Rett Syndrome: What we have learned from the Natural History Study.

Objective: To characterize sleep problems and seizures in individuals with RTT (RTT).

Background: The Rett Syndrome Natural History (RSNH) study currently in progress in the United States has an enrollment of 1117 participants, ages 3–66 years, 952 with classic RTT (one male, the reminder females) and 163 with atypical RTT. The RSNH study is part of the rare diseases clinical research network. The initial evaluation includes confirmation of the diagnosis based on current clinical diagnostic criteria for RTT, and documentation of MECP2 mutational status. All participants are evaluated in person by physicians with extensive experience with RTT and include the collection of extensive data concerning clinical characteristics and severity. This database provides a rich source of information for characterization of clinical problems such as sleep problems and seizures in RTT. These particular problems represent significant concerns of parents for their daughters with RTT.

Methods: The database of the RSNH study was reviewed and information collected to evaluate the character and occurrence of sleep problems and seizures in the participants with RTT. Additionally, a subgroup of 264 children and adolescents with Classic RTT and a MeCP2 mutation, and under 19 years of age, and 322 typically developing siblings (under 19 years of age and serving as a control population) were evaluated at baseline and one-year follow-up; parents completed four validated questionnaires regarding sleep problems (overall sleep problems, daytime sleepiness, and sleep disordered breathing) in these individuals. Also, the prolonged video–EEG studies of 60 girls and women with RTT ages 3 years–40 years) were reviewed in order to characterize epileptic seizures and non-seizure behaviors.

Results:

Sleep: Overall for the participants in the RSNH study, greater than 80% have sleep problems; 29.6% experienced problems with going to sleep; 43.6% had frequent nighttime wakings; 18.3% have difficult difficulty waking up in the morning.

The subgroup of participants with classic RTT for parents completed the sleep questionnaires were found at baseline and one-year follow-up in comparison to the control group of age matched siblings had more overall sleep problems, more problems with sleep disordered breathing (sleep apnea) and more problems with daytime sleepiness. The sleep problems persisted in the group with RTT over the one-year follow-up period.

Seizures: For the participants in the RSNH study with a confirmed diagnosis of RTT (1117), the following were noted: 55% were reported to have seizures at the first visit; 28% at their first seizure during the study; 41% experienced no seizures for greater than 6 months; 26% were hospitalized for seizures.

In 33% seizures occurred daily or weekly; in 16% seizures occurred occasionally; 2% of the participants were noted to have possible seizures; 19% were on medications for seizures and were seizure free; 30% never had a seizure. Of all the participants who had a history of seizures 45% remained seizure-free for greater than 5 years and only 16% continued to have frequent seizures over time despite treatment.

Prolonged video-EEG monitoring (average 46 hours for individual participants) were reviewed: During 12 of these recordings (20%) was (epileptic seizures were recorded and included partial seizures as well as generalized seizures. For 24 (40%), events of concern were recorded and were not epileptic seizures. For 16 (27%), epileptic seizures and nonepileptic behaviors were recorded during the same session. Non-epileptic behaviors included the following: Motor episodes (jerking, stiffening, head turning, head drops); staring episodes; breath holding episodes; episodes of gastroesophageal reflux; autonomic behaviors such as changes in heart rate or pupil size; episodes of agitation.

Summary:

Sleep problems occur frequently in RTT and include insomnia, daytime sleepiness, and obstructive sleep apnea. In comparison to age-matched typically developing siblings, these sleep problems occur more frequently in individuals with RTT and are chronic and persistent.

Individuals with RTT frequently experience seizures. However, a significant number remained seizure-free for greater than 5 years and may not require lifetime medication for control of seizures. Many repetitive, stereotypic behaviors represent non-epileptic behaviors and are not epileptic seizures. Prolonged video-EEG monitoring to record and characterize these behaviors may be helpful in making decisions regarding the treatment of seizures in RTT.