Rett Syndrome: Clinical and Electrophysiologic Aspects

Sonya Jourdan Moser, MD, Peter Weber, MD, and Juerg Lütschg, MD

Rett syndrome is a neurodevelopmental disorder that almost exclusively affects females. The clinical course as well as the electroencephalogram pattern are characteristic and have been correlated to the clinical stages of the disease. Sixty to 70 percent of the patients develop epilepsy. The aim of this retrospective study was to investigate the correlation between clinical stages and electroencephalogram stages and to more specifically correlate epileptic activity in electroencephalograms with the clinical symptoms of patients. The clinical development and electroencephalogram results of 11 patients diagnosed with Rett syndrome between 1 and 33 years old are compared. In 8 of 11 patients, a correlation was found between electroencephalogram stage and clinical stage. In three of them, epileptic activity in the electroencephalogram was not associated with clinical seizures. Some typical symptoms of Rett patients (hand stereotypies, vacant spells) can be difficult to differentiate from seizures. Therefore application of antiepileptic treatment should be well evaluated, as the clinical course is decisive.

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Introduction

Rett syndrome is a neurodevelopmental disorder first described by the Austrian pediatric psychiatrist A. Rett in 1966. Prevalence varies between 1:10,000 and 1:20,000 [1], making Rett syndrome the second major cause of mental retardation in females, following Down syndrome. In 1985, diagnostic criteria were presented for the first time. These (repeatedly updated) clinical criteria form the basis for diagnosing Rett syndrome. Criteria necessary for diagnosing classic Rett syndrome follow the consensus criteria established in 2001 [2]: a normal prenatal and perinatal history and an apparently normal early development for the first 6 months, a normal head circumference at birth, and a postnatal deceleration of head growth in most. The normal early development is followed by a loss of achieved purposeful hand skills between 6 months and 2½ years, characteristic movements and social withdrawal, communication dysfunction as well as cognitive impairment. A further necessary criterion is gait dysfunction, beginning between 1 and 4 years of age. There are some supportive criteria, such as: breathing disturbances while awake, bruxism, impaired sleep pattern, abnormal muscle tone, progressing scoliosis/kyphosis, and growth retardation. Another underlying neurologic or metabolic disease must first be excluded before the clinical diagnosis can be made.

Mutations in methyl-CpG-binding protein 2 gene (MECP2) located in Xp28 were first identified in 1999 [3]. At present, more than 225 mutations have been reported [4,5]. In 70% of the patients who fulfilled the consensus criteria, eight common mutations were found [4]. However, mutations in MECP2 were present in normal female carriers, in females with variant clinical patterns for Rett syndrome, and in females with Angelman syndrome. Mutations in the same gene have also been reported in males with Klinefelter syndrome, fatal encephalopathy, familial X-linked mental retardation, somatic mosaicism, and in males with features of Rett syndrome [4].

In the past years, the neurobiologic role of the MECP2 gene in Rett syndrome and normal development has spurred intense studies. However, the role of MECP2 in the normal brain remains unclear. The protein first appears at 10 to 14 weeks of gestation. There is evidence that MECP2 plays an important role in the maturation, maintenance, and function of neurons [4,6]. Studies found that MECP2 was reduced throughout the brain, with the most severe reductions in the brainstem and thalamus in brains of females with Rett...
syndrome [4,6,7]. In Rett syndrome, the size of the brain and the individual neurons is decreased and the neurons manifest less dendritic arborization and spines [6]. The fact that in Rett syndrome a deceleration in growth of the head circumference occurs during the time that rapid synaptogenesis is occurring has led to the hypothesis that the synaptogenesis is deficient in Rett syndrome [6]. With fewer synapses, the expression of MECP2 is reduced in the Rett syndrome brain [6]. There is evidence in animal model studies that MECP2 deficiency alters some of the proteins required for neuronal outgrowth and cell connections [6].

