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## **Degenerative Central Nervous System (CNS) Disease**

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## In Brief

### Degenerative Central Nervous System (CNS) Disease

**Rett Syndrome: Clinical Update and Review of Recent Genetic Advances.**

Ellaway C, Christodoulou J. *J Pediatr Child Health*. 1999;35:419–426

**Heredodegenerative Disease.** In: Menkes J, ed. *Child Neurology*. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000:171–227

**Clinical Characteristics of Children With Cerebral White Matter Abnormalities.** Kristjansdottir R, Uvebrant P. *Europ J Pediatr Neurol*. 2000;4:17–26

**The Inherited Neurodegenerative Disorders of Childhood: Clinical Assessment.** Percy AK. *J Child Neurol*. 1987;2:82

**Second International Rett Syndrome Workshop and Symposium.** Percy AK. *J Child Neurol*. 1993;8:97

The hallmark of degenerative disorders of the CNS is the progressive loss of previously acquired abilities. In infants and young children, a deceleration in the rate of development is often the first presentation: the child falls progressively behind other children and only subsequently loses previously acquired milestones. When the declining developmental quotient is not due to an extrinsic agent or event or to secondary involvement of the CNS by a generalized systemic disease, neurodegenerative disease becomes a consideration.

The acquisition of new developmental milestones does not exclude the existence of a degenerative disorder. In healthy infants, strides in development occur sporadically, with a child often appearing to have reached a plateau for several weeks. Initially, it may be only the prolongation of one of these plateaus that leads to suspicion of a progressive neurodegenerative disease

Most degenerative CNS disorders can be divided clinically into three

groups: gray-matter diseases, white-matter diseases, and system diseases. The gray-matter diseases, which primarily involve the neurons, occur with or without histologic evidence of storage of abnormal metabolic products. They lead to neuronal death and secondary degeneration of axons. In the white-matter diseases, myelin is disrupted, either by the destruction of normal myelin or by the production of biochemically abnormal myelin. The system diseases are a heterogeneous group of conditions involving progressive degeneration of anatomically defined systems, such as the dorsal columns, pyramidal tracts, or cerebellar nuclei. Typically, both neurons and myelin are destroyed in these disorders.

The first clinical task in evaluating a child for any neurodegenerative disorder is to document that he or she has lost previously acquired milestones or has a decelerating developmental quotient. In either instance, the most important diagnostic tool is repeated developmental evaluations.

The major clinical features that differentiate gray-matter from white-matter diseases are related directly to the functional roles of the neurons and myelin. Neuronal involvement in gray-matter disease leads to the early onset of dementia, the progressive loss of cognitive abilities, and seizures that frequently are myoclonic. The basal ganglia and cerebellar nuclei are collections of neurons, so extrapyramidal and cerebellar signs, such as ataxia, are common. Ganglion cells of the retina are affected in many of the gray-matter disorders, producing pigmentary degeneration of the retina. Abnormal storage of lipid in retinal ganglion cells (eg, in Tay-Sachs disease) makes the perifo-

veal area look gray and opaque. The fovea, which contains no ganglion cells, appears red by contrast, producing the clinically detected "cherry red spot."

The majority of degenerative diseases of white matter stem from biochemical defects resulting in abnormal myelin that breaks down rapidly. These "dysmyelinating" disorders are called leukodystrophies. Clinically, the earliest sign of most white-matter degenerations is spasticity. Dementia and seizures can occur, but usually later in the clinical course. Extrapyramidal signs are rare, but involvement of cerebellar pathways can cause ataxia. Rather than the cherry-red spot of gray-matter disease, optic atrophy is the most characteristic ocular change seen in white-matter disease. Some patients even have cortical blindness from demyelination of the optic pathways in the cerebral hemispheres.

Each of the so-called system diseases has its own signs and symptoms, depending on the particular neural pathways involved. One such disease is Rett syndrome (RS), which is characterized by a period of normal development followed by the loss of developmental milestones and the onset of stereotypic hand movements akin to those seen with autism, followed by seizures and dementia. RS affects girls, probably exclusively, and occurs worldwide. Although most cases are sporadic, the disease has long been suspected of having a genetic basis. Recent genetic advances suggest that the gene for RS is located on the distal arm of the X chromosome.

