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Rett Syndrome

Rett syndrome is an X-linked neurodevelopmental condition characterised by loss of spoken language and hand use with the development of distinctive hand stereotypies. It is a pervasive developmental disorder (PDD).

PDDs are a spectrum of diseases that impair or arrest a child's development, or cause its regression.

The condition was first reported in 1966 by Dr Andreas Rett (an Austrian paediatric neurologist) but has only recently become widely recognised as a discrete disease entity.

Pathogenesis

The culprit gene, methyl-CpG binding protein-2 (MECP2) was discovered in 1999.^[1] This gene encodes for a protein that is involved in the methylation and regulation of other genes' activities. Although the target genes that are affected are unknown, they obviously play a crucial role in CNS development.

Mutations in MECP2 are found in 95-97% of those with typical Rett syndrome. However, in atypical cases, only 50-70% of cases have mutations in MECP2.^[2]

It appears to arise as a sporadic mutation or chromosomal abnormality affecting the X chromosome:

- There is a small subgroup of affected sufferers who have a preserved-speech variant of the illness.
- Variable X-chromosome inactivation (lyonisation) may account for its non-pedigree pattern inheritance, variable phenotypic expression and rare presence in boys.
- A severe early-onset Rett syndrome-like illness that often includes seizures or infantile spasms can be caused by mutation in the cyclin-dependent kinase-like 5 (CDKL5) gene.

Epidemiology

It is a moderately rare condition, but a relatively common cause of PDD. Rett syndrome affects approximately 1 in 10,000 live female births.^[2]

Characteristic features

The cascade of clinical symptoms with evolving communicative dysfunction and loss of acquired skills and motor performance was delineated in a staging system designed to help clinicians to discriminate between the very nonspecific developmental profile early in life and the more specific profile for the disorder in later life.^[3] These stages are:

Stage 1 - developmental arrest

- Typically from 6-18 months.
- Tends to be gross motor developmental delay, loss of eye contact and a waning interest in play.
- Hypotonia may be present.
- Hand-wringing is noted and is a very characteristic feature.
- Symptoms can be vague and the only abnormality may be unusual placidity when compared with a normal child.

Stage 2 - rapid developmental deterioration or regression

- Typically age 1-4 years.
- May be a sudden onset of deterioration with an identifiable day when things changed; however, it may be a more subtle onset and progression in some cases.

- Early growth restriction may be noted in falling off of head circumference from growth curve.
- There are autism-like behaviours with loss of verbal and other communication, hand use and social interaction.
- There are abnormalities of hand movements when the patient is awake, with the hands usually held in midline; there may be hand-wringing, clapping, hand washing or movements from hand to mouth.
- There may be episodes of hyperventilation or breath-holding.
- There can be vacant spells (may resemble some forms of partial seizure) and actual fits.
- Sleep is often disrupted. There may be difficulty falling to sleep or frequent awakenings during the middle of the night
- Intermittent strabismus may be noted.
- The child may present with irritability.
- Cold hands and feet are common and are due to poor perfusion as a consequence of altered autonomic control. Secondary vascular changes in the long-term lead to abiotrophic changes in the lower limb and feet.

Stage 3 - stationary or pseudostationary phase

- Typically aged 2-10 years.
- There may be an improvement in behaviour, use of the hands and communication skills.
- Eye contact returns and non-verbal communication may be exploited.
- There is persisting intellectual impairment with stereotyped hand movements.
- Generalised rigidity, bruxism and movements of the tongue may occur.
- Motor dysfunction or dystonia may be present.
- Breathing abnormalities can persist.
- Children may eat well, but put on little weight and are very low in the centile charts.
- Feeding may start to present difficulties due to oral motor dysfunction.

Stage 4 - late motor deterioration

- Typically occurs after the age of 10 years.
- Cognitive, communication and hand skills usually remain stable.
- Generalised motor dysfunction such as dystonia, hypertonia and Parkinsonism can present.
- Walking may cease.
- If there are fits, they tend to be less frequent in this stage.

NB: epilepsy is present in up to 80% of affected cases at some time in their lives. The most common seizure types are complex partial, tonic-clonic, tonic, and myoclonic.

Signs

Stage 1

Developmental assessment will reveal:

- Gross motor developmental delay.
- Loss of eye contact.
- Growth deceleration as revealed by weight, height and head circumference charts.
- Hypotonia with hand-wringing.

