The spectrum of phenotypes in females with Rett Syndrome

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Abstract

Since the discovery of mutations in the methyl-CpG binding protein-2 (MECP2) gene in Rett Syndrome (RTT) a large number of females have been diagnosed worldwide. In this article we present the clinical and developmental data of 120 RTT females with mutations in the MECP2 gene and individually describe typical and atypical cases. We found a broad spectrum of phenotypes in females. At the severest end we have females with primary developmental delay who never learned to turn, sit or walk and who developed severe epilepsy. At the mildest end of the spectrum, there are females with only minor neurological symptoms who have good gross motor function, speak and have relatively well-preserved hand function. A number of girls either do not fulfil all the necessary diagnostic criteria or present with symptoms that have not been described in RTT before. Comparing our data with the normal population we found that girls with RTT have a smaller occipito-frontal circumference, shorter length and lower weight at birth. As a result of molecular genetic analysis a broad spectrum of phenotypes in RTT females has evolved. We found evidence that the defect in MeCP2 influences the somatic growth before birth.

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1. Introduction

Rett Syndrome (RTT; [MIM 312750]) was first described in 1966 by Andreas Rett, however international recognition was not until 1983 when Hagberg et al. described 35 patients \cite{1,2}. They reported on a group of girls with a neurodevelopmental disorder characterized by severe mental retardation and decelerated head growth. An initial period of normal development was followed by a phase of stagnation and then motor and mental regression notably affecting hand function and speech \cite{2,3}. In 1984 a panel of paediatric neurologists formulated diagnostic criteria for RTT \cite{4}. In the absence of a biological marker RTT was defined by these criteria. However, soon after the description of the diagnostic criteria, a number of females who lacked some of the essential characteristics were described, namely: forme fruste, preserved speech variant, early seizure onset RTT, congenital RTT, late regression RTT \cite{5}.

In 1999 the first mutations in the methyl-CpG binding protein-2 (MECP2) gene were described \cite{6}. The MECP2 gene codes for the methyl-CpG binding protein-2 (MeCP2) which is involved in the long term silencing of genes \cite{7,8}. It is expressed in all tissues but the genes that are regulated by MeCP2 are unknown so far \cite{9,10}. In more than 80% of females with RTT these mutations can be found \cite{11–15}.

Before 1999 the description of the RTT phenotype was problematic because in any case not fulfilling all the diagnostic criteria the diagnosis was uncertain. Now it is possible to diagnose RTT in the absence of some of the diagnostic criteria and we are able to give a more precise picture of the spectrum of phenotypes in females with RTT.

In this study we analysed the developmental data of 120 patients with mutations in the MECP2 gene and describe cases with an unusual presentation.

2. Subjects and methods

We evaluated the developmental data of 120 females with mutations in the MECP2 gene. The following data was collected: weight, height and occipito-frontal circumference (OFC) at birth and at the time of diagnosis, ages when they learned to sit, walk and speak, time when they lost the ability to speak, time when a loss of hand function was first noted (preserved hand function was defined as being able to
finger feed) and onset of hand stereotypes and epilepsy. (Some of the developmental data was presented earlier [16].)

2.1. Case reports

2.1.1. Case 1 (congenital RTT)  
Patient I was born after an uneventful pregnancy. She had no period of normal development, the head control was always poor and she never learned to turn, sit or walk. At age 10 months she developed severe epilepsy. However, at 12 months of age she spoke two words and had some hand function but shortly after lost both abilities. Her head circumference was normal at birth (35 cm) but decelerated within the first 12 months to below the 3rd percentile. The genetic analysis revealed a 1364–1365 C insertion in the MECP2 gene.

2.1.2. Case 2 (forme fruste)  
Patient II has a normal family history and had no birth complication. The motor development was normal (walking at 12 months) and the language development was rather fast. At age 24 months she was speaking 3–4 word sentences, singing songs and counting to ten. At 33 months of age the parents noted that she refused body contact, lost manual skills and that she spoke less frequently and only single words. Six months later she lost her autistic behaviour again and showed developmental progress. At presentation at age 9 years her height, weight and OFC were within the normal range (90th percentile). Her gait was undisturbed, she was able to walk long distances, climb stairs and use a scooter and swing. Her hand function was not age appropriate but she was able to drink from a glass and eat with a spoon. Hand stereotypes occurred only occasionally. Notable was her speech ability. She spoke three word sentences, answered questions, followed instructions, counted to 20 and sang English songs (her mother language is German). The genetic analysis revealed a R306C->T mutation in the MECP2 gene.

