Rett Syndrome (RTT)

Rett Syndrome (RTT, OMIM no 312750) is a rare neurological disorder characterized by a broad spectrum of symptoms.

First description

Rett Syndrome (RTT) was first described (in German) by an Austrian neurologist, Dr. Andreas Rett, in 1966, following his observation of the characteristic "hand washing" movements of his patients (Rett, 1966). It was not until the 1980s, however, that the syndrome began to be recognised more widely, as a result of English-language publications written by a Swedish neurologist, Dr. Bengt Hagberg (Hagberg, 1985; Hagberg, Aicardi, Dias, & Ramos, 1983). It was he who proposed the name "Rett syndrome" in recognition of the role played by Andreas Rett in first identifying the disorder.

Genetics

In the majority of individuals with RTT, the cause can be attributed to de novo mutations in the X-linked Methyl-CpGbinding protein 2 gene (MECP2) located at Xq28 (Amir et al., 1999). MECP2 is a transcriptional repressor that binds methylated DNA and influences many different biological pathways on multiple levels (Lyst & Bird, 2015). Phenotype-genotype correlation studies indicate that certain mutations may contribute to higher or lower levels of neurologic function and developmental skills (Fabio et al., 2014; Fehr, Downs, Bebbington, & Leonard, 2010; Leonard et al., 2005; Neul et al., 2014). Other (epigenetic) factors are also playing a role in determining severity, such as X chromosome inactivation and distribution of the abnormal gene in specific brain regions (Cuddapah et al., 2014; Neul et al., 2008). However, mutations in MECP2 cannot be identified in all cases (or may be detected when no phenotypic characteristics are present) and the primary diagnosis still remains clinical rather than genetic.

FOXG1 and CDKL5 are known genes, which also cause RTT-like phenotypes. These now fall under a banner of RTT-related disorders. The number of known genes, in which variation can cause a RTT-like phenotype, increased drastically in the last few years; there have been 69 new genes identified which can cause a RTT (classic or variety) like phenotype (Ehrhart, Sangani, & Curfs, 2018). We are possibly heading towards a RTT spectrum disorder with many causative genes (Ehrhart et al., 2018). How much influence a particular mutation has and how much is contributed by other genetic aspects or environmental influences is an open question (Ehrhart et al., 2021).

Incidence/prevalence

As RTT is an X-linked disorder it is seen predominantly in females, with an estimated prevalence of 1 in 9,000-15,000 live female births (Bienvenu et al., 2006; Fehr et al., 2011), making this one of the most

frequent causes of developmental disorder in girls. It is more rarely found in males, in whom early deaths have been reported.

Life expectancy/mortality

Individuals with RTT commonly have a reduced life span compared with the general population (Halbach et al., 2013), with the most physically challenged being at increased risk of early death and the most able surviving into adulthood in good health. There is a high incidence of sudden death, which may be related to central autonomic dysregulation (Kerr, Armstrong, Prescott, Doyle, & Kearney, 1997). Some deaths are related to epilepsy, to aspiration pneumonia or nutritional difficulties but less severely affected individuals are likely to die from causes unrelated to RTT.

Physical features and natural history

Typically, RTT has been characterised by seemingly-normal development in the early months of life following which there is a stagnation and regression of skills, beginning between 6 and 18 months of age (Lee, Leonard, Piek, & Downs, 2013; Smeets, Pelc, & Dan, 2012). Recent retrospective studies have, however, shown that early development does not follow quite as typical a trajectory as supposed (Einspieler, Kerr, & Prechtl, 2005; Marschik et al., 2014; Marschik et al., 2013). Developmental regression in RTT remains still a puzzling and complex phenomena (Einspieler & Marschik, 2019; Smeets, Townend, & Curfs, 2019; Zhang et al., 2019).

One of the first noticeable signs is a deceleration in head growth. Other symptoms include loss of motor and communication skills, namely the loss of verbal language and purposeful hand use, accompanied by stereotypic hand movements (the handwashing/clapping noticed by Andreas Rett). Additional features include abnormal gait and an inability to walk; abnormal breathing and sleep patterns, altered muscle tone, scoliosis, growth retardation and small cold hands and feet (Neul et al., 2010). Poorly regulated central autonomic function leads to disturbed cardio-respiratory control with episodes of breath-holding, shallow breathing, hyperventilation and valsalva breathing. Epilepsy is present in 60%–80% of individuals (Operto, Mazza, Pastorino, Verrotti, & Coppola, 2019). Early hypotonia gives way to hypertonia with the risk of contractures and episodes of dystonia are common. Abnormal oral movements may make feeding difficult. Gastric reflux, aerophagy and constipation are common.

