Rett syndrome: Neurologic and metabolic aspects
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Outline of the thesis

Rett syndrome (RTT) is a neurodevelopmental disorder that occurs almost exclusively in females. It was described in 1954 by Andreas Rett, an Australian neuropediatrician. After a period of apparently normal development, affected patients experience loss of speech and purposeful hand use, stereotypic hand movements, and gait abnormalities. Additional findings include deceleration of head growth, autistic features, breathing abnormalities, and seizures.

In the majority of patients, Rett syndrome is caused by mutations in the MECP2 gene, which maps to Xq28 and encodes methyl-CpG binding protein 2. How MECP2 mutations lead to Rett syndrome is not yet established. The diagnosis of classic Rett syndrome rests on clinical diagnostic criteria.

This thesis comprises a number of studies, aimed to improve the knowledge of neurologic and metabolic aspects of Rett syndrome, and to summarize a number of clinical trials which have been conducted.

**Chapter 1**, gives an overview of the neurological and clinical symptoms of classic Rett syndrome. Besides this, recent developments which led to a better understanding of the various aspects of epilepsy, cardiorespiratory and sleep disturbances are discussed. The pathophysiology and molecular genetics are reviewed. Furthermore, recent neurometabolic and intervention studies are described in more detail and summarized in an overview table.

**Part I: Clinical trials in Rett syndrome**

In a few Rett patients, low levels of CSF 5MTHF were present. Supplementation with folinic acid restored these low CSF 5MTHF levels. We aimed to gain more insight in the potential effect of folinic acid supplementation on seizures, electroencephalography (EEG), clinical and biochemical evaluations. Therefore, we performed a randomized, double-blind placebo controlled, cross over trial of folinic acid supplementation in a Dutch cohort of 12 Rett patients. The follow up was more than 2 years. **Chapter 2** presents the effect of folinic acid supplementation on seizure severity and EEG abnormalities.

**Chapter 3** evaluates the change in several specific Rett clinical outcome scales, during folinic acid therapy, in these patients.

**Chapter 4** describes the metabolic evaluations in 16 Dutch Rett patients, of whom 12 initially participated in our randomized trial of folinic acid supplementation.
Part II: Respiratory and sleep disturbances in Rett and CDKL5 patients.
Studies into respiratory and sleep disturbances in Rett and CDKL5 patients are presented. Seizures and day-time breathing disturbances belong to the most detrimental clinical phenotype in Rett. Less is known of overnight respiratory disturbances.

Chapter 5 shows the results of overnight polysomnography (PSG), in combination with a questionnaire.

In Chapter 6 we evaluated whether brainstem auditory evoked potentials (BAEP) can be used to measure brainstem dysfunction related to respiratory disturbances in the Rett syndrome patients.

Chapter 7 describes 4 female children, diagnosed with atypical Rett syndrome, caused by mutations in the CDKL5 gene, with drug-resistant seizures and developmental delay from birth on. We studied respiratory and sleep abnormalities in these patients.

Part III consists of a General discussion, with respect to future research and some implications for clinical practice and a Summary.