Clinical Aspects of Rett Syndrome

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Rett syndrome (RTT) is a severe neurodevelopmental disorder and is the second most common form of severe mental retardation in females. RTT affects 1 in 8,000 births by the age of 15 and does not discriminate between racial or ethnic groups. It is a devastating condition characterised by progressive loss of speech and movement and the development of intellectual disability at a very young age. Affected girls develop normally for the first 6 to 12 months of life then, mysteriously development stops, and in some cases even regresses. The disorder results in severe disability and for most, the inability to communicate or be independently mobile. Many patients die before they reach 20. Some die under the age of 10.

The disorder was initially identified by the Austrian physician Dr Andreas Rett, who first described it in a journal article in 1966. However, it was not until a second article was published in 1983 by a Swedish researcher Dr Bengt Hagberg, that RTT was recognized as a disorder.

The diverse nature of the disabilities suffered by the girls includes loss of purposeful use of their hands, mobility problems, epileptic seizures, intellectual disability, osteoporosis, scoliosis (spinal curvature) and digestive disorders, which together put an enormous demand on family and community resources. Girls with RTT often exhibit autistic-like behaviour and thus RTT has been considered to be in the autistic spectrum of disorders. Other features may include walking on their toes, sleep problems, teeth grinding and difficulty chewing, slowed growth, breathing difficulties while awake such as hyperventilation, air swallowing and apneas (breath holding). These girls often require major surgical interventions, in particular corrective spinal surgery. In fact, the care required for a young woman with RTT has been compared to that required for a person with high- level quadriplegia.

The most severe handicap in Rett Syndrome is apraxia, which is the inability to perform any purposeful movement. This interferes with everyday activities including walking, speech and even eye gaze. Most girls need assistance for all activities of daily living such as feeding, dressing, and toileting. A quarter of all girls may never walk at all, and about half of those who do walk will lose the ability at some time. The majority have epileptic seizures, which can range from mild to severe. All patients are at risk of developing scoliosis (curvature of the spine).

In October 1999 a gene called *MECP2 (*Methyl CpG binding protein 2) was identified by researchers in Texas, which appears to be the cause of RTT in most affected girls. The identification of this gene, located on the X chromosome, is a major breakthrough in our understanding of RTT. Over 290 different mutations have been found in *MECP2* in RTT patients ranging from small changes in the DNA to large sections of DNA being removed. These changes lead to the MeCP2 protein becoming less efficient or totally ineffective, thus resulting in RTT. To complicate the issue further, mutations in *MECP2* have been observed in other disorders such as Angelman syndrome and the mental retardation syndrome with psychosis, pyramidal signal and macro-orchidism (P-MMX) syndrome. Subsequently two other genes, *CDKL5* (Cyclin-dependent kinase-like 5) and *FOXG1* (Forkhead box protein G) have also been identified to be the cause of RTT in patients classified with variant RTT. These

landmark discoveries have led to the initiation of exciting new research aimed at understanding the biology of Rett syndrome.

The severity of RTT in girls is largely due to the number of their cells that express a normal copy of the *MECP2* gene. Because *MECP2* is located on the X chromosome its expression is subject to X chromosome inactivation (XCI) in girls, where one X chromosome in each cell is usually randomly inactivated. This produces a mosaic of MeCP2 expression whereby some cells express the mutant gene and others express the normal gene. If the active X chromosome that is carrying the mutated *MECP2* gene is turned off in a large proportion of cells, the symptoms will be mild, but if a larger percentage of cells have the X chromosome with the normal *MECP2* gene turned off, onset of the disorder may occur earlier and the symptoms may be more severe.

Boys can also suffer from RTT. Owing to the fact that males have only one X chromosome, boys with RTT lack a backup copy that could compensate for the defective one, and thus they have no protection from the harmful effects of the disorder. Boys usually experience severe problems and die either before birth or in early infancy. A small number of boys have however, been reported to have a less severe form of RTT. These boys have either a different mutation in the *MECP2* gene, a sporadic mutation occurring in some but not all of their cells after conception (somatic mosaicism), or an extra X chromosome (Klinefelter syndrome XXY) with a mutation in the *MECP2* gene, resulting in some degree of intellectual disability and developmental problems, but not severe enough to result in early death.

Although RTT is regarded as a genetic disorder, it is very rarely inherited. Most cases are spontaneous, which means the mutation occurs by chance. However, there are some cases where female family members of RTT children carry a mutation in the *MECP2* gene but do not show any clinical symptoms. These are known as "asymptomatic female carriers".

At present, there is no cure for RTT patients and therefore treatment is largely symptomatic. However, with integrated multidisciplinary health care and symptomatic drug treatment, patients with RTT have a better quality of life and a considerably longer lifespan with medications and other therapies available to reduce symptoms such as seizures, movement difficulties, breathing irregularities. Supportive medical management includes physical, occupational, speech therapy, special academic, social, vocational, and supportive services. Early intervention is also often required to reduce the possibility of inadequate weight gain resulting in growth failure, and some girls may require nasogastric or gastrostomy feeding.

RTT is an extremely diverse disorder, with girls showing numerous different types of symptoms, which has in the past, caused diagnosis to be a challenge. Recently an international group of researchers and clinicians have published a revised version of the clinical classification of the different types of RTT with the aim to aid diagnosis of the disorder and thus have an opportunity to apply the appropriate treatment regimens earlier. Girls can be classified into two main groups of RTT, either classical RTT or variant RTT depending on their symptoms and genotype. Variant RTT patients can also be further subdivided into distinct clinical groups such as preserved speech variant, early seizure variant and congenital variant.

Researchers now know that the main RTT gene product, MeCP2 is a master control protein, regulating the activity of a number of other genes important for brain development and function. Much attention has been focused in recent years on identifying which are the key target genes and whether their function could be restored back towards normal, hopefully leading to improvement of the health and well-being of affected girls. The MeCP2 protein is now known to have a number of other functions in cells of the body, and whether these functions influence the problems associated with RTT remains to be established.

A number of clinical trials have been conducted in RTT patients. To date, five completed clinical trials, with the aim of testing potentially new medications have been reported for RTT. However, the outcomes from these studies showed only small effects in the girls. Presently there are a small number of new clinical trials being conducted in RTT testing potential new medications.

A few years ago amazing research findings by scientists showed that some of the symptoms observed in a mouse model for RTT could be reversed. This exciting news provides a very promising outlook for RTT, raising the possibility that potentially curative therapy for RTT could be a feasible option. There are currently a number of mouse models being investigated and scientists are now in a position to pursue whether this reversibility can be achieved using specific medications.