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Rett Syndrome

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Synonyms of Rett Syndrome

- classic Rett syndrome
- RTT
- variant (atypical) Rett syndrome

Disorder Subdivisions

- No subdivisions found.

General Discussion

Summary
Rett syndrome is a progressive neurodevelopmental disorder that almost exclusively affects females. Only in rare cases are males affected. Infants with Rett syndrome generally develop normally for about 7 to 18 months after birth. At this point, they lose previously acquired skills (developmental regression) such as purposeful hand movements and the ability to communicate. Additional abnormalities occur including impaired control of voluntary movements (ataxia) and the development of distinctive, uncontrolled hand movements such as hand clapping or rubbing. Some children also have slowing of head growth (acquired microcephaly), Affected children often develop autistic-like behaviors, breathing irregularities, feeding and swallowing difficulties, growth retardation, and seizures. Most Rett syndrome cases are caused by identifiable mutations of the MECP2 gene on the X chromosome and can present with a wide range of disability ranging from mild to severe. The course and severity of Rett syndrome is determined by the location, type and severity of the MECP2 mutation and the process of random X-inactivation (see Causes section below). Therefore, two girls of the same age with the same mutation can appear significantly different.

Introduction
Rett syndrome was first described in the medical literature by an Austrian physician named Andreas Rett in 1960s. Many researchers now consider Rett syndrome as part of a spectrum of disease relating to mutations of the MECP2 gene. This spectrum, sometimes referred to as MECP2-related disorders, includes classic Rett syndrome, variant Rett syndrome, MECP2-related severe neonatal encephalopathy, and PPM-X syndrome. Another disorder, MECP2 duplication syndrome, has recently been described in the medical literature. This disorder is caused by duplicated material involving the MECP2 gene on the X chromosome.

Symptoms

The symptoms, progression, and severity of Rett syndrome can vary dramatically from one person to another. The disorder primarily affects females and most likely represents a spectrum of disease associated with mutations of the MECP2 gene. A wide range of disability can potentially be associated with Rett syndrome. Symptoms generally appear in stages. It is important to note that affected individuals may not have all of the symptoms discussed below. Affected individuals should talk to their physician and medical team about their specific case, associated symptoms and

overall prognosis.

CLASSIC RETT SYNDROME

Affected infants are generally described as having normal development until approximately 6 to 18 months of age. However, researchers have noted that affected infants are often described as being very placid and having a poor sucking ability and a weak cry. Low muscle tone (hypotonia) is also common before 6 months of age. Head growth can slow down as early as 3 months of age. Slow head growth can result in acquired microcephaly, a condition characterized by head circumference that is smaller than would normally be expected for age and gender.

Between 6 and 18 months of age, affected girls may enter a period of developmental stagnation. Loss of eye contact and a lack of interest in play or games may also occur. Infants may demand little to no attention from their parents. Irritability, crying and restlessness may be seen. In some cases, development may continue but at a delayed rate. For example, an infant may learn to sit upright, but not to crawl.

After this period, approximately between 1-4 years of age, affected individuals begin to lose previously acquired skills, specifically spoken language skills and hand skills. Some individuals may lose the ability to interact socially. Affected people may also exhibit a decline in intellectual function. This deterioration can be rapid or gradual. Parents may notice a sudden change in their child’ s behavior and health. Affected children may show diminished interest in people and objects.

During this time period, the loss of ability to make purposeful hand and finger movements occurs. Affected people then exhibit a characteristic finding of Rett syndrome, the development of stereotypic hand movements including hand wringing or squeezing, clapping, rubbing, washing, or hand to mouth movements. Screaming fits and inconsolable crying may also occur.

Additional symptoms may develop including autistic-like features, panic attacks, teeth grinding (bruxism), tremors and apraxia. Apraxia is a condition characterized by the inability to perform learned (familiar) movements on command, even though the command is understood and there is a willingness to perform the movement. Apraxia can affect movement but also communication skills. Seizures are common during this period in individuals with Rett syndrome. Some individuals may experience balance issues due to problems coordinating voluntary muscles of the legs (gait ataxia). Disordered breathing patterns that occur when a child is awake such as hypoventilation or hyperventilation have also been reported. Affected people may also exhibit forced expulsion of air and saliva, swallowing air (aerophagia), temporary stopping (cessation) of breathing (apnea), and holding of one’ s breath. Breathing

problems tend to worsen with stress.