Clinical Features

The spectrum of clinical involvement is broad. There is evidence that females with later onset of regression, combined with a less severe deceleration in head growth, have a lower overall clinical severity score [2]. The clinical picture of Rett syndrome is typical and has been classified in four stages. This report describes the stages following the classification of Hagberg and Witt-Engerström [8,9].

Stage I: Prenatal and early psychomotor development was considered to be generally normal. Careful studies, however, have found that video records indicate that the children exhibit an abnormal quality of general movements, an excess of repetitive limb and trunk movements, and inattentive behavior [10,11]. These first symptoms are nonspecific, and diagnosis is usually made during stage II when stagnation of development becomes evident.

Stage II: Typically between 1 and 3 years of age, the females suffer from a rapid loss of social interaction and communicative skills or a loss of acquired language. During this time, hand stereotypes appear. In this stage, up to 15% of patients suffer from seizures. Truncal hypotonia and indicators of ambulant dyspraxia become evident. Head growth exhibits a deceleration, head circumference falling below the mean.

Stage III: This stage usually begins between 2 and 10 years of age, after stage II has occurred. Communicative skills improve; neuromotor problems slowly worsen, as rigidity becomes more obvious. A significant hand dyspraxia develops. More females develop seizures during this stage. Patients may stay in this stage most of their lifetime.

Stage IV: Motor deterioration is the main feature of this stage. Hagberg et al. differentiate between stage IVa, when the patients lose their ability to walk and stage IVb, when patients were never ambulatory.

Some typical symptoms, including hand characteristics, episodic hyperventilation, apneas while awake, laughing and crying spells, and the intense gaze, can appear like seizures to caregivers. A study by Glaze [12] reported that 42% of the clinical events identified by parents as their child’s typical seizures were demonstrated, under electroencephalographic monitoring, not to be associated with electroencephalographic seizure discharges. On the other hand, 15% of the patients with a seizure history had clinical events correlating with electroencephalographic seizure discharges that were not identified as epileptic fits by the parents. The authors conclude that the occurrence of epileptic seizures may be overestimated as well as underestimated in Rett syndrome.

Typical electroencephalographic changes and a characteristic developmental pattern of the electroencephalogram have described the course of Rett syndrome. Four stages of electroencephalographic abnormalities have been proposed [1,13], and electroencephalographic findings have been correlated with the clinical stages [8].

The aim of this study was to investigate the correlation between the clinical and electroencephalographic stages and to more specifically correlate epileptic activity in electroencephalograms with the absence or presence of clinical signs of seizures.

Methods

This study follows the internationally accepted criteria for the definition of classic Rett syndrome [4]. Patients were classified as “classic Rett” when all data necessary for the diagnosis were available and “incomplete classic” when no atypical features were present but data were incomplete owing to fragmentary early history. For clinical staging, we used Hagberg’s classification [8] as described above; the classification of Glaze et al. was followed for the electroencephalographic stages [1,13].

Stage 1: The electroencephalogram is usually normal or displays minimal slowing of the occipital-dominant rhythm during wakefulness and normal during sleep.

Stage 2: Slowing of occipital-dominant rhythm and background activity is observed during wakefulness. A loss of non–rapid eye movement characteristics during sleep is typical. Focal spike or sharp–wave discharges occur, initially during non–rapid eye movement sleep and then during wakefulness (Fig 1).

Stage 3: Moderate to marked slowing of background activity with dominant theta and delta activity and no occipital dominant rhythm. Absent non–rapid eye movement sleep characteristics. Multifocal epileptiform discharges and generalized slow–spike–wave patterns appear more often during sleep and wakefulness. Prominent rhythmic theta activity may be recorded in central regions (Fig 2).

Stage 4: No occipital dominant rhythm and marked slowing of background activity (delta activity) is the characteristic finding in the electroencephalogram. Multifocal epileptiform discharges in wakefulness and almost continuous generalized slow spike–wave activity during sleep are frequent (Fig 3).