2.1.3. Case 3 (electrical status epilepticus during sleep)  
Patient III was born after an uneventful pregnancy into a healthy family. The birth weight was 3280 g, the length 52 cm and the OFC 33.5 cm. Initially the development was normal. She smiled at 3 months and sat unsupported at 7 months. There was also some babbling but no words. At age 12 months she was able to stand unsupported. Then the development slowed down, however there was no regression. At age 2 she could walk unsupported and at the time of first presentation at age 7 she had a normal gait, good hand function and spoke three words. The OFC was in the 3rd percentile and stereotypic hand movements were present. The diagnosis at the time was infantile autism. The EEG at age 7 years showed an electrical status epilepticus during sleep (ESES). Treatment with pulsed steroids resulted in an EEG improvement but only minor changes in the behaviour and was therefore discontinued. The genetic analysis revealed a 880–884 deletion in the MECP2 gene.

2.1.4. Case 4 (precocious puberty)  
Patient IV was the first child of healthy parents. Her birth weight was 2850 g, length 48 cm and OFC 35 cm. The development during the first year was normal. Head control was achieved at 2.5 months, she learned to sit at age 7 months, and was crawling by 10 months. After speaking two words at age 13 months she stopped and never spoke again. At age 28 months she learned to walk. During this time her hand function deteriorated and stereotyped hand movements occurred. At age 7 years precocious puberty was noted (stadium B3, PH4 according to Tanner [17]). The bone age was accelerated (9 years according to Greulich and Pyle [18]). The LH-RH Test demonstrated a 3–4-fold rise of LH and FSH 30 min after stimulation. The MRI showed no abnormality of the hypophysis. She was subsequently treated with leuprorelin (Enanonte® Takeda) which stopped further pubertal development. The genetic analysis revealed an R168X mutation in the MECP2 gene.

2.2. Mutation analysis  
The entire coding region and flanking intron sequences were sequenced using the method described earlier. A detailed Report on the results of the mutation analysis has been published elsewhere [13,14].

2.3. Statistical analysis  
Heights, weight and OFC were analysed using growth charts from Prader et al. [19]. The data at birth was corrected for gestational age. The χ² test was used to compare the data of our patients with the normal distribution of birth weight, height and OFC. The association between the ability to walk and the time of regression was calculated using the Mann–Whitney U-test. A P value below 0.05 was considered significant.

3. Results

3.1. Somatic growth

In 88 patients the OFC at birth was available. The median was on the 30th percentile, three patients had an OFC under the 3rd percentile and one patient had an OFC above the 97th percentile. When compared with the normal population, RTT females tend to have a smaller OFC at birth (P = 0.000025) (Fig. 1a).

The length at birth was recorded in 99 patients. The median was on the 30th percentile. Four females had a length under the 3rd percentile and four patients had a length above the 97th percentile. On comparison with the
normal population, patients with RTT tend to have a shorter birth length ($P = 0.000018$) (Fig. 1b). The median birth weight (104 patients) was on the 30th percentile. Six patients had a birth weight under the 3rd percentile and two were above the 97th percentile. RTT patients tend to have a lower birth weight than the average population ($P = 0.00001$) (Fig 1c).

Fig. 2 demonstrates the height and OFC at the time of diagnosis (100 Patients). 46% of the RTT patients were found to have a height under the 3rd percentile and 40% presented with microcephaly (Defined as an OFC under the 3rd percentile).

3.2. Developmental data

Out of 120 patients 12 (10%) never learned to sit. The remaining patients achieved this milestone between 6–30 months of age (median 8 months). Six patients (5%) lost the ability to sit during the time of regression. Walking was achieved at age 10 months by the earliest patients and at 48 months by the latest (median 19 months). Fifty-four patients (45%) never learned to walk and six patients (5%) lost the ability. Forty patients never spoke (33%). The first words were spoken at a minimum age of 6 months and at a maximum of 36 months. The ability to speak was lost at a median of 24 months (range 12–54 months). Eleven patients (9%) retained their speech. Hand function was lost at a median age of 18 months (range 8–75 months). Nineteen patients (16%) never had good hand function and 16 patients (13%) showed preserved hand function. Hand stereotypes were present in 96% of patients, the median age of onset was 24 months (range: 6–116 months). Thirty-one percent of the females had no sign of epilepsy at the time of diagnosis, the youngest girl to develop epilepsy was 6 months old (Fig. 3a–g). Correlation between the ability to walk and the onset of speech and hand function loss showed that those girls that never learned to walk had an early loss of both language ($P = 0.001$) and hand function ($P = 0.0002$).

