ABC of Rett Syndrome: A General Introduction

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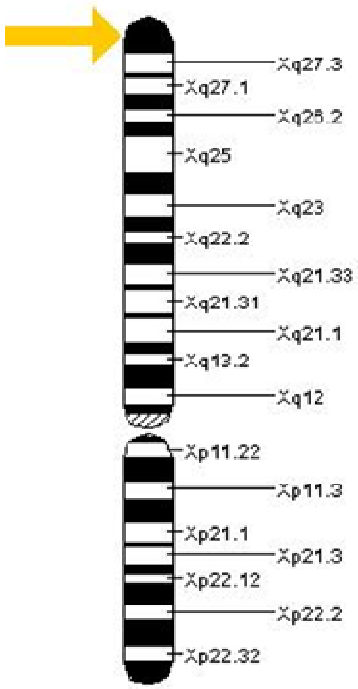
Historical Background



Rett syndrome (RTT), the most common cause of severe learning disability in females, was initially described in 1966 by Professor Andreas Rett. Paralleling the sequence of events in autism, the condition went largely unnoticed until the first English language paper on the subject, a series of 35 cases reported by Bengt Hagberg and colleagues in 1983. By the early 1990s the classical picture of a period of regression, culminating in severe neurological impairment and the appearance of characteristic repetitive hand movements, had become well recognised world-wide. The challenge of finding the genetic basis of the condition was particularly difficult given that less than 1% of cases are familial and affected individuals rarely reproduce. Nevertheless, the virtual absence of affected males and the presence of affected half-sisters in the few familial cases gave the clue that this was an X-linked dominant gene with male lethality. It was not until 1999, when Ruthie Amir et al discovered mutations on the MECP2 gene at Xq28 (see picture opposite) that this hypothesis was verified, opening the way for new avenues of research on genotype-phenotype correlations, as well as on the underlying neuropathology, neurochemistry and central autonomic disturbance.

MECP2 : The arrow above shows the Xq28 part of the MECP2 gene where RTT mutation often occurs.

Clinical Diagnosis

Prior to the discovery of the MECP2 gene, diagnosis was entirely dependent on application of a set of essential and supporting criteria overleaf:

Essential Criteria

- Apparently normal pre- and prenatal period
- “Normal” early development in first 5-6 months
- Normal head circumference at birth, followed by deceleration in head growth
- Loss of purposeful hand skills (6 months to 2½ years)
- Appearance of characteristic stereotyped hand movements
- Regression in hand use, oromotor and communication skills, and emerging cognitive impairment.
- Impairment of locomotion, appearance of gait / truncal “apraxia”

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Supporting criteria include breathing dysfunction (with intermittent hyperventilation and breath-holding spells), EEG abnormalities and seizures, dystonia, peripheral vasomotor disturbances, scoliosis and growth retardation.

Because the gene mutation is currently only found in approximately 90% of cases, clinical diagnosis remains essential. However, genetic diagnosis has now enabled us to recognise a broader phenotype amongst those individuals who have been classified as 'atypical' rather than 'classical'. We now know that development prior to regression is not always normal, but may be suboptimal from the outset and that regression may occur early, late or not at all. In milder cases there may be no reduction in head growth and hand stereotypies may be minimal. There may also be preservation of good motor skills, and occasionally speech. As well as recognising the broader phenotype in females, we are also seeing a small number of affected males.

Genetics

Geneticists had predicted that since mutations on the paternal X-chromosome would be inherited by daughters but not sons, there would be a high paternal:maternal ratio of de novo mutations to explain the low incidence of affected males. This prediction has now proved to be correct, with > 95% of MECP2 mutations originating in paternal germ cells.

Where a MECP2 mutation is not found, this may be a reflection of the limitations of current testing and / or the presence of a different gene mutation resulting in a similar disorder. For example, more recently mutations have been identified in the CDKL5 and FOXG1 genes in patients with a clinical phenotype that strongly overlaps with RTT, but is characterised by early onset seizures in the first 6 months of life.

Implications for Practice

- The person who looks like they have Rett syndrome clinically should be diagnosed as such, even in the absence of MECP2 mutations.
- The person in whom Rett syndrome is suspected should have genetic testing, even in the absence of full diagnostic criteria.
- Atypical cases are less likely to be MECP2 positive than those with classical RTT. In those with early onset seizures, screening for CDKL5 is indicated.

The empirical risk of having a 2nd affected child with RTT is in the order of 1%, and can result from two possible but rare causes. The first is that there are further germ-line mutations (gonadal mosaicism). The second is that the mother is an asymptomatic carrier due to skewed X-inactivation or somatic mosaicism. Where a MECP2 mutation has been identified in a child, the parents (more specifically the mother) can be offered genetic testing. Clearly this will not exclude further germ cell mutations, and despite the low recurrence risk, parents may occasionally wish to go on and have amniocentesis in further pregnancies. Where a MECP2 mutation has not been diagnosed in the proband case, and the child's presentation is atypical, the risk of having a 2nd affected child may be harder to quantify.

Parents may wish to have further information about the implications of the specific MECP2 mutation in their child. Genotype-phenotype correlations are generalisations, based on large sample sizes, so should be interpreted with caution. However, studies to date indicate the following:

- The p.R133C mutation is typically mild, whilst p.R255X & p.R270X mutations are typically more severe.

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- Individuals with early truncating mutations have a more severe outcome than cases with missense and late truncating mutations.
- Individuals with late truncating mutations have a less typical presentation than cases with missense and early truncating mutations, presumably reflecting greater residual function of MeCP2 protein.
- Missense mutations appear to cause milder symptoms
- All of the above can be modified by skewed X-inactivation

Gene to brain

In RTT there is low brain weight, a reduced branching of dendrites and a decrease in dendritic spines, with frontal, temporal and brainstem areas being particularly affected. This distribution is consistent with the clinical features of the disorder, and the relative sparing of visual function.

How does the finding of the MECP2 mutation help us to understand the pathological findings? The MECP2 gene is responsible for production of the MeCP2 protein, which in turn has a regulator function in shutting down the activity of other 'downstream' genes. Failure to terminate the transcription of these 'secondary' genes is assumed to result in the clinical features that we find in RTT. Although the precise link between gene expression and brain function remains unclear, a number of studies have shown that MECP2 is essential for neuronal maturation and synapse formation, perhaps acting through various other proteins involved in nerve growth and migration (possible candidates being BDNF, MAP2 and UBE3). However, precise mechanisms are complex and remain the target of intensive research efforts.

The 2007 report and 2009 update on the reversal of RTT in a mouse model by reactivation of MECP2 caused a considerable stir in the field, and raised hopes for many families . This Rett UK funded research has been built upon and has moved research forward enabling clinical trials of drugs and therapies may lead to future breakthroughs.

Clinical management

In the absence of curative therapies, current management remains symptomatic. The two key aspects are to support families in understanding the condition and to adopt a multi-disciplinary approach to the main clinical problems.

It is beyond the scope of this article to fully detail the interventions required by each member of the multi-disciplinary team. However, it is important to point out that the bulk of clinical care is similar to that provided to other children with profound and multiple learning disability. Hence by developing an understanding of the 5-10% of issues that are different for RTT, a good PMLD team will be able to provide families with a first-rate service, with only occasional advice and input from more specialist services. The box below highlights some of the particular problems or issues to be aware of:

- Epilepsy – the main risk is of over diagnosis. Although epilepsy is common, affecting up to 65% of people with RTT, there are many episodes that can mimic seizures, including breath-holding spells, vacant episodes, dystonic posturing and painful gastro-oesophageal reflux. The situation can be more difficult to manage in people who have definite epilepsy alongside a variety of other episodes. If in doubt, video-EEG monitoring and / or a specialist opinion should be sought before resorting to poly-pharmacy.

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- Scoliosis – develops in a majority of people with RTT. Those with early hypotonia are at particular risk. There should be close monitoring of the spine, with baseline X-rays as soon as asymmetry of spinal mobility is detected. Proactive involvement of an orthopaedic surgeon with experience of RTT is important, and bracing should be considered as an early intervention. An active physiotherapy and hydrotherapy programme is essential, supplemented if possible with a horse-riding programme (Hippotherapy).
- Nutrition – people with RTT are at risk of growth failure throughout their lives, but weight loss can be a marked feature in their teens and early adulthood. The combination of higher than normal calorific requirements, perhaps related to the movement disorder, and dysphagia, often seems to decompensate in young adults. Vigilance is needed at a time when paradoxically the transition from child to adult services may make close monitoring more difficult.
- Mobility – some people never achieve independent ambulation, but for those that do, there is a risk of them 'going off their feet' in adolescence or early adulthood. As is the case with feeding and nutrition, proactive management is needed to maintain mobility at a time when therapy input may well be reduced.
- Communication – people with RTT are socially motivated, and their most effective communication channel is direct (e.g. through eye pointing) rather than through the use of communication aids. They are particularly responsive to music, and many benefit from music therapy to support social interaction and communication.
- Screaming episodes – can be troublesome, particularly in young adults. A careful evaluation of potential precipitants should be undertaken. This may include physical causes such as infection or pain (e.g. due dental caries, dysmenorrhoea, reflux, pressure points), as well as clinical depression. An ABC analysis is essential. Empirical treatment may include environmental manipulation, and (as appropriate) a trial of analgesia, anti-depressants, night sedation, or in the last resort, major tranquillisers.

Rett UK is a national non-profit charity, founded in 1986, to give help, advice and support to all those affected by RTT and the professionals who support them.

Our aims are to:

- support families and carers and to ensure that all people with Rett syndrome have access to the best practice in diagnosis, treatment and care
- promote, support and encourage research into the scientific, therapeutic and social aspects Rett syndrome
- increase the awareness of Rett syndrome and the issues facing all people with Rett syndrome, their families and carers

Activities include a quarterly magazine, a Family Weekend, self-help support groups across the UK, and peer to peer support through a regional contact network. Rett UK's Family Support Manager provide proactive support, advice and information to families, carers and professionals. Rett UK funds research and works in partnership internationally. We rely entirely on donations and grants for our income.

We can be contacted by telephone on 01582 798911, or through email on support@rettuk.org or you can find out more details on the website www.rettuk.org

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