Electroencephalogram and clinical manifestations of Rett syndrome in children

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ABSTRACT
Background Rett Syndrome (RS) is a severe neurodevelopmental disorder. Epileptic seizures occur in 80-90%; grandmal, psychomotor (complex partial), and focal motor seizures have been reported. The electroencephalogram (EEG) is almost always abnormal.
Objective This study aimed to investigate the EEG and clinical manifestations of children with RS
Results We investigated EEG on 5 patients with RS aged 30–66 month. One patient was in clinical stage II and 4 patients in clinical stage III. Four patients had history of seizures, however only two patients suffered from epilepsy. The EEG demonstrated slowing background activity in occipital region in two patients. In addition, epileptic form activities were observed in 4 of 5 patients.
Conclusion We concluded that epileptic spike discharge with or without clinical seizures were found in almost all of our RS patients. These paroxysmal discharges suggested the process and the sequences of cortical involvement. Compelling clinical, neurophysiological evidences were very important to decide the stage of Rett disorder. [Paediatr Indones 2003;43:121-125].

Keywords: Rett Syndrome, EEG, clinical manifestation

Rett syndrome (RS) is a devastating neurological illness. The major impact of the disease is during postnatal brain growth involving synapse formation. The disorder almost exclusively affects females and is one of the most common causes of mental retardation. The typical child with RS can first be recognized between 6 and 18 months of age with clinical features that consist of the loss of communication skills and purposeful hand use and the appearance of stereotypic hand movement in late infancy, following a period of seemingly normal development. Certain diagnostic studies may provide supportive evidence but are hardly specific. Perhaps, the most useful are those of clinical neurophysiology, in which typical patterns of electroencephalography (EEG) abnormalities may be detected along with alterations in sleep stages and a marked reduction in rapid eye-movement (REM) sleep. EEG of RS raises much interest because of its unique feature and age-dependent change. The EEG is usually normal or nonspecifically abnormal during stage I and early stage II of the disease. Seizures of various types occur in one third of the patients, although virtually all have abnormal EEG. Another authors wrote that most patients have either generalized convulsive, complex partial or simple motor seizure. Recently, systematic mutation analysis on the critical region results in the identification of mutations in the methyl-CpG-binding protein 2 gene (MECP2).

In our study, we focused on EEG examination; therefore, we investigated the EEG in 5 RS patients.
Methods

We evaluated 5 girls with classical RS, aged from 30 to 66 months (Table 1). The patients were recruited from the Department of Child Health, Cipto Mangunkusumo Hospital and Sardjito Hospital, Indonesia. The diagnosis of RS was based on clinical criteria and the clinical stage was determined using established diagnostic and staging criteria. The age of the patients on the first examination in our hospital ranged from 15 months to 54 months with diagnoses of delayed speech and other development, microcephaly, generalized tonic clonic seizure, and atonic epilepsy. On first examination, the diagnosis of RS was only established in one patient.

Results

Of the 5 individuals with RS, all had the classical criteria. One patient was in clinical stage II and 4 in clinical stage III. We did not have any patients in either clinical stage I or IV. Four patients were able to walk, 4 had a history of seizures, however only two patients suffered from epilepsy. All of them were taking anticonvulsants. Three patients weighed less than 3rd percentile, 1 was between 3rd percentile and 10th percentile and the other was between 50th percentile and 75th percentile. For the height, three of them had less than 3rd percentile, 1 were between 10th percentile and 25th percentile, and 1 were between 50th percentile and 75th percentile. All patients had microcephaly with head circumference between – 2 SD and – 5.2 SD. Purposeful hand use was completely lost in all patients.

Of the 5 patients, EEG examinations showed abnormality in all patients and demonstrated slowing background activity in occipital region in two patients. However the rest of the patients showed a tendency of decreased of background activity (Table 2). In addition, epileptic form activities were observed in 4 of 5 patients. The prominent rhythmic theta activities of 4-6 Hz were found during sleep in all regions with focus in frontal, central, and parietal leads in all patients (Table 2).