After this period of rapid deterioration, neurological features stabilize. Some affected individuals may even show slight improvement with eye contact, communication skills, regression of autistic traits, and overall improvement with behavior and social interactions.

However, many issues remain including characteristic hand movements, seizures, teeth grinding (bruxism), and breathing irregularities. Intellectual disability in Rett syndrome is difficult to access because of the inability to speak or use hands. Eventually, after 10 years of age, affected individuals may exhibit late motor impairment. Some people with classic Rett syndrome may never be able to walk. Others may lose the ability to walk. They may also experience increasing muscle weakness, joint contractures, and spasticity, a condition characterize by involuntary muscles spasms that result in slow, stiff movements of the legs. Affected people may have underdeveloped (hypotrophic) hands and feet that are frequently cold. Most affected individuals may develop dystonia, a condition characterized by sustained muscle contractions associated with abnormal, uncontrolled movements and postures. Some affected people may develop symptoms similar to those seen in Parkinson’ s disease (parkinsonism), such as a decreased expression in face (hypomimia), rigidity, and tremor.

Approximately 85-90% of affected people may experience growth failure and muscle wasting that worsens with age. These symptoms are due, in part, to difficulties with chewing and swallowing, which leads to poor food intake. On the other hand, some people with Rett syndrome, especially those with more retained function, may have excessive food intake and become obese.

A variety of additional symptoms and physical findings can occur in people with classic Rett syndrome including gastrointestinal abnormalities such as abnormal muscle contractions or dysfunction of nerves of the bowel (bowel dysmotility), constipation, gastroesophageal reflux, and abnormal widening (dilation) of the colon (functional megacolon); cold hands and feet (vasomotor abnormalities); intermittent crossed eyes (esotropia); varying degrees of side-to-side curvature of the spine (scoliosis); and gallbladder dysfunction and gallstones, which have been show to occur with greater frequency in individuals with Rett syndrome than in the general population. Some people with Rett syndrome develop osteopenia, a condition characterized by decreased bone mineralization and bone loss. Osteopenia can result in weak, fragile bones.

Many people with Rett syndrome live well into adulthood, although they may require

constant care and supervision. However, there is an increased risk of sudden death in people with Rett syndrome. Approximately one quarter of deaths in Rett are sudden and unexpected. This may be due, in part, to heart irregularities, specifically a prolonged QT interval and T-wave abnormalities. The functioning of the heart is controlled by electrical nerve impulses that regulate normal rhythmic pumping activity of the heart muscle. After each heartbeat, this electrical system recharges, a process known as repolarization. During electrical stimulation, the heart muscle contracts, a process known as depolarization. The QT interval measures the amount of time required for these two processes to occur. When the QT interval is longer than normal (prolonged), the heartbeat may become irregular.

VARIANT RETT SYNDROME

Variant Rett syndrome refers to people who have atypical cases or presentations of Rett syndrome. These cases may also be known as atypical Rett syndrome. These forms of Rett syndrome include:

The preserved speech variant of Rett syndrome (Zappella variant) is characterized by the symptoms of classic Rett syndrome, but with the recovery of some language and motor skills. Mutations of the MECP2 gene have been found in the majority of cases. Head size is often normal in the Zapella variant, and people with this variant may be obese, more aggressive, and have more autistic features.

The late childhood regression form is characterized by later and more gradual regression of motor and language skills than is found in classic Rett syndrome. Affected females have a normal head circumference.

Some affected individuals have a form that is associated with seizures that occur before 6 months of age (Hanefeld variant). This variant form is rarely associated with mutations of the MECP2 gene, but rather another gene known as CDKL5. For more information on CDKL5 see the Related Disorders section below.

A form known as the congenital variant of Rett syndrome (Rolando variant) is characterized loss of muscle tone and severe developmental delays during the first few months of life. This form is rarely associated with mutations in the MECP2 gene. Many children with this variant form of Rett syndrome have been shown to have mutations of the FOXG1 gene. For more information on FOXG1 see the Related Disorders section below.

The ‘ forme fruste’ variant of Rett syndrome is characterized by an overall milder expression than is seen in classic Rett syndrome. The clinical course is shorter (protracted) and incomplete. Regression occurs later than it does in the classic form.

