

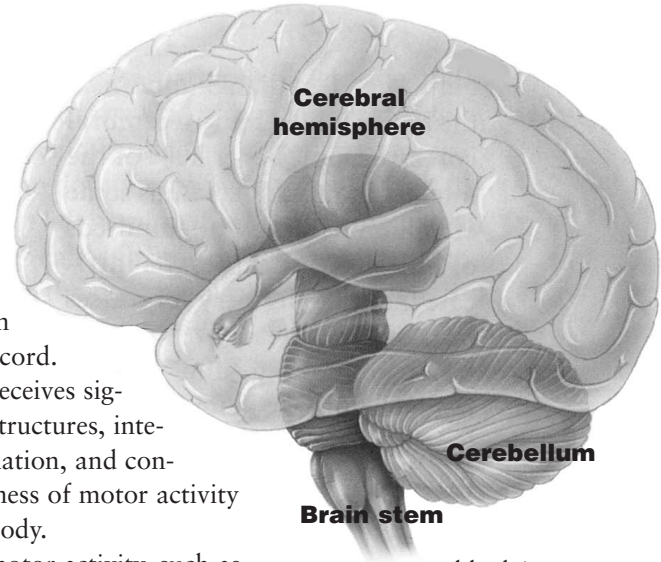
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Ataxia

A complex group of diseases

By Lawrence Schut, MD



Descending the steps in Todd Amphitheater at the University of Minnesota Medical School on a wintry day in 1950, Dr. John Schut knew immediately why he was spilling his coffee. Schut, a neurology resident, was acutely aware that his balance was off—a telltale sign that, at 29, he had the ataxia disorder that had stricken his father at age 32, killing him at 48. The disease was already slowly disabling Schut's sister and brother and two dozen of his cousins.

In the Army from 1946 to 1948, Schut had performed microscopic studies on the brain and spinal cord of several of his relatives. He also examined dozens of relatives to evaluate their neurologic status. He published three important scientific papers on the clinical, genetic, and pathologic features of the disease, which had become known as hereditary ataxia. The presence of this cruel disease in his family impelled him to make the search for its cause and cure his life's work.

What is ataxia?

The word ataxia is derived from the Greek word "ataxis," meaning "without order." Medically, the term indicates a lack of coordination. The center for coordination is the cerebellum, which is at the base of the skull, behind and below the cerebral hemispheres. It has nerve fiber connections to other nervous system structures—the cerebral

hemisphere, brain stem, and spinal cord. The cerebellum receives signals from these structures, integrates the information, and controls the smoothness of motor activity throughout the body.

A complex motor activity, such as shooting a basketball, requires balance, directional control, proper force, timing, velocity control, and appropriate termination of movement. The cerebellum functions as an error detector and corrector. Thus, any condition that interferes with normal cerebellar function causes ataxia.

Symptoms of ataxia

Symptoms of ataxia come on either suddenly or gradually.

When symptoms appear suddenly, possible causes include:

- Head trauma
- Stroke
- Cardiac or respiratory arrest
- An infection such as an abscess or chicken pox
- Exposure to certain drugs or toxins such as alcohol or seizure medication
- Tumor in the cerebellum, either from childhood brain cancer or metastases from other sites

When symptoms appear gradually, the cause may be:

- Deficiencies in vitamin E or B-12
- Multiple sclerosis (which also can

come on suddenly)

- Exposure to certain drugs or toxins (chronic alcohol use, lead, and cadmium)
- Congenital abnormalities such as deformity of the cerebellum or genetic biochemical defects
- Remote effects of cancer somewhere in the body
- Slow-growing tumors
- Degenerative disorders (spinocerebellar ataxia, both hereditary and sporadic)

Strokes, tumors, abscesses, and trauma are more likely to affect just one side of the cerebellum and thus cause one-sided ataxia. A person with a one-sided cerebellar lesion may be considerably disabled, but still has one side that functions well.

Conditions affecting both sides of the cerebellum or its connections cause imbalance, gait ataxia, right and left extremity incoordination, and slurred speech. These include drug toxicity, alcohol abuse, vitamin deficiency, and the spinocerebellar degenerations or ataxias. All of these conditions result in temporary or permanent loss of nerve

cell function and may lead to nerve cell death and shrinkage of the spinal cord, brain stem, and cerebellum. Some ataxias appear in individuals without any family history of ataxia. These sporadic ataxias are as disabling as the hereditary ataxias and can be lethal as well.

