

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

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.

Arthur Beisang, M.D., is a pediatrician at Gillette Children's Specialty Healthcare. He sees children who have cerebral palsy, Rett syndrome, and other complex medical conditions. Beisang received a medical degree from St. George's School of Medicine in Grenada, West Indies. He completed a residency in pediatrics at the University of Minnesota.



Beisang is an assistant professor of pediatrics at the University of Minnesota. He has board certification from the American Board of Pediatrics. To refer a patient to Beisang or to make an appointment with him, call 651-290-8707 or 800-719-4040 (toll-free).



Raymond Tervo, M.D., is a neurodevelopmental pediatrician and medical director of Pediatrics at Gillette Children's Specialty Healthcare. He earned a medical degree at McMaster University in Hamilton, Ontario, Canada, and did his core pediatric residency training at the Hospital for Sick Children in Toronto. He also completed his subspecialty training in

developmental pediatrics at McMaster, and he is board-certified in neurodevelopmental disabilities.

Tervo has served on the faculty of the University of Saskatchewan, the University of Toronto and the University of South Dakota. He is an associate professor in the department of Pediatrics at the University of Minnesota. To refer a patient to Tervo or to make an appointment with him, call 651-290-8707 or 800-719-4040 (toll-free).

Robert Wagner, M.D., is a family medicine physician and medical director of adult services at Gillette Lifetime Specialty Healthcare. He provides selected, direct patient-care services that include gynecology, wound-care, tube-feeding, medication-management and pulmonary assessments. Wagner also performs presurgical evaluations and does discharge planning and integrative-care management for nonsurgical patients.



After receiving his medical degree from the University of Minnesota in Minneapolis, Wagner completed a family medicine residency at St. Paul Ramsey Medical Center (now Regions Hospital). Before joining Gillette, Wagner served as section head of family medicine at Regions Hospital. He is board-certified in family medicine and a member of the Minnesota Academy of Family Physicians. To refer a patient to Wagner or to make an appointment with him, call 651-290-8707 or 800-719-4040 (toll-free).

Volume 17, Number 1
2008

A *Pediatric Perspective* focuses on specialized topics in pediatrics, orthopaedics, neurology and rehabilitation medicine.

Please send your questions or comments to:

A Pediatric Perspective
Publications
Gillette Children's Specialty Healthcare
200 University Ave. E. • St. Paul, MN 55101
651-229-1744
bspatterson@gillettechildrens.org

Editor-in-Chief.....Steven Koop, M.D.
Editor.....Beverly Smith-Patterson
Designer.....Kim Goodness
Photographers.....Anna Bittner
.....Paul DeMarchi

Copyright 2008, Gillette Children's Specialty Healthcare.
All rights reserved.

Referral Information

Gillette accepts referrals from physicians, community professionals and outside agencies. To schedule an outpatient appointment, contact New Patient Services at 651-290-8707, Monday through Friday between 8 a.m. and 5:30 p.m. Physicians who are on staff can admit patients by calling 651-229-3890.

New Patient Services	651-290-8707
Center for Cerebral Palsy	651-290-8712
Center for Craniofacial Services	651-325-2308
Center for Gait and Motion Analysis	651-229-3868
Center for Pediatric Neurosciences	651-312-3176
Center for Pediatric Orthopaedics	651-229-1758
Center for Pediatric Rehabilitation	651-229-3915
Center for Pediatric Rheumatology	651-229-3893
Center for Spina Bifida	651-229-3878
Gillette Lifetime Specialty Healthcare	651-636-9443



Gillette Children's
Specialty Healthcare

200 University Ave. E.
St. Paul, MN 55101
651-291-2848
TDD 651-229-3928
800-719-4040 (toll-free)
www.gillettechildrens.org

Nonprofit
Organization
U.S. Postage
PAID
St. Paul, MN
Permit No. 5388

Gillette Achieves Magnet Designation

Gillette has achieved Magnet designation for excellence in nursing services from the American Nurses Credentialing Center's (ANCC) Magnet Recognition Program. Magnet designation is one of the highest honors given to health-care organizations. By receiving Magnet designation, Gillette has demonstrated its adherence to strict national standards for excellence in nursing services. Gillette is one of only six Minnesota hospitals to achieve Magnet designation.

Experience Gillette's New Advanced Imaging Center

Gillette's new Advanced Imaging Center on our St. Paul campus will begin welcoming patients later this spring. We will offer magnetic resonance imaging (MRI), computed tomography (CT), fluoroscopy and ultrasound scans in an environment designed specifically for children and adults who have disabilities.

All of our providers are experts in caring for people who have complex medical needs, and the services we provide reflect our patients' most common needs. For example, we offer sedation medicine for patients who are unable to remain still during imaging scans. In addition, by using special sound, video and lighting to create a soothing environment, our positive-distraction technology will help patients relax.

You are invited to experience our Advanced Imaging Center firsthand at an **open house on Wednesday, May 21**, from 5 to 8 p.m. For more information and directions, visit our Web site at www.gillettechildrens.org.

Online CME Available

A *Pediatric Perspective* and additional case studies are available for continuing medical education (CME) credit online. To access our online CME, visit www.gillettechildrens.org.

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