Affected individuals may retain hand use and the stereotypic hand movements of Rett syndrome may be mild.

In rare cases, some girls with MECP2 mutations may only have mild learning disabilities or autistic features. Without regression of hand skills and language and the development of the characteristic repetitive hand stereotypies, these children should not be considered to have Rett syndrome as the prognosis is different for these people compared to people who have the characteristic features of Rett.

ADDITIONAL MECP2 - RELATED DISORDERS
In rare cases, males can develop distinct symptoms associated with a mutation of the MECP2 gene.

Some males with MECP2 mutations develop brain dysfunction during infancy (neonatal encephalopathy). Affected males may also exhibit microcephaly. The disorder is progressive resulting in abnormal muscle tone, involuntary movements, severe seizures and breathing irregularities. The brain dysfunction is often severe and the disorder can be fatal by 2 years of age.

Some individuals with MECP2 mutations develop X-linked intellectual disability. Affected females may have mild, non-progressive intellectual disability. Affected males may develop mild to severe intellectual disability including a disorder known as PPM-X syndrome. This acronym stands for manic depressive (p)sychosis, (p)yramidal signs, (p)arkinsonism, and (m)acro-orchidism. Affected individuals may have psychotic disorders such as bipolar disorder. Additional symptoms include parkinsonism, increased muscle tone and exaggerated reflexes. Abnormal enlargement of the testes (macro-orchidism) may also occur.

Some girls with a diagnosis of autism have been shown to have mutations in the MECP2 gene.

Causes

Approximately 90-95% of Rett syndrome cases are caused by identifiable mutations of the MECP2 gene. More than 200 different mutations have been identified. In 99% of cases, these mutations occur sporadically and are not possessed or transmitted by a child’ s parents (de novo mutations). Therefore, in the vast majority of cases Rett syndrome is not an inherited disorder. In such cases, the parents have normal chromosomes and the mutation arises in one of the parent’ s reproductive (germ) cells, usually on the paternal side.

The chance of recurrence in subsequent children for parents who have one affected child is approximately 1%. In rare cases, more than one child can be affected. This rare occurrence may occur because of germline mosaicism. In germline mosaicism, one parent has some reproductive cells (germ cells) in the ovaries or testes that have the MECP2 gene mutation. The other cells in the parent's body do not have the mutation, so these parents are unaffected. As a result, one or more of the parent's children may inherit the germ cell MECP2 gene mutation. The likelihood of a parent passing on a mosaic germline mutation to a child depends upon the percentage of the parent's germ cells that have the mutation versus the percentage that do not. There is no test for germline mutation prior to pregnancy. Testing during pregnancy may be available and is best discussed directly with a genetic specialist.

In extremely rare cases, Rett syndrome may be inherited from a carrier mother who has favorable skewing of random X-chromosome inactivation and no symptoms or extremely mild symptoms of the disorder. When a mother is a known carrier of the MECP2 mutation, there is a 50% chance of passing that mutation on to her children.

Random X-chromosome inactivation is a normal process in females. Females have two X chromosomes, whereas males have one X chromosome and one Y chromosome. In females, certain disease traits on the X chromosome such as a mutated gene may be "masked" by the normal gene on the other X chromosome (random X-chromosome inactivation). Basically, in each cell of the body one X chromosome is active and one is turned off or "silenced." This occurs randomly and generally happens as a 50-50 split. However, in some cases, females may have favorable X-inactivation, in which the affected X chromosome is silenced in most of the cells. In such cases, affected females may only have mild symptoms of the disorder. In other cases, females may have unfavorable X-inactivation, in which the unaffected X chromosome is silenced in most of the cells. In such cases, affected females usually have a severe expression of the disorder.

Because males only have one X chromosome, such disorders are usually fully expressed. Consequently, it is believed that in most cases MECP2 mutations are not compatible with life in males, usually resulting in miscarriage or stillbirth.

In some cases, females who have a MECP2 gene do not develop symptoms of the disorder suggesting that in some cases additional factors (such as modifier genes) may serve to protect such individuals from the effects of the mutated gene. More research is necessary to fully understand the complex, underlying mechanisms that ultimately cause Rett syndrome.

The MECP2 gene is located on the long arm (q) of the X chromosome (Xq28).

Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22 and the sex chromosomes are designated X and Y. Each chromosome has a short arm designated "p" and a long arm designated "q". Chromosomes are further sub-divided into many bands that are numbered. For example, "chromosome Xq28" refers to band 28 on the long arm of the X chromosome. The numbered bands specify the location of the thousands of genes that are present on each chromosome.

The MECP2 gene contains instructions for creating a protein (Methyl-CpG-binding protein 2) that may regulate the activity of many other genes in the body. Mutations to the MECP2 gene leads to low levels of functional MECP2 protein in the body, which, in turn, leads to the abnormal function of other genes within the body. For example, genes that should be silenced or turned off will remain active at certain times during development, ultimately leading to impaired brain development. The exact genes involved and the exact functions of the MECP2 protein are unknown or not fully understood. Rett syndrome is believed to affect normal brain development during early childhood. More research is necessary to determine the how MECP2 gene mutations ultimately cause Rett syndrome.

Affected Populations

Rett syndrome occurs almost exclusively in girls. The incidence of Rett syndrome in the United States is estimated to be 1 in 10,000 girls by age 12. Cases of Rett syndrome can go undiagnosed or misdiagnosed, making it difficult to determine the disorder’ s true frequency in the general population. Rett syndrome is the second most common cause of severe intellectual disability after Down syndrome.

Related Disorders

Symptoms of the following disorders can be similar to those of Rett syndrome. Comparisons may be useful for a differential diagnosis.

Angelman syndrome is a rare genetic and neurological disorder characterized by severe developmental delays and learning disabilities; absence or near absence of speech; inability to coordinate voluntary movements (ataxia); tremulousness with jerky movements of the arms and legs and a distinct behavioral pattern characterized by a happy disposition and unprovoked episodes of laughter and smiling. Although those with the syndrome may be unable to speak, many gradually learn to communicate through other means such as gesturing. In addition, children may have enough receptive language ability to understand simple forms of language communication. Additional symptoms may occur including seizures, sleep disorders

and feeding difficulties. Some children with Angelman syndrome may have distinctive facial features but most facial features reflect the normal parental traits. Angelman syndrome is caused by deletion or abnormal expression of the UBE3A gene. (For more information on this disorder, choose "Angelman" as your search term in the Rare Disease Database.)

CDKL5 is a rare X-linked genetic disorder that results in early onset, difficult to control seizures, and severe neurodevelopmental impairment. CDKL5 stands for cyclin-dependent kinase-like 5, and is a gene located on the X chromosome. Most of the children affected by CDKL5 suffer from seizures that begin in the first few months of life. Most cannot walk, talk or feed themselves, and many are confined to a wheelchair. Many also suffer with scoliosis, visual impairment, sensory issues and various gastrointestinal difficulties. CDKL5 mutations were initially thought to be specifically associated with the Hanefeld variant of Rett syndrome, in which earlier seizures are a prominent feature. However, the characteristics of the disorder (phenotype) have been expanded to include early epileptic seizures and later onset intractable seizure disorders commonly including myoclonus without clinical features of Rett syndrome. More recent studies suggest that the predominant phenotype caused by CDKL5 mutations is the so-called epileptic encephalopathy, the onset of severe seizures in the first six months of life (often within the first 3 months), and poor subsequent neurocognitive development and commonly the presence of repetitive hand movements (stereotypies). CDKL5 mutations have been found in children diagnosed with infantile spasms, West syndrome, Lennox-Gastaut syndrome, Rett syndrome, and autism. The full spectrum of CDKL5 disorders is unknown at this time. It is likely that there are many people affected by CDKL5 who have mild symptoms and no seizures. (For more information on this disorder, choose "CDKL5" as your search term in the Rare Disease Database.)

FOXG1-related disorders are a group of disorders that occurs in individuals who have a mutation of the FOXG1 gene. Affected individuals develop normally before and shortly after birth (perinatal). However, infants may develop progressive microcephaly, seizures, developmental delays, and severe intellectual disability. Some affected individuals may experience gastrointestinal abnormalities including constipation and gastroesophageal reflex, scoliosis, and foot deformities. Affected individuals may experience a variety of movement disorders including stereotypic hand movements. FOXG1-related disorders are caused by mutations of the FOXG1 gene. The FOXG1-related disorders are sometimes referred to as the congenital variant of Rett syndrome.

