result from myopathies with errors in muscle structures. Charcot-Marie-Tooth (CMT) disease — also known as hereditary motor and sensory neuropathy — is one of the most common inherited neurological disorders, affecting about one in 2,500 people in the United States.

CMT Disease

CMT disease is a disorder affecting the peripheral nerves that carry information to and from the spinal cord. Symptoms include weakness and loss of sensation in the limbs.

Etiology and Symptoms

The most common genetic defect that causes CMT disease affects the myelin sheath — the coating that insulates the nerve fibers so nerve impulses can travel freely over the fibers. When myelin is defective, the impulses travel very slowly.

The areas of the body most affected are those farthest from the spinal cord — the arms, hands, legs and feet. Weakness of the foot and lower-leg muscles often results in highly arched feet and weak ankles. This leads to foot drop, which causes frequent trips and falls. Degeneration of the sensory nerves reduces a patient’s ability to feel heat, cold and pain.

Diagnosis and Treatment

To diagnose CMT disease, begin with a patient history, family history and neurological examination. During the neurological exam, look for:

- Weakness in the feet, legs and hands
- Decreased muscle bulk, especially in the feet and lower legs
- Reduced tendon reflexes
- Sensory loss

Look for evidence of foot deformities, such as high arches, hammertoes, inverted heels and flat feet. Also watch for mild scoliosis, hip dysplasia and other orthopaedic problems.

If you suspect CMT disease, consider ordering electrodiagnostic tests. The tests — which are performed by physicians trained in this type of analysis — have two parts: nerve-conduction studies and an EMG. During nerve-conduction studies, electrodes are placed on the skin over a peripher-

al motor or sensory nerve. The electrodes produce a small electric shock that can cause mild discomfort. The electrical impulse stimulates sensory and motor nerves and provides quantifiable information through which physicians can arrive at a diagnosis.

Although no treatments exist to prevent CMT disease from progressing, there are ways to reduce the physical symptoms that cause movement and coordination problems. Physical therapy can improve muscle flexibility with range-of-motion and balance exercises. Stretching the muscles can help reduce muscle-shortening (contractures), which often occurs with CMT disease.

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