On the basis of their medical records, we retrospectively studied the clinical course and electroencephalographic patterns of 11 female patients with Rett syndrome who were treated in our neuropediatric polyclinic between 1980 and 2003. The diagnosis of Rett syndrome has been made by experienced pediatric neurologists. Patients were aged between 1 and 33 years during the assessment. All four clinical stages and electroencephalographic stages were included. The clinical course and electroencephalographic pattern could be retrospectively correlated several times as the disease progressed in six patients.

Clinical and electroencephalographic stages of the patients were observed. The raters of electroencephalograms were not systematically blinded to the clinical status of the patient; but each electroencephalogram was analyzed by two different neurologists, at least one not being the attending physician. We noted if clinical seizures were present. If sufficient data were available, the seizure type was classified according to the 1981 criteria of the International League Against Epilepsy [14]. We analyzed if clinical seizures and epileptic
discharges in electroencephalograms correlated and in which clinical stage epilepsy became evident.

The antiepileptic treatment administered and whether drug-resistant epilepsy was present were recorded. Drug-resistant epilepsy was classified as when the patient suffered from more than one seizure per month over a period of 18 months under the treatment of two first-line antiepileptic drugs, following the definition of Berg et al. [15].

Results

The clinical course of 11 females with Rett syndrome was studied. Eight of 11 patients were classified as “classic Rett”; three were classified as “incomplete classic.” We were able to investigate the long-time clinical course over several years (up to 7 years) in six patients. Table 1 summarizes the clinical features and the electroencephalographic stage of the 11 patients included in this study.

Correlation Between Clinical and Electroencephalographic Stage

A correlation between the clinical stage and electroencephalographic stage was documented in 8 of 11 patients (Table 2; note that only the most current electroencephalographic record of each patient is summarized in this table). No correlation was present in three patients; these females were in the clinical stages III to IV. Two of these patients had an electroencephalographic stage IV but were still ambula-

Figure 1. Electroencephalogram stage II during wakefulness. Patient 1 in Table 1; the patient is 3½ years old and in clinical stage 2; she suffers tonic seizures. Note the less dominant occipital background activity and the epileptiform discharges. 26.5 mm/s, 15 μV/mm.

Figure 2. Electroencephalogram stage III during wakefulness. Patient 1 in Table 1; the patient is 4 years old and in clinical stage III. She presents seizures. Note the marked slowing of background activity and loss of occipital dominant rhythm. Generalized epileptiform discharges, 26.5 mm/s, 15 μV/mm.
tory at 18 and 32 years of age and manifested no further motor deterioration at time of assessment (clinical stage III). The third patient at age 15 was never ambulatory, had passed clinical stage III, and was therefore in clinical stage IV; her electroencephalogram was classified as stage III.

**Epileptic Discharges in the Electroencephalograms**

Epileptic discharges were observed in the electroencephalogram of 7 of the 11 females. No epileptic discharges were found in four patients; these females were in clinical stages III-IV. One of these patients no longer had seizures, and antiepileptic drugs had been successfully withdrawn. At the time, her electroencephalogram disclosed no hypersynchronous activity. In another patient, epileptic discharges had never been registered in the electroencephalogram. She suffered from two different seizure types and was under antiepileptic drug treatment but was not seizure-free.

In the course of the disease of the single patients—even if they were in the same clinical and electroencephalographic stage (usually stage III)—variable findings concerning the number of epileptic discharges and the absence and presence of hypersynchronous activity were documented.

**Clinical Seizures**

Eight of the 11 patients have had clinical seizures (Table 1). The following seizure types were observed: generalized seizures including tonic clonic seizures 3/8,

