Rett syndrome: Neurologic and metabolic aspects
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General discussion, unresolved questions and future research
Clinical trials in Rett patients

In the Netherlands, clinical trials in Rett syndrome (RTT) patients are difficult to perform due to the relatively small number of patients that are available. Since Rett is a progressive neurodevelopmental disorder, preferably only Rett patients of a similar age and clinical stage are included in such trials. Using specific reproducible outcome measures of clinical severity, such as the validated Rett Syndrome Motor Behavioral Assessment scale, comparative measurements over time can be performed. In order to distinguish between actual change as a result of treatment and the natural course of the disease, long-term follow-up evaluations are required.

It is now established that a genotype-phenotype correlation exists in RTT and that the clinical course and evolution of RTT patients is determined by the type of mutation. Therefore, to test the clinical efficacy of treatment in Rett patients, determination of the responsible mutation is important. Due to increasing awareness based on excellent reviews and guidelines, the diagnosis of Rett is nowadays made at younger age and, therefore, potential therapies might start at an earlier age.

Neurometabolic evaluations

Although a wide variety of tests have demonstrated biochemical abnormalities in Rett, the clinical effects of correction of these abnormalities remain disappointing. Also in our trial with folinic acid treatment, there was no relevant clinical improvement despite normalisation of spinal fluid levels of 5-methyltetrahydrofolate (5MTHF) (Chapters 2, 3 and 4).

In the majority of patients, the time course of RTT includes a more or less symptom-free interval prior to the development of the clinical signs. It is possible that some accumulation of metabolites/storage products has to take place in order to trigger the onset of disease. A metabolomics study of the CNS compartment, such as the cerebrospinal fluid or the intracellular content of brain tissue, may provide additional clues for our understanding of the disease process. There is growing evidence that oxidative stress is involved in the pathogenesis in the early stages of RTT. Furthermore, oxidative stress biomarkers seem to relate to neurological symptom severity, clinical presentation and mutation type in RTT.
**Animal models**

To clarify the pathophysiology of Rett animal models have been used. Since 2001, several animal Rett mouse models have been developed which show phenotypic abnormalities resembling those of the human RTT. The main characteristic symptoms of Rett are expressed in different phenotype RTT mouse models, focusing on gross motor dysfunction, shortened lifespan and general health, respiratory and autonomic disturbances, or cognitive defects. However, behavioral disturbances and anxiety are difficult to investigate in a mouse model. To evaluate potential therapies, Rett mouse models can be used prior to long-term clinical trials in Rett patients.

**Genetics and gene therapy**

Remarkably, some Rett symptoms in mouse models have even been shown to be reversible, by subtle influence of the MeCP2 function based on transgene therapy. Unfortunately, because these studies have only been performed in Rett mouse models, the clinical implications have not yet been established. Issues concerning the fluctuating clinical course, phenotypic variability and possibility of influencing MECP2 gene expression are still unresolved. There remains a challenge in exploring the different functions and target genes of the MECP2 gene, and in increasing the knowledge of specific MECP2 function in the different regions of the brain.

**Breathing disturbances**

Breathing disturbances in RTT patients are often severe and, in the case of central apnea during wakefulness, no proven therapy is available. Recommended treatment options, such as buspirone in combination with fluoxetine, or carbogen, have been tested in only a few RTT patients. Our studies have shown that, besides central breathing disorders, obstructive breathing problems may exist and may warrant polysomnographic evaluation in RTT patients (Chapters 5). The central breathing disorders in RTT patients may be of the hypocapnic type and may indicate failure of the respiratory feedback loop and central regulatory nuclei in the brainstem. Supplying acetazolamide in order to stabilize this breathing pattern has been used, for instance, in Pitt-Hopkins syndrome. Currently a
trial with acetazolamide in RTT patients with hyperventilation followed by central apneas is in progress. Meanwhile, evaluation of brainstem auditory evoked potentials (BAEP) in selected RTT patients did not identify breathing-related brainstem dysfunction (Chapter 6).

Seizures

In our study on RTT patients (Chapters 2 and 3) we aimed to improve the often refractory epilepsy by addition of folinic acid to the anti-epileptic drugs; unfortunately this was without success. Alternative treatment options for seizure control need to be developed in RTT and CDKL5 patients. In RTT patients, vagus nerve stimulation has been used with success and without respiratory or other complications. However, no data are available on the use of vagus nerve stimulation in CDKL5 patients. Therefore, a prospective trial to study the effect of vagus nerve stimulation in Dutch MECP2 and CDKL5 patients is warranted.

Prognosis

Despite the increased risk of sudden death in RTT, there is a potential for survival into middle age. Specialized RTT centers in which a multidisciplinary team (consisting of a pediatrician, pediatric neurologist, orthopedic surgeon, rehabilitation physician, physiotherapist and speech therapist) may improve the prognosis and quality of life of Rett patients. Collaboration with other Rett centers or European Rett investigators is recommended in order to increase and expand the study populations. With information provided by parents and physicians pooled into an internet Rett database, additional and more effective studies may be designed and facilitated.