Predictors of seizure onset in Rett syndrome

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Background and Objectives: Rett syndrome (RTT) is a severe neurodevelopmental disorder mainly affecting females and caused by mutations in the MECP2 gene. Major features include loss of acquired skills, such as speech and purposeful hand use, and the development of characteristic repetitive hand stereotypies, after relatively normal early development. Other features include deceleration of head growth, impaired locomotion, autonomic dysfunction (manifest particularly by respiratory abnormalities), scoliosis and epilepsy. Epilepsy, which occurs in 50% to 94% of cases and may be medically refractory, is among the most challenging of the co-morbidities for those affected and their families. However, little is known about the predictors for epilepsy, including the relationship, if any, to the underlying gene defect. This study explores possible genetic and other risk factors for seizure onset in RTT using an Australian population-based longitudinal dataset.

Methods: Information provided mainly from parental report on presence and age at onset of seizures, and perinatal and developmental history was abstracted from the Australian Rett Syndrome Database (ARSD). Most cases had had genetic mutation testing. Survival analysis was used to investigate the effects of genetic and developmental factors on age at seizure onset.

Results: Seizures were reported in 81% of 275 cases and the median age of onset was 48 months. In 9% seizure onset occurred in the first year of life. Not having gained the ability to walk and developmental problems in the first 10 months of age were significantly associated with an almost twofold increased risk of seizures. Pathogenic mutations were identified in 73% of 254 individuals who had genetic analysis undertaken. Cases without a detectable MECP2 mutation had a significantly higher risk of seizure onset up to 4 years of age, but a significantly lower risk after 4 years.

Conclusions: Seizure onset in RTT is associated with early developmental factors. The association between markers of cortical function (mobility and early development) with onset of seizures is not surprising, in view of the widespread abnormalities in neuronal circuitry and synaptic plasticity in RTT suggested by neurophysiological, neuropathological and neurochemical studies. Seizure onset is influenced by the genotype. Some mutations appear to be associated with a later age of onset of seizures (e.g. p.R294X), whereas others may increase the risk of earlier age of onset of seizures (e.g. p.R255X). Those without identified mutations overall appear to have an earlier age of onset of seizures. As more is learnt about the functions and effects of the MECP2 gene, its role in epilepsy in RTT and other neurological disorders may be better understood. We have produced a model to help clinicians predict the onset of seizures after an initial diagnosis of RTT syndrome has been made.

References