One patient never had seizures, however the EEG showed spike slow waves in the right central (C4) and right parietal (P4) regions (Figure 1). Two patients had epilepsy and their EEG showed epileptic form discharges (Figure 2). The other two patients only had febrile convulsion once, but the EEG revealed epileptic form discharges and slowing background activity in another case (Figure 3).

Table 1. Patients’ profiles

| Case | Case 1 (PK) | Case 2 (KS) | Case 3 (M) | Case 4 (FA) | Case 5 (NW) |
|------|------------|------------|------------|------------|------------|
| Age at examination (month) | 43 | 65 | 49 | 29 | 43 |
| Date at examination | Feb 2002 | Feb 2002 | March 2002 | Feb 2002 | April 2002 |
| Weight (kg) | 11.6 (< 3rd P) | 11.7 (<3rd P) | 11.2 (<3rd P) | 10.5 (P3-P10) | 11.6 (<3rd P) |
| Height (cm) | 86 (<3rd P) | 97 (<3rd P) | 89 (<3rd P) | 78 (P50-P75) | 86 (<3rd P) |
| Head circumference (cm) | 46 (-2SD) | 43 (-5.2 SD) | 45.5 (-3 SD) | 45 (-1.6 SD) | 46 (-2SD) |
| Walking alone (month) | not yet | 66 | 24 | 24 | not yet |
| Psychomotor retardation | + 12 M | + | + | + | + 12 M |
| Autistic behavior | + | + | + | + |
| Language regression | + | + | ? | + | + |
| Disturbance of purposeful hand movements | + | + | + | + |
| Stereotypical hand movements | hand clapping | hand clapping, hand wringing, hand mouthing and sucking | hand tapping | hand tapping | hand clapping |
| Gait dyspraxia | not gait yet | + | + | not gait yet | not gait yet |
| Seizure onset (month) | no seizure | 24 | 8 | not gait yet | no seizure |
| Seizure frequency | - | Free of seizure | 1x (febrile seizure) | 4 frequent |
| Treatment | CBZ | PB change to CBZ | CBZ | CBZ + phenobarbital + topiramate |

+: present; - : absent
Discussion

Rett syndrome is a severe developmental disorder caused by mutations in MECP2. Affected girls are usually developmentally normal for the first 6 to 18 months, although subtle signs may already present in the first 6 months. This is followed by a period of developmental stagnation, then regression and social withdrawal. The patients lose functional hand skills and the use of spoken language and gait and/or truncal ataxia. Growth is characterized by early deceleration of head growth, leading to microcephaly in some patients and a subsequent deceleration by later childhood. In our study all patients had microcephaly and 3 of them had short stature. Diagnosis is based on consistent constellation of clinical features and the utilization of established diagnostic criteria. The natural history of the disorder has been divided into four clinical stages. We have one patient in clinical stage II and four in clinical stage III.

One third of children experience seizures, and approximately 80%-90% have epilepsy. In this study 4 of 5 patients had seizure, however, only 2 patients suffered from epilepsy that responded well to carbamazepin therapy in one patient and combined therapy of carbamazepine, valproic acid, and topiramate in the others. In the treatment of the syndrome, besides supportive therapy, convulsions should be controlled by anticonvulsant agents such as valproic acid, phenobarbital, carbamazepine, and lamotrigine. Although only two patients had epilepsy, all patients had abnormality in EEG. The EEG is almost abnormal, shows slow background, spikes are a common finding and are generally noted over the central, central-temporal, or central-parietal regions, especially during sleep. In some patients, central of the
Spikes can be suppressed by stimulation of the hand or elicited by tapping the contralateral hand. Classification of EEG based on stages is as follows: Stage I EEG shows normal or minimal slowing of posterior rhythm; stage II EEG shows slowing and gradual loss of normal sleep activity, focal or multifocal spikes and waves; stage III EEG shows gradual disappearance of posterior rhythm, generalized slow, absent vertex, and spindle activity, epileptic form abnormalities activated during sleep; and stage IV EEG shows poor background spikes and slow spikes and waves pattern activated by sleep.

The EEG may be helpful in confirming the diagnosis of RS in a patient who fits the clinical syndrome, and if any of the following patterns present abundant centrotemporal spikes.

In conclