Gillette Children's Specialty Healthcare

A PEDIATRIC Perspective

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Rett Syndrome: Infancy to Adulthood

by Arthur Beisang, M.D., Raymond Tervo, M.D., and Robert Wagner, M.D.

Rett syndrome (RS) is a complex neurological disorder that affects brain growth. The syndrome occurs almost exclusively in females and produces severe autism-like symptoms. One in 10,000 to 22,000 females has the condition, as do a few boys. In this article, we will focus on females who have RS. We will discuss the symptoms and stages of RS and medical issues that are important when evaluating and caring for children and adults with RS. We also will discuss how to diagnose the condition.

Etiology

Between 90 and 95 percent of children with RS have a mutation on the methyl CpG binding protein 2 (MECP2) gene. The gene, found on the X chromosome, typically makes a protein that is critical to normal brain development.

The mutation causes the MECP2 gene either to make insufficient amounts of the protein or to make a damaged protein that the body cannot use. As a result, there might not be enough protein for the brain to develop normally. The severity of RS depends on the percentage of cells that inactivate the X chromosome with the mutated gene.

Almost always, the genetic mutation is spontaneous, not inherited. Other than being more common in females, there are no prevalence factors for RS.

Diagnosing RS

RS is most often mistaken as autism, cerebral palsy, or nonspecific developmental delay. In the past, making the correct diagnosis called for a long list of diagnostic tests and procedures to rule out other disorders. As new symptoms appeared, it often took months or years to confirm a diagnosis.

Since the discovery of the MECP2 gene, a simple blood test — available since 1999 — can confirm whether a child has the gene mutation that causes RS. Because the MECP2 mutation also is seen in other disorders, the sole presence of the mutation is not enough to diagnose RS. Providers should also consider patients' symptoms and clinical histories as a basis for diagnosing RS. Not all symptoms are present in every patient, and the severity of symptoms varies among patients.

Symptoms and Progression of RS

Health-care providers commonly view RS symptoms in four stages. The symptoms vary, depending on the stage and severity of the disease.

Stage 1

Infants with RS typically have no symptoms during the first six months of life. In Stage 1 (early-onset phase, between 6 to 18 months of age), development stalls or stops. Sometimes, the change is so subtle that parents and health-care providers do not notice it at first. For instance, there often is a deceleration in head growth between 2 and 4 months old, but the slowdown is often unrecognizable until the child's developmental delay becomes obvious.

Babies in this stage of RS might show less eye contact and start to lose interest in toys. There also might be delays in a child's sitting or crawling abilities. In infants, RS often resembles benign congenital hypotonia. If cognitive delays accompany the head-growth deceleration, RS could resemble Prader-Willi syndrome.

Stage 2

In Stage 2 (rapid-destructive phase, between 1 and 4 years of age), children lose skills quickly. They develop apraxia and lose the ability to walk properly. Purposeful hand movements and speech are usually the first abilities lost. Repetitive, purposeless hand movements — such as wringing, washing, clapping or tapping motions — begin. Children might stop saying particular words or phrases; later, they might make grunting and moaning sounds. During Stage 2, tooth grinding is common, and breathing problems start. At times, children will be inconsolable; such crying spells will eventually subside. Slowing of head growth is usually noticeable during this stage.

Stage 3

In Stage 3 (plateau phase, between 2 and 10 years of age), regression slows, and other problems might seem to lessen. While problems with mobility continue, behavior might improve. Children in this stage often display less crying and irritability; they can show improved alertness, attention span and nonverbal communication skills. Seizures and

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movement problems are common in this stage. It is not uncommon for people to remain in Stage 3 for the remainder of their lives.

Stage 4
In Stage 4 (late-motor deterioration phase), severe motor dysfunction is apparent, along with characteristic deformities in the arm and leg joints. The onset of scoliosis is common during this stage. Understanding, communication and hand skills typically remain stagnant; repetitive hand movements might decrease.

Transitioning From Pediatric to Adult Care

Between the ages of 16 and 18, RS patients might need different clinical care. For example, as girls with RS grow up, they need gynecological services, just as other maturing women do. Long-term care for women with RS should include all of the appropriate screening, prevention and treatment efforts common to community-based primary care. Accomplishing the best specialty care for these patients requires providers to understand and address the clinical changes that accompany aging. It requires supporting caregivers with information and expertise, as well as providing palliative and end-of-life resources that cannot readily be found elsewhere. Most women with RS live into their 40s or 50s.

Treatment

To date, there is no cure for RS, but there are a variety of ways to minimize its effects. Rather than addressing the syndrome as a whole, most treatments try to alleviate specific symptoms. The treatments generally aim to slow the loss of abilities, improve or preserve movement, and encourage communication and social contact.

Other options, such as medication or surgery, also can be effective. For example, surgery can correct scoliosis for some people with RS. Similarly, medications can effectively control seizures for people with RS. Other medications can reduce breathing problems and eliminate problems with heartbeat rhythm.

People with RS often benefit from a team approach to care. Members of a care team might include, but are not limited to:
- Developmental specialists
- Developmental pediatricians
- Orthopaedic surgeons
- Gastroenterologists
- Pulmonologists
- Cardiologists
- Neurologists
- Nurses
- Special-education teachers

Other members of the team might include:
- Physical therapists, who can help patients improve or maintain mobility and balance
- Occupational therapists, who can help patients improve or maintain use of their hands and reduce stereotypic hand movements
- Speech and language pathologists, who can help patients communicate nonverbally and improve social interaction

The involvement of family members is critical to ensuring the well-being of those with RS.

Case Study

CK, a 2-year-old girl, was unable to crawl, walk, speak, and use her arms or hands. She also had difficulty sleeping. Her family became concerned about her development when CK was 6 months old and failing to achieve milestones. At 9 months, CK was not sitting or crawling. CK was full-term, and there were no complications during her mother's pregnancy.

CK's pediatrician referred her to a neurodevelopmental pediatrician for an initial opinion. An MRI, a high-resolution chromosome analysis, a molecular analysis, and metabolic studies for fragile X were unremarkable. To that point, there was no known cause for CK's delay.

A physical therapist, an occupational therapist, and a speech therapist evaluated CK when she was 22 months of age. They noted substantial delays in all functional areas. She began to receive special-education services in the early childhood intervention program.

On physical examination, CK was well-nourished and hydrated. Her length and weight were at the 25th percentile. She had microcephaly and generalized hypotonia. Neurodevelopmentally, her functioning was between 6 and 8 months of age.

CK's physician ordered a MECP2 sequence analysis and mutation scanning. The result was abnormal; CK has Rett syndrome (RS).

The reason for this young girl's neurodevelopmental delay is that, in RS, a child's brain development is markedly affected. There is poor neuronal maturation, arborization and synapse formation. There are changes in neurotransmitters and their receptors, which play a vital role in activity-dependent synaptic plasticity and morphogenesis. What follows are prominent cognitive and motor delays. There is a significant loss of function that happens between infancy and the fifth year of life.

Evaluations for Related Conditions

When caring for patients of all ages who have RS, providers should inquire about and evaluate the following conditions.

Seizures

Approximately 90 percent of people with RS have some type of epilepsy. The types of seizures that affect RS patients are the same as those that occur in the general population. A patient's first seizures usually occur between the ages of 2 and 4.

Many people with RS display movements that resemble seizures. Often, a video electroencephalogram (EEG) is necessary to sort out movements typical in RS and movements caused by actual seizures.

Cardiovascular Concerns

Some females with RS have cardiac or heart problems — specifically, difficulties with their heart rhythms. Providers should consider screening for Long QT syndrome by using a 12-lead electrocardiogram. Providers should re-evaluate patients for the condition every few years.

Motor Coordination

As RS progresses, patients experience a loss of motor coordination and muscle strength. Patients will require periodic evaluations for orthoses and other assistive equipment throughout their lifetimes.

Orthopaedic Issues

Orthopaedic issues, such as scoliosis, are common in children with RS. In some cases, the curving of the spine is so severe that the children require surgery. For other patients, bracing relieves the problem, prevents it from getting worse, and delays or eliminates the need for surgery. It is important for providers to periodically monitor patients for the onset of scoliosis.

Breathing Problems

Many RS patients experience abnormal breathing, particularly in stages 2 and 3 of the disease. Such abnormalities might include hyperventilation, breath holding or apnea. Such problems can be severe enough to interfere with a child's responsiveness.

Gastrointestinal Problems

When caring for patients with RS, it is very important to pay attention to gastrointestinal motility. Constipation and dehydration can become significant issues when fluid intake is limited. Some RS patients require a gastrostomy tube to maintain nutrition and fluid intake. The tube rarely replaces oral feedings, but it can be used as an adjunct. Patients with RS are more prone to gallstones than the general population is, and they should receive regular monitoring for them.

Authors' PROFILES

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Please send your questions or comments to:

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