Communicative, cognitive and behavioural characteristics

Anxiety and mood disorders are frequently reported. Perhaps the most significant factor influencing quality of life for individuals with RTT and their families, however, is the severe limitation in their ability to communicate through conventional channels such as speech and hand signs/gestures (Cass et al., 2003). To what extent apraxia rather than any deeper language and cognitive impairments influences these limitations, is a subject for ongoing debate. In general, older studies suggest that most individuals with RTT operate at pre-linguistic, pre-intentional levels of communication. Several studies also point to low levels of language comprehension and cognitive functioning (Berger-Sweeney, 2011), especially when standardised receptive language, IQ or adaptive behaviour tests are employed. In contrast, parents

frequently report that their children know more than they are able to express or to demonstrate on assessment (Bartolotta, Zipp, Simpkins, & Glazewski, 2011; Urbanowicz, Leonard, Girdler, Ciccone, & Downs, 2014) and there is growing (anecdotal) evidence that the population of individuals with RTT spans a broader range of cognitive ability than previous thought. They are universally recognised as engaging in "intense eye communication" (Neul et al., 2010) (p. 946) and many parents and professionals advocate an approach of "presumed competence". There is growing interest in the potential benefits that eye gaze/eye-tracking technologies can offer to individuals with RTT (Townend et al., 2016). This has led to calls for the development of more objective eye gaze/eye-tracking based cognitive and receptive language assessments, which can be used to validate parental reports (Byiers & Symons, 2013; Urbanowicz et al., 2014).

Differential diagnosis

Clinical criteria for the diagnosis of classic RTT and its atypical variants e.g. Preserved Speech Variant (Renieri et al., 2009) were revised in 2010 by members of the Rett Search consortium (Neul et al., 2010). Following clinical identification by core and supportive consensus criteria the diagnosis may be confirmed by genetic analysis.

Historically, individuals with RTT were labelled as having an "autism spectrum disorder" (ASD) (Young et al., 2008), however, RTT was removed from the umbrella of ASD in the 2013 publication of DSM-V. While individuals with RTT pass through an autistic-like phase during regression, many regain social awareness and are especially noted for their sociability. Those with milder atypical forms of RTT (e.g. PSV) may continue to display features of ASD (Kaufmann et al., 2012).

Management

In 2007 Bird and colleagues first demonstrated that the symptoms of RTT could be reversed in mice (Guy, Gan, Selfridge, Cobb, & Bird, 2007). Since then much research has been devoted to both the treatment and potential cure of RTT (although this continues to be quite some way off) as well as the development of more functional therapies which address day to day care and seek to enhance the participation and quality of life of individuals living with this rare disorder. Due to their complex physical and psychological needs individuals with RTT and their families require lifelong access to assessment and intervention from expert multidisciplinary teams (Borloz, Villard, & Roux, 2021; Nissanholtz-Gannot, Zigdon, & Lotan, 2015). Parent associations can also play a vital role in supporting families (Townend et al., 2016). Specialist advice is needed in relation to aspects such as feeding and nutritional, epilepsy and non-epileptic autonomic attacks, movement and posture, and communication. Furthermore, fundamental RTT research findings are providing a better understanding of the underlying mechanisms of the disease and paving the road towards therapies (Sandweiss, Brandt, & Zoghbi, 2020).

Available guidelines

In recent years, guidelines have been written for the management of scoliosis (Downs et al., 2009), growth and nutrition (Leonard et al., 2013), and bone health (Jefferson et al., 2016) in RTT. An international

consortium with 650 participants from 43 countries led by the Rett Expertise Centre Netherlands-GKC developed consensus based guidelines for the assessment, intervention and long-term management of communication in RTT (Townend, Bartolotta, Urbanowicz, Wandin, & Curfs, 2020)

Conclusion

We do not yet fully understand the biological pathways underlying the phenotypic presentation of the syndrome. Next generation sequencing, especially whole genome sequencing, combined with the use of bioinformatics analysis and mutation databases find more and more genes in patients who were clinically diagnosed with RTT or RTT like syndrome (Ehrhart et al., 2021; Ehrhart et al., 2018). Integrative analysis of omics data and creating a better interoperability between genotype-phenotype databases will increase our power to do so. Further research into the pathophysiology of RTT for a better understanding of the multifunctionality of MECP2 and at the same time offering patients and their families' good clinical care is the way to go.

Useful websites/associations for more information

http://www.rettsyndrome.org

http://www.rettsyndrome.eu/association-rse/europe/

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