Rett Syndrome

Introduction

Rett syndrome (RTT, OMIM 312750) is a progressive neurodevelopmental disorder that occurs almost exclusively in females, with an incidence of 1 in 10,000. It was described in 1966 by Andreas Rett, an Austrian paediatrician and neurologist.

Patients with classic RTT appear to develop normally until 6–18 months of age, then gradually lose speech and purposeful hand use, and develop microcephaly, seizures, autism, intermittent hyperventilation, stereotypic hand movements and truncal apraxia/ataxia between1 and 4 years of age. After initial regression, the condition stabilizes and patients usually survive into adulthood. As RTT occurs almost exclusively in females, it has been proposed that RTT is caused by an X-linked dominant mutation with lethality in hemizygous males, most cases result from mutations in the MECP2 gene.

Genetics

In the majority of patients, RTT is caused by mutations in the *MECP2* gene, which maps to Xq28 and encodes methyl-CpG binding protein 2 (MeCP2). Although MeCP2 is expressed in all tissues, it is most abundant in the brain, which may be more sensitive to abnormal MeCP2 than other tissues. Mutations in *MECP2* have been detected in approximately 95 percent of classic sporadic RTT cases and 75 percent of atypical RTT cases. A minority of patients have atypical RTT caused by mutations in *CDKL5* or *FOXG1* genes.

Mutations of the *MECP2* gene have also been detected in other neurologic disorders. These include girls with non-Rett phenotypes such as autism, girls and boys with nonspecific X-linked mental retardation, and boys with progressive spasticity, congenital encephalopathy with respiratory arrest, or non-fatal neurodevelopmental disorders.

Epidemiology

The prevalence of typical Rett syndrome is estimated at 1 in 10 000 women aged 32 years. Almost all the causes are sporadic. RTT occurs in all ethnic and racial groups, and at similar rate

Classification and Major Features

The clinical phenotype of RTT is broad and is divided into two main categories:

- Typical (classic) RTT
- Atypical (variant) RTT

Typical RTT:

The clinical picture of typical (classic) RTT is unique. Affected patients initially develop normally and then experience loss of speech and purposeful hand use and onset of stereotypic hand movement and gait abnormalities. Additional manifestations can include deceleration of

head growth, seizures, autistic features, intermittent breathing abnormalities, autonomic nervous system dysfunction, cardiac abnormalities, and sleep disturbances.

Deceleration of head growth beginning as early as two to three months of age is often the first sign of RTT, although this feature is not present in all individuals with typical RTT and is no longer considered one of the necessary criteria for RTT. At 12 to 18 months, loss of acquired fine motor, intellectual, and communicative abilities is seen. In some cases, this regression is rapid, with parents reporting "She woke up and was no longer speaking." More often, regression is slow and insidious, occurring over weeks to months with diminished interest in the surroundings and loss of purposeful hand use. During this phase, unprovoked episodes of inconsolable screaming may occur during the day or at night, disrupting sleep. These begin abruptly, may last for hours, and often provoke an exhaustive evaluation for other medical conditions if RTT has not yet been diagnosed.

In the beginning of the regression phase, stereotypic hand movements may be subtle and interspersed with purposeful hand use. They typically consist of periodic hand-to-mouth licking or grasping of the hair or clothing.

Following the regression phase, there is a period of some recovery of nonverbal communication, with improved eye contact and nonverbal interactions with the environment. This is followed by a slow, insidious deterioration in gross motor function.

Atypical RTT:

Atypical RTT is the term used for variants of RTT that have many but not all of the clinical features of typical RTT. There are three defined atypical forms of RTT:

- The preserved speech variant of RTT is a less severe form of the syndrome that is characterized by recovery of language after regression, with most girls able to speak in sentences, and generally milder expression of typical RTT features. The majority of girls with this variant have pathogenic *MECP2* mutations.
- The early-onset seizure variant of RTT is caused by mutations in the *CDKL5* gene and is characterized by a Rett-like picture with the onset of epilepsy between the first week and fifth month of life as a significant feature. Some cases of the early-seizure variant may be caused by mutations in *CACNA1A*.
- The congenital variant of RTT caused by mutations in the *FOXG1* gene is distinct from RTT due to *MECP2* mutations by onset within the first six months of life.

Diagnosis

Diagnostic criteria — Diagnostic criteria for RTT, revised in 2010, are divided into main, exclusionary, and supportive categories (see table below). The diagnosis should be considered when postnatal deceleration of head growth is observed, although this feature is not a necessary criterion for RTT.

