Rett Syndrome (RTT)

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 [1]. 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 [2, 3]. 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-CpG-binding protein 2 gene (MECP2) (OMIM 312750) located at Xq28. MECP2 is a transcriptional repressor that binds methylated DNA and influences many different biological pathways on multiple levels [4]. The link to MECP2 was discovered and reported upon by Amir and colleagues in 1999 [5]. To date, several hundred possible mutations have been identified, each contributing to the specific RTT phenotype and severity of symptoms experienced. 67% of all MECP2 mutations are found in eight hotspots: R106, R133, T158, R168, R255, R270, R294, R306. A number of phenotype-genotype correlation studies indicate that certain mutations may contribute to higher or lower levels of neurologic function and developmental skill [6-9]. According to Neul et al. [6], for example, data from the US-based Natural History Study suggests that individuals with R133C, R294X, R306C and 3’ truncations present with milder symptoms, acquiring more gross motor skills and losing fewer fine motor and expressive language skills. Other (epigenetic) factors are also thought to play a role in determining severity, such as X chromosome inactivation and distribution of the abnormal gene in specific brain regions [10, 11]. However, mutations in MECP2 cannot be identified in all cases (or may be detected when no phenotypic characteristics are present) and the primary diagnosis remains clinical rather than genetic.

Mutations in two other genes FOXG1 and CDKL5 have also been found to be responsible for RTT-like phenotypic presentations; these now fall under a banner of RTT-related disorders.

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 [12, 13], 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 [14], 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 [15]. 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 [16, 17]. Recent retrospective studies have, however, shown that early development does not follow quite as typical a trajectory as supposed [18-20].

One of the first noticeable signs is a deceleration in head growth following which individuals with RTT demonstrate a 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), abnormal gait and an inability to walk; additional features include abnormal breathing and sleep patterns, altered muscle tone, scoliosis, growth retardation and small cold hands and feet [20]. Poorly regulated central autonomic function leads to disturbed cardio-respiratory control with episodes of breath-holding, shallow breathing, hyperventilation and Valsalva breathing. Generalised or focal epilepsy is present in over 50% of individuals. 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 [21]. 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 [22], 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 [23, 24] 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” [25] (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 [26]. 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 [23, 27].

Differential diagnosis

Clinical criteria for the diagnosis of classic RTT and its atypical variants (e.g. Preserved Speech Variant, PSV [28]) were revised in 2010 by members of the Rett Search consortium [25]. Following clinical identification, the diagnosis may be confirmed by genetic analysis.

Historically, individuals with RTT were labelled as having an “autism spectrum disorder” (ASD) [29], 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 [30].

Management

In 2007 Bird and colleagues first demonstrated that the symptoms of RTT could be reversed in mice [31]. 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 [32]. Parent associations can also play a vital role in supporting families [33]. Specialist advice is needed in relation to aspects such as feeding and nutritional, epilepsy and non-epileptic autonomic attacks, movement and posture, and communication. Hippo-, hydro- and music therapy are all felt to be of value as is the introduction of augmentative and alternative communication systems [34-36], in particular those which make use of eye gaze/eye-tracking technology as a form of access.

Available guidelines

In recent years, guidelines have been written for the management of scoliosis [37], growth and nutrition [38], and bone health [39] in RTT. An international consortium led by the Rett Expertise Centre Netherlands is currently funded by a HeART Award from Rettsyndrome.org to develop international guidelines for the assessment, intervention and long-term management of communication in RTT. These guidelines are being developed according to the model utilised by the other guidelines, notably combining available evidence with expert consensus. The final guidelines are expected to be published in 2017.

Useful websites/associations for more information

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

References

1. **Rett, A.**, [On an unusual brain atrophy syndrome in hyperammonemia in childhood]. Wien Med Wochenschr, 1966. 116(37): p. 723-6.

2. **Hagberg, B.**, Rett's syndrome: prevalence and impact on progressive severe mental retardation in girls. Acta Paediatr Scand, 1985. 74(3): p. 405-8.

3. **Hagberg, B., et al.**, A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. Ann Neurol, 1983. 14(4): p. 471-9.

4. **Lyst, M.J. and A. Bird**, Rett syndrome: a complex disorder with simple roots. Nat Rev Genet, 2015. 16(5): p. 261-75.

5. **Amir, R.E., et al.**, Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet, 1999. 23(2): p. 185-8.

6. **Neul, J.L., et al.**, Developmental delay in Rett syndrome: data from the natural history study. J Neurodev Disord, 2014. 6(1): p. 20.

7. **Leonard, H., et al.**, Genotype and early development in Rett syndrome: the value of international data. Brain Dev, 2005. 27 Suppl 1: p. S59-S68.

8. **Fehr, S., et al.**, Atypical presentations and specific genotypes are associated with a delay in diagnosis in females with Rett syndrome. Am J Med Genet A, 2010. 152A(10): p. 2535-42.

9. **Fabio, R.A., et al.**, Recent insights into genotype-phenotype relationships in patients with Rett syndrome using a fine grain scale. Res Dev Disabil, 2014. 35(11): p. 2976-86.

10. **Neul, J.L., et al.**, Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. Neurology, 2008. 70(16): p. 1313-21.