Stage 2

- Autism-like behaviour begins to emerge - particularly, poor social interaction, poor communication and loss of language.
- The abnormal, stereotyped midline hand movements will be evident.
- Episodes of hyperventilation or breath-holding may be witnessed, along with vacant episodes or seizures.

Stage 3

- Bruxism (grinding the teeth).
- Involuntary movements of the tongue.
- Poor weight gain.
- Scoliosis.

Stage 4

- Dystonias.
- Rigidity.
- Quadriparesis.
- Muscle wasting.
- Scoliosis/kyphoscoliosis.
- Growth restriction.
- Breathing abnormalities.

NB: hand movements and eye contact tend to improve.

Differential diagnosis

These vary with the stage of the illness.

Differential diagnosis of Rett syndrome according to stage of illness			
Stage 1	Stage 2	Stage 3	Stage 4
<ul style="list-style-type: none"> • Cerebral palsy. • Benign congenital hypotonia. • Angelman's syndrome. • Prader-Willi syndrome. • Metabolic abnormalities, - eg, organic acidoses. 	<ul style="list-style-type: none"> • Autism. • Tuberosus sclerosis. • Angelman's syndrome. • Encephalitis. • Diseases affecting vision or hearing. • Landau-Kleffner syndrome. • Psychoses. • Slow virus encephalopathies or prion disease. • Metabolic disease - eg, phenylketonuria, infantile neuronal ceroid lipofuscinosis. 	<ul style="list-style-type: none"> • Spastic ataxia. • Cerebral palsy. • Spinocerebellar degeneration. • Leukodystrophies. • Neuroaxonal dystrophy. • Lennox-Gastaut syndrome. • Angelman's syndrome. 	<p>A variety of (usually rare) neurodegenerative conditions that may affect children in their second decade.</p>

Diagnostic Criteria for Rett Syndrome

In spite of molecular genetics, Rett syndrome remains a clinical diagnosis. The diagnostic criteria were updated in 2010.^[2] The diagnosis of Rett syndrome should be considered when there has been a postnatal deceleration of head growth.

Typical or classic Rett syndrome

For this, the following are required:

- A period of regression followed by recovery or stabilisation.
- All main criteria and all exclusion criteria fulfilled.
- Supportive criteria are not required, although they often present in typical Rett syndrome.

Atypical or variant Rett syndrome

For this, the following are required:

- A period of regression followed by recovery or stabilisation.
- At least two of the four main criteria.
- Five out of eleven supportive criteria.

The main criteria

These are:

- Partial or complete loss of acquired purposeful hand skills.
- Partial or complete loss of acquired spoken language.
- Gait abnormalities: impaired (dyspraxic), or absence of, ability.
- Stereotypic hand movements such as hand-wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms.

Exclusion criteria for typical Rett syndrome

- Brain injury secondary to trauma (perinatally or postnatally), neurometabolic disease, or severe.
- Infection that causes neurological problems.
- Grossly abnormal psychomotor development in first six months of life.

Supportive criteria for atypical Rett syndrome

- Breathing disturbances when awake.
- Bruxism when awake.
- Impaired sleep pattern.
- Abnormal muscle tone.
- Peripheral vasomotor disturbances.
- Scoliosis/kyphosis.
- Growth restriction.
- Small cold hands and feet.
- Inappropriate laughing/screaming spells.
- Diminished response to pain.
- Intense eye communication - 'eye pointing'.

As MECP2 mutations are now identified in some cases prior to any clear evidence of regression, the diagnosis of 'possible' Rett syndrome should be given to those individuals under 3 years old who have not lost any skills but otherwise have clinical features suggestive of Rett syndrome. These individuals should be reassessed every 6-12 months for evidence of regression. If regression manifests, the diagnosis should then be changed to definite Rett syndrome. However, if the child does not show any evidence of regression by 5 years of age, the diagnosis of Rett syndrome should be questioned.

Earlier age of diagnosis has been shown to result in families experiencing less stress and emotional strain compared to those with delayed diagnosis.^[4]

Investigations

To make the diagnosis definitively, sequencing of the MECP2 gene is performed through specialist laboratories.