A wide variety of additional disorders may have symptoms or physical findings that are similar to Rett syndrome. Such disorders include autism, cerebral palsy, certain

metabolic disorders, perinatal or postnatal brain injury, a variety of neurodegenerative disorders, and acquired neurological disorders such as may result from trauma or infection. (For more information on these disorders, choose the specific disorder name as your search term in the Rare Disease Database.)

Standard Therapies

Diagnosis

A diagnosis of Rett syndrome is based upon identification of characteristic symptoms, a detailed patient history, and a thorough clinical evaluation. A variety of specialized tests may be conducted to rule out other conditions that can cause similar symptoms. A set of updated diagnostic criteria was recently published (Neul et al 2010). The fulfillment of these diagnostic criteria can lead to a clinical diagnosis of Rett syndrome. The report also includes diagnostic criteria for variant forms of Rett syndrome.

Molecular genetic testing can detect the presence of mutations of the MECP2 gene and confirm the clinical diagnosis of Rett syndrome.

Treatment

The treatment of Rett syndrome is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, pediatric neurologists, gastroenterologists, speech therapists, psychiatrists, nutritionists, and other healthcare professionals may need to systematically and comprehensively plan an affect child’ s treatment. Genetic counseling may be of benefit for affected individuals and their families.

Treatment options that may be used to treat individuals with Rett syndrome are complex and varied. The specific treatment plan will need to be highly individualized. Early developmental intervention is important to ensure that affected children reach their potential. Most affected children will benefit from occupational, physical and speech therapy. Various methods of rehabilitative and behavioral therapy may be beneficial. Additional medical, social and/or vocational services including special remedial education may be necessary. Psychosocial support for the entire family is essential as well.

Other treatment is symptomatic and supportive. Additional therapies for Rett syndrome depend upon the specific abnormalities present and generally follow standard guidelines.

Some general therapies common for infants or children with Rett syndrome include

nutritional supplements to ensure maximum caloric intake. In some cases, children may require the insertion of a tube through a small opening in the stomach (gastronomy). Some affected individuals are encouraged to follow a diet high in calories and fat.

Drugs may be used to treat a variety of symptoms associated with Rett syndrome including seizures, anxiety, sleep disturbances, breathing problems, stereotypic hand movements, and certain gastrointestinal abnormalities. Drugs may also be used to improve spasticity and muscle rigidity.

Individuals at risk of prolonged QT interval may benefit from drugs known as beta-blockers or cardiac pacing. These individuals also need to avoid certain medications that can aggravate the condition.

Scoliosis is common in individuals with Rett syndrome. Guidelines have been published detailing specific recommendations for the management of scoliosis in Rett syndrome (Downs et al 2009).

Investigational Therapies

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, in the main, contact:
www.centerwatch.com

Contact for additional information about Rett syndrome:

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Organizations related to Rett Syndrome

NORD offers an online community for this rare disease. RareConnect was created by EURORDIS (European Rare Disease Organisation) and NORD (National Organization for Rare Disorders) to provide a safe space where individuals and families affected by rare diseases can connect with each other, share vital experiences, and find helpful information and resources. You can view these international, rare disease communities at www.rareconnect.org.

- Child Neurology Foundation

  2000 West 98th Street
  Bloomington, MN 55431 USA
  Phone #: 952-641-6100
  800 #: 877-263-5430
  e-mail: jstone@childneurologyfoundation.org
  Home page: http://www.childneurologyfoundation.org

- Genetic and Rare Diseases (GARD) Information Center

  PO Box 8126
  Gaithersburg, MD 20898-8126
  Phone #: 301-251-4925
  800 #: 888-205-2311
  e-mail: N/A
  Home page: http://rarediseases.info.nih.gov/GARD/

- International Rett Syndrome Foundation

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- Madisons Foundation

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- March of Dimes Birth Defects Foundation

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  e-mail: Askus@marchofdimes.com
  Home page: http://www.marchofdimes.com

- Medical Home Portal

  Dept. of Pediatrics
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  Phone #: 801-587-9978
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  Home page: http://www.medicalhomeportal.org

- MUMS National Parent-to-Parent Network

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e-mail: mums@netnet.net
Home page: http://www.netnet.net/mums/

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- The Arc

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- WE MOVE (Worldwide Education and Awareness for Movement Disorders)

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