Clinical criteria alone can point to a diagnosis of RS. Usually the antenatal and birth histories are normal, but most girls affected with RS pass through four predictable stages:

Stage 1 (birth to ~18 mo): Deceler-

ation of head growth, beginning between 2 and 4 months of age, results in an acquired microcephaly. This insidious failure of brain growth can be missed if head circumference is not meticulously measured and plotted at health supervision visits. Early in the disease, babies show decreased interest in their environment and become markedly hypotonic.

Stage 2 (~1 to 2 y): The loss of both expressive language and gross motor milestones, and the onset of abnormal hand movements, seizures, irritability, and insomnia are typical of progressing RS.

Stage 3 (2 to 10 y): Severe mental retardation, seizures, and persistent stereotypic hand wringing movements characterize the childhood phase of RS. Most patients develop ataxic and wide-based gaits, but many affected girls never walk. Tremulousness is a common finding, as are breath-holding spells. Many children who have RS are misdiagnosed as having Angelman syndrome or ataxic cerebral palsy.

Stage 4 (older than 10 y): As girls who have RS approach adolescence, they develop progressive scoliosis, muscle wasting, and can become wheelchair-bound. By the early teenage years, they reach a plateau in their neurologic regression, but death usually occurs during late adolescence from infection or cardiac arrhythmia.

Many disorders that have different etiologies may resemble neurodegenerative diseases in clinical presentation: hydrocephalus, hypothyroidism, mass and structural lesions of the brain, chromosomal defects, poorly controlled

seizures, environmental deprivation, subdural hematomas, and congenital and chronic infections, such as human immunodeficiency virus. Neurodegenerative disorders, unlike these others, are predominantly hereditary. Although the biochemical basis of many neurodegenerative disorders is not fully understood, a precise biochemical diagnosis always should be sought to make possible an accurate discussion of prognosis, to provide counseling, and sometimes to administer specific treatment.

Over the past decade, the availability of molecular genetic testing has improved the accuracy of diagnosis in symptomatic patients, prenatally when genetic risk has been identified, and for carrier testing. Many neurodegenerative disorders can be diagnosed by biochemical testing of blood or urine without invasive procedures to obtain tissue for direct examination. Even so, a diagnosis of an altered enzyme disease should be confirmed histologically.

In general, treatment is available for only a few of the neurodegenerative diseases. Unfortunately, most remain invariably fatal by late childhood. Dietary therapy, restriction of a substrate or substrate precursor, modification of enzyme activity with cofactor vitamin therapy, and enzyme replacement all have been attempted with only limited success. Hope for more effective treatment comes from developments in molecular genetics that may allow the repair of specific point mutations in the human genome.

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**Comment:** In 1966, Rett described a syndrome of cerebral atrophy and hyperammonemia that appeared to affect girls exclusively. Experience has shown that elevated ammonia levels are an exception rather than the rule, and no other laboratory or imaging test provides diagnostic confirmation. Once again, we are thrown back on our clinical skills. Girls who have RS develop normally through the first few months of life, until their brains begin to atrophy, leading to acquired microcephaly. They progress to gait apraxia and truncal ataxia, autistic-like behavior, loss of cognitive function, rather typical "hand-washing" movements, seizures, and pyramidal tract signs. The dementia is devastating.

We usually think of X-linked disorders, which RS appears to be, as primarily affecting boys: factor VIII deficiency, glucose-6-phosphate dehydrogenase deficiency, and ornithine transcarbamylase deficiency. Whereas these disorders are recessive, RS may well be inherited dominantly and be lethal to boys because they have only one X chromosome. Hopefully, as Dr Rich remarks, advances in our understanding of the molecular genetics of neurodegenerative disorders like RS will lead to effective treatment.

*Henry M. Adam, MD  
Editor, In Brief*

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