Hereditary ataxias

The hereditary ataxias are due to a gene defect or mutation and are grouped into:

- Dominantly inherited ataxias, which are passed from an affected parent to child, with each child having a 50–50 chance of inheriting the gene abnormality.
- Recessively inherited ataxias, in which the ataxia is hidden in the genes of both healthy parents, and the child can develop the disease only if he/she inherits the defective gene from both parents.
- X-linked recessive ataxias, due to a genetic defect on the X-chromosome. The ataxia appears only in males and is carried by females who themselves are not affected.

Classifying ataxias

In 1863, Nicholas Friedreich, in Germany, described cases of childhood ataxia, showing they were different from multiple sclerosis. In 1893, Pierre Marie, in France, noted the hereditary nature of some adult cases of ataxia. Afterward, most cases of ataxia were categorized as Friedreich's (recessive) or Marie's (dominant). However, merely looking at the hereditary patterns or observing the clinical and pathologic features did not help doctors and scientists understand the basic cause of the ataxias.

John Schut knew that the answer lay in finding the defective gene, so in the decade following the development of his own ataxia he searched for a genetic linkage between known blood factors and ataxia. He believed each ataxia could be clearly distinguished by identifying the gene causing it.

Due to his progressive disability, Schut could not continue his research. Shortly after his death in 1972, Drs. Robert D. Currier and John F. Jackson reported convincing evidence that the ataxia gene in a large Mississippi family was related to a complex of genes located on the sixth chromosome. Using the same technique, Dr. Jonathan Haines at the University of Minnesota established in 1984 that the ataxia gene in the Schut family was linked to the same genes on chromosome six, thus confirming John Schut's supposition. The exact mutant gene had yet to be isolated, but scientists were able to narrow their focus to a very small area on this one chromosome. In 1986, Dr. Harry Orr, a molecular biologist at the University of Minnesota, analyzed hundreds of blood samples from the Schut family. Meanwhile, Dr. Huda Zoghbi at Baylor University assumed work on the Mississippi family. Their combined efforts resulted in the discovery of the ataxia gene in 1993. It was the same mutation in both families and the first spinocerebellar ataxia gene to be discovered. The mutation, designated SCA1, is found worldwide, but it is very rare and less common than some of the other ataxias.

A total of 28 genetically distinct varieties of dominant SCA have been reported. Among these, a dozen defective genes have been discovered. Genetic testing can now be used to diagnose the type of ataxia a person has. It can also be used to confirm whether an "at-risk" person is carrying the gene.

Unfortunately, there are many families with ataxia who have, as yet, unidentified gene mutations. Further, many individuals with ataxia of unknown type have no family history of ataxia and gene testing is negative. These sporadic ataxias occur randomly in the general population and there are no specific tests to identify what they are.

Diagnosis

Most people don't know what ataxia is and may overlook the early symptoms. Anyone with progressive gait disorder or imbalance should be evaluated by a neurologist. MRI is recommended in all cases. If a treatable cause is not discovered, a gene test should be done. In about 60 percent of the cases, the gene test will determine the type of ataxia.

What to expect

All ataxias have gait disturbance and imbalance as initial symptoms. Progression into associated symptoms such as slurred speech and difficulty swallowing vary greatly with the type of ataxia. For example, SCA5 patients can expect slower onset of total disability in comparison to SCA1, SCA2, or SCA3. Some ataxias end in premature death due to severe problems with swallowing and an inability to cough because of degeneration of the brain stem.

Such was the case for John Schut, who died at 52, more than 20 years after making his own diagnosis. The ataxia rendered him totally dependent the last five years of his life.

National Ataxia Foundation

The National Ataxia Foundation (NAF) was formed by John Schut and his brother, Henry, in 1957. Its purposes are to promote awareness of the degenerative ataxias, support research into the causes and cure of the disease, and provide support and comfort to ataxia patients and their families.

Research on the ataxia disorders is going on worldwide. At this time, no new treatments or cures are available, but great efforts are under way to find the answers. ❏

Lawrence Schut, MD, is a nephew of Dr. John Schut. He did not inherit the family ataxia, but became a neurologist because of the disease in his extended family. Now semi-retired, he practices at CentraCare Clinic in St. Cloud and is medical director of the National Ataxia Foundation (www.ataxia.org).