11. **Cuddapah, V.A., et al.**, Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome. J Med Genet, 2014. 51(3): p. 152-8.

12. **Fehr, S., et al.**, Trends in the diagnosis of Rett syndrome in Australia. Pediatr Res, 2011. 70(3): p. 313-9.

13. **Bienvenu, T., et al.**, The incidence of Rett syndrome in France. Pediatr Neurol, 2006. 34(5): p. 372-5.

14. **Halbach, N.S., et al.**, Aging in Rett syndrome: a longitudinal study. Clin Genet, 2013. 84(3): p. 223-9.

15. **Kerr, A.M., et al.**, Rett Syndrome: analysis of deaths in the British Survey. European Child & Adolescent Psychiatry 1997. 6 (Suppl1): p. 71-74.

16. **Lee, J., et al.**, Early development and regression in Rett syndrome. Clin Genet, 2013.

17. **Smeets, E.E., K. Pelc, and B. Dan**, Rett Syndrome. Mol Syndromol, 2012. 2(3-5): p. 113-127.

18. **Einspieler, C., A.M. Kerr, and H.F. Prechtl**, Is the early development of girls with Rett disorder really normal? Pediatric Research, 2005. 57(5 Pt 1): p. 696-700.

19. **Marschik, P.B., et al.**, Three different profiles: early socio-communicative capacities in typical Rett syndrome, the preserved speech variant and normal development. Dev Neurorehabil, 2014. 17(1): p. 34-8.

20. **Marschik, P.B., et al.**, Changing the perspective on early development of Rett syndrome. Res Dev Disabil, 2013. 34(4): p. 1236-9.

21. **Cass, H., et al.**, Findings from a multidisciplinary clinical case series of females with Rett syndrome. Dev Med Child Neurol, 2003. 45: p. 325-337.

22. **Berger-Sweeney, J.**, Cognitive deficits in Rett syndrome: what we know and what we need to know to treat them. Neurobiol Learn Mem, 2011. 96(4): p. 637-46.

23. **Urbanowicz, A., et al.**, Parental perspectives on the communication abilities of their daughters with Rett syndrome. Dev Neurorehabil, 2014.

24. **Bartolotta, T.E., et al.**, Communication skills in girls with Rett Syndrome. Focus on Autism and Other Developmental Disabilities, 2011. 26(1): p. 15-24.

25. **Neul, J.L., et al.**, Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol, 2010. 68(6): p. 944-50.

26. **Townend, G., et al.**, Eye Gaze Technology as a Form of Augmentative and Alternative Communication for Individuals with Rett Syndrome: Experiences of Families in The Netherlands. Journal of Developmental and Physical Disabilities, 2015: p. 1-12.

27. **Byiers, B. and F. Symons**, The need for unbiased cognitive assessment in Rett syndrome: is eye tracking the answer? Dev Med Child Neurol, 2013. 55(4): p. 301-2.

28. **Renieri, A., et al.**, Diagnostic criteria for die Zappella variant of Rett syndrome (the preserved speech variant). Brain Dev, 2009. 31: p. 208-16.

29. **Young, D.J., et al.**, The diagnosis of autism in a female: could it be Rett syndrome? Eur J Pediatr, 2008. 167(6): p. 661-9.

30. **Kaufmann, W.E., et al.**, Social impairments in Rett syndrome: Characteristics and relationship with clinical severity. Journal of Intellectual Disability Research, 2012. 56(3): p. 233-247.

31. **Guy, J., et al.**, Reversal of neurological defects in a mouse model of Rett syndrome. Science, 2007. 315(5815): p. 1143-7.

32. **Nissanholtz-Gannot, R., A. Zigdon, and M. Lotan**, The Time is Now: The Need for an Intensive Appropriate Individual Intervention for Individuals with Rett Syndrome. Journal of Syndromes, 2015. 2(1): p. 1-7.

33. **Townend, G.S., et al.**, Rett syndrome and the role of national parent associations within a European context. Rare Diseases and Orphan Drugs 2015. 2(2): p. 17-26.

34. **Simacek, J., J. Reichle, and J.J. McComas**, Communication intervention to teach requesting through aided aac for two learners with rett syndrome. Journal of Developmental and Physical Disabilities, 2015.

35. **Stasolla, F., et al.**, Technological aids to support choice strategies by three girls with Rett syndrome. Res Dev Disabil, 2015. 36: p. 36-44.

36. **Stasolla, F., et al.**, Comparing PECS and VOCA to promote communication opportunities and to reduce stereotyped behaviors by three girls with Rett syndrome. Research in Autism Spectrum Disorders, 2014. 8(10): p. 1269-1278.

37. **Downs, J., et al.**, Guidelines for management of scoliosis in Rett syndrome patients based on expert consensus and clinical evidence. Spine (Phila Pa 1976), 2009. 34(17): p. E607-17.

38. **Leonard, H., et al.**, Assessment and management of nutrition and growth in Rett syndrome. J Pediatr Gastroenterol Nutr, 2013. 57(4): p. 451-60.

39. **Jefferson, A., et al.**, Clinical Guidelines for Management of Bone Health in Rett Syndrome Based on Expert Consensus and Available Evidence. PLoS One, 2016. 11(2): p. e0146824.

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