For the diagnosis of **typical or classic RTT**, the following are required:

- A period of regression followed by recovery or stabilization
- Meet all main criteria and no exclusionary criteria

Supportive criteria are not required, although they are frequently present in typical RTT

For the clinical diagnosis of **atypical or variant RTT**, the following are required:

- A period of regression followed by recovery or stabilization
- Meet at least 2 of the 4 main criteria
- Meet at least 5 of the 11 supportive criteria

Diagnostic criteria for RTT:

Main criteria	Supportive criteria	Exclusion criteria
1. Partial or complete loss of acquired purposeful hand skills 2. Partial or complete loss of acquired spoken language 3. Gait abnormalities: impaired (dyspraxic) or absence of ability 4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms	1. Breathing disturbances when awake 2. Bruxism when awake 3. Impaired sleep pattern 4. Abnormal muscle tone 5. Peripheral vasomotor disturbances 6. Scoliosis/kyphosis 7. Growth retardation 8. Small cold hands and feet 9. Inappropriate laughing/screaming spells 10. Diminished response to pain 11. Intense eye communication ("eye pointing")	1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurologic problems 2. Grossly abnormal psychomotor development in first six months of life

Evaluation

The clinical evaluation for suspected RTT includes the history, examination, and genetic testing. In some cases, additional studies may be helpful.

History:

- Timing of developmental milestones
- Presence of a period of regression
- Loss of hand skills and spoken language.

Examination:

- Measurements typically show impaired growth.
- Serial measurements often show decelerating head growth, and, microcephaly.
- Variety of neurologic manifestations may be seen, including intellectual disability or developmental delay.
- Loss of or poor communication skills
- Stereotypic hand movements.

DNA analysis:

A blood or saliva sample should be obtained for DNA analysis to identify mutations of *MECP2* in a female with characteristic signs of RTT. Testing should also be considered in male infants with severe encephalopathy. The diagnosis of RTT (*MECP2* positive) is made if a pathogenic MECP2 mutation is found and clinical criteria are met.

For those who have a negative analysis for known pathogenic mutations in *MECP2*, further genetic testing should include analysis for mutations in *FOXG1* (if features of the congenital variant are present) and *CDKL5* (if features of the early seizure variant are present). A comprehensive genetic evaluation is recommended if a pathogenic variant is not detected in *MECP2*, *CDKL5*, or *FOXG1*. Whole exome sequencing can identify mutations in other genes that lead to the development of phenotypes resembling RTT. Specialized genetic panels are available now one of them is the Invitae Rett and Angelman Syndromes panel analyzes up to 28 genes associated with early-onset developmental disorders related to the Rett/Angelman spectrum, the test is done by testing saliva and the results are collected within 2-3 weeks times. (https://www.invitae.com/en/physician/tests/03404/)

Other studies:

Suggested studies to exclude these disorders include the following:

- Brain MRI
- Serum amino acids
- Urine organic acids
- Genetic testing for Rett-like phenotypes, including Angelman and Angelman-like syndromes and/or Pitt-Hopkins syndrome if clinically suspected
- White cell enzymes (if regression)
- Hearing test
- Ophthalmologic evaluation

The patient could be considered to have RTT without the MECP2 mutation if these studies are nondiagnostic, clinical criteria for RTT are met, and mutation analysis of genes causing very similar disorders has failed to identify an alternative diagnosis; however, this "working diagnosis" should be revisited periodically with repeat genetic analysis as genetic/genomic testing improves.

Electroencephalography (EEG):

It is not used for diagnosis; it is always abnormal in RTT and shows characteristic changes. The epileptiform abnormalities typically begin at approximately two years of age. These include focal, multifocal, and generalized epileptiform abnormalities, and the occurrence of rhythmic slow (theta) activity primarily in the frontal-central regions.

Management

No specific therapy is available for RTT. Management consists of treating the associated conditions. A multidisciplinary approach is optimal.

Seizures:

Seizures may occur during sleep or may not be recognized by caregivers. Most seizures associated with RTT are easily controlled and respond to standard antiepileptic drugs. Nevertheless, some patients with RTT have intractable seizures, and polytherapy with three or more anticonvulsant drugs has been used in up to 19 percent of patients with RTT and seizures. A ketogenic diet or vagus nerve stimulator may improve intractable seizures. The best anticonvulsive results were seen in the RTT group that was treated with carbamazepine, while valproate was significantly less effective. Hormonal therapy or treatment with vigabatrin may be helpful in patients with infantile spasms.

Other treatments:

- Nutrition
- GI dysfunction
- Bone quality and fractures
- Breathing dysfunction
- Sleep disturbance
- Motor dysfunction.