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**Table 1. Clinical features of the patients included in the study**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis (Year of Diagnosis)</th>
<th>MECP 2</th>
<th>Head Circumference</th>
<th>Clinical Stage</th>
<th>EEG Stage</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3½ years (2001)</td>
<td>Positive</td>
<td>50th percentile</td>
<td>I-III</td>
<td>I-III</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>10 years (1999)</td>
<td>Negative</td>
<td>Below 3rd percentile</td>
<td>III-IV</td>
<td>III-IV</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
<td>III</td>
<td>III</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Not known</td>
<td>Positive</td>
<td>Below 3rd percentile</td>
<td>III</td>
<td>III</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
<td>III-IV</td>
<td>IV</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>6 years (1992)</td>
<td>Positive</td>
<td>10th percentile</td>
<td>II-III</td>
<td>II-IV</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>3½ years (1996)</td>
<td>No examination</td>
<td>Below 3rd percentile</td>
<td>II-III</td>
<td>II-III</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>3 years (1998)</td>
<td>Negative</td>
<td>10th–25th percentile</td>
<td>II-III</td>
<td>IV</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Not known (before 1990)</td>
<td>No examination</td>
<td>Not known</td>
<td>III-IV</td>
<td>IV</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>4 years (2005)</td>
<td>Positive</td>
<td>3rd-10th Percentile</td>
<td>II</td>
<td>II</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>Not known</td>
<td>Positive</td>
<td>Not known</td>
<td>IV</td>
<td>III</td>
<td>Yes (Currently seizure-free)</td>
</tr>
</tbody>
</table>

In this table we summarize the clinical features of each patient included in the study. We noted if the patient has been tested for the methyl-CpG-binding protein 2 gene.

Abbreviation:

MECP2 = Methyl-CpG-binding protein 2 gene
In this table the correlation of clinical stage with the electroencephalographic (EEG) stage is noted. The numbers indicate the number of patients in the defined clinical and electroencephalographic stage. Note that only the most current electroencephalographic record of each patient is summarized in this table for better understanding.

<table>
<thead>
<tr>
<th>Clinical Stages</th>
<th>EEG Stage I</th>
<th>EEG Stage II</th>
<th>EEG Stage III</th>
<th>EEG Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I Pre-regression</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage II Rapid regression</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage III Late regression</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Stage IV Late motor deterioration</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

In this study, patients with Rett syndrome were not seizure-free using one antiepileptic drug. Drug-resistant epilepsy was present in three patients. Two had no antiepileptic treatment at the time of assessment. The electroencephalogram was helpful in differential diagnosis. Asking the parents to make video recordings should be accompanied by video recordings. Asking the parents to make home video recordings of their children’s typical seizures during electroencephalographic monitoring was not associated with electroencephalographic seizure discharges in 42% of the cases. On the other hand, 15% of the patients with a seizure history had clinical events that correlated with electroencephalographic seizure discharges not identified as epileptic fits by the parents. The authors conclude that the occurrence of epileptic seizures may be overestimated as well as underestimated in Rett syndrome. In our retrospective study there may be an overestimation of events interpreted as seizures.

With regard to epilepsy management and long-term care for Rett syndrome patients, it is necessary to critically revise the events described as seizures. Whenever possible, electroencephalographic recordings should be accompanied by video recordings. Asking the parents to make home video recordings of their children’s typical seizures or events that may be epileptic fits can help in this difficult differential diagnosis.

In accordance with previous observations, the onset of seizures in our patients occurred most often during clinical stage III [16]. An earlier onset of seizures does not seem to affect the long-term course of Rett syndrome [16]. On the other hand, smaller head growth was correlated with a higher percentage of intractable epilepsy, according to Steffenburg et al. [16]. These authors observed that this finding is compatible with more marked brain hypoplasia. The number of patients in the present study is too small to draw a conclusion whether a smaller head circumference is correlated with a higher percentage of intractable epilepsy.
epilepsy. We could not find differences in females (5/11) who were MECP2 positive compared with patients who were MECP2 negative (2/11) regarding progression of the disease, epilepsy, or head circumference, but the cohort is too small to draw a conclusion based on these observations.

There is evidence that the severity of epilepsy tends to decrease after 20 years of age [16] as in other conditions of severe mental retardation. Steffenburg et al. [16] found a cumulative probability of 40% of being seizure-free for 1 year in 50 females with Rett syndrome. Therefore the antiepileptic treatment should be revised critically in the course of the disease to consider withdrawing antiepileptic drugs when patients are free of seizures.

References