- Neuroimaging may be used to exclude other causes of the neurological manifestations.
- ECG and possibly 24-hour ECG may be needed, as there is an association with cardiac arrhythmias.
- Gastrointestinal motility problems may be investigated by barium swallow, endoscopy, manometry and pH studies.
- Electroencephalography (EEG) may be used to investigate seizures, along with video-EEG recording. Polysomnography and investigations of respiratory pattern and function may be needed to assess those with sleep disturbance or breathing abnormalities.

Management

A co-ordinated multidisciplinary specialist team approach, preferably with close involvement of the primary care team, is the best model for care of this complex illness. Early intervention and comprehensive lifelong management of Rett syndrome can significantly improve the health and longevity of affected cases.

Rett UK have recently produced the National Best Practice Management and Care Guidelines which are aimed at families and healthcare professionals.^[5] They also provide contact details for Rett syndrome treatment clinics in the UK - see 'Further reading' at the end of this article.

Epilepsy

This should be investigated, with consideration of EEG-video recording, particularly to assess nocturnal disturbance:

- Vacant spells are not always due to epilepsy, so should not necessarily be treated unless there is good evidence that symptoms are connected to EEG disturbances.
- Conventional antiepileptic drugs such as carbamazepine and sodium valproate have been used with success.
- Other therapeutic avenues include newer antiepileptic drugs such as topiramate and lamotrigine, ketogenic diets and vagal nerve stimulator medications or implants.

Long QT syndrome

This should be checked for and managed according to specialist advice, to lessen the risk of fatal cardiac arrhythmias.

Poor sleep patterns

Melatonin has been shown to be a potential treatment option for the management of sleep.^[6]

Feeding

This is usually a problem to some degree, as is maintaining weight, so a high-calorie, relatively high-fat content diet helps, and is also of help to some patients with epilepsy, through its ketogenic effect:

- Assessment of oral motor function with use of correct positioning and other practical aids to ingestion and swallowing should be explored.
- Supplemental feeding by nasogastric or gastrostomy routes may be used.
- If medical therapy for gastro-oesophageal reflux is ineffective, then surgical procedures such as fundoplication may be useful.
- Constipation can be a problem and should be monitored and managed carefully.

Scoliosis

Those cases with severe or function-limiting spinal curvature may benefit from surgical intervention.

Osteoporosis

Osteoporosis is common in people with Rett syndrome. Vitamin D supplementation may be necessary for many cases.^[7]

Communication

This may be difficult; however, non-verbal means should be assessed, explored and enhanced as much as possible:

- The use of picture boards and other visual aids to communication can be very helpful.

Holistic therapy

This is thought to help some patients and appears to be popular with them and their families:^[8]

- Hydrotherapy, massage and horse riding have been used to help patients and their families cope with this condition.
- Families need empathetic social and sometimes psychological support; advice and advocacy for interactions with educational authorities can be beneficial. Screaming and nocturnal disturbance are often troublesome issues.
- Expert input may be helpful to exclude an organic cause that cannot be communicated, or to come up with practical solutions.
- The patient's home may need adaptations and aids to improve mobility and safety.

Mobility aids

These include aids such as:

- Hinged ankle-foot orthoses to overcome hypertonia, which may help maintain independent walking.
- Hand splints that prevent the stereotyped hand movements, can reduce self-injury and agitation where they are particularly severe.

Complications

- Cardiac arrhythmias.
- Severe intellectual impairment.
- Loss of ability to walk.
- Gastrointestinal complaints.
- Epilepsy.
- Cachexia.
- Screaming episodes.
- Nocturnal disturbance and poor sleep with alertness for up to 18 hours per day in many cases.
- Difficulties in coping with the condition for families/carers.

Prognosis

- Epilepsy usually starts after the age of 4 years and tends to diminish in severity in adulthood.
- Prognosis is variable where the developmental difficulties are concerned:
 - Achievement and maintenance of some useful hand and communication skills is the norm for some patients.
 - About 60% of patients can continue to walk throughout adulthood.
 - The remainder never walk, or lose the ability, as global motor dysfunction sets in.
- The annual death rate in classic Rett syndrome has been estimated at about 1.2% in the UK and little change in survival has been found in a period of some 30 years.
- Most of deaths are between the ages of 15 and 20 years with causes related to the disorder (eg, pneumonia and epilepsy).
- However, individuals with Rett syndrome have potential for prolonged survival with approximately 60% surviving to early middle age.^[9]

Further reading & references

- [List of UK Rett's syndrome clinics](#); Rett UK
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