4. Discussion

The normal pre and perinatal history is one of the hallmarks of RTT. Recent experiments in mice with MeCP2 deficiency have suggested that it is important for the stability of mature neurons but not for brain development [20,21]. The MeCP2 deficient mice were normal at birth but following a delay of several weeks the first symptoms occurred, similar to the course of the disease in humans. They also found that the isolated central nervous system defect is sufficient to cause the typical symptoms. However, in our group of 120 females with mutations in the MECP2 gene we found that the birth weight, length and OFC...
measurements were significantly lower than in the normal population. This finding implies that MeCP2 has a role in intrauterine development. Our observations are supported by the findings of Engerström and Nomura who reported in their studies that in a large subgroup subtle prodromes could be traced to early infancy [22,23]. Studying the monoamine system Nomura and Segawa dated the developmental disturbances between the 36th gestational week and the 2nd–3rd postnatal weeks [24,25]. It seems likely that the most dramatic effect of the MECP2 mutations occurs in mature neurones at 8–18 months when the stagnation and regression of the development is seen but that there are also subtle effects earlier and in tissues other than neurones.

Molecular genetic analysis enables us to diagnose RTT in the absence of characteristic symptoms and in the presence of uncharacteristic features. A broad spectrum of phenotypes has evolved. Case 1 and 2 present the extremes of this spectrum in our study. The patient S.L. (case 1) never had a period of normal development, never learned to turn, sit or walk. She lost her hand function completely and does not speak. Patient S.S. (case 2), representing the mild end of the spectrum, is able to count to 20, sing songs and ride a
scooter. Therefore the spectrum is broad with severely handicapped girls with almost no development on one end and females with only a mild mental handicap on the other. Congenital RTT and forme fruste described before the discovery of MECP2 gene mutations represent these extremities. However, two RTT variants that have been described are not present in our group of patients: the late childhood regression variant and the infantile seizure onset variant. None of our patients developed epilepsy before the onset of regression nor did any of them display a regression phase later than 6.5 years. This might be by chance or these two variants represent separate entities with a different genetic background.

The fact that the detection rates for mutations are above 80% in most studies shows that the diagnostic criteria for RTT describe the clinical picture very well. However in our subset patients a number of necessary criteria are not fulfilled. Some had primary developmental delay (case 1) or showed no phase of regression (case 3), others had microcephaly at birth, show no deceleration of head growth, have no stereotypic hand movements or have undisturbed locomotion (case 2). Some girls present with symptoms that are not usually seen in RTT like ESES in case 3 and precocious puberty in case 4. This shows that the diagnosis of RTT should not be dismissed because some characteristic features are absent or because uncharacteristic symptoms are present.

We correlated the ability to walk with the age when handfunction and language was lost and found that children with an early regression are less likely to walk. Either the girls that are severely affected have an early regression or once the regression sets in the developmental process required to learn to walk is not possible any more.

The developmental data shows some characteristics of RTT that are useful when counselling parents and for therapy planning. Many parents of children that never had a period of regression are worried that the regression is still about to come. In our RTT females we found that loss of hand function or language rarely happens after 4 years of age. Of course this is only true in childhood. Studies with adult patients have shown that later in life many women lose the ability to walk again [22]. Nevertheless there seems to be a certain time span in which the girls with RTT learn to sit, walk and speak and if it is not achieved during this time it will not be achieved. None of our patients learned to sit after the age of 30 months, walk after the age of 48 months and speak after the age of 36 months although almost all girls in our study received physiotherapy and most of them occupational therapy. This has to be taken into account when realistic goals for these therapies are being planned to avoid frustration for both therapists and parents.

The availability of genetic testing has broadened the spectrum of phenotypes seen in RTT females, particularly the mild variants. However, it may also lead to the exclusion of some other variants (early seizure onset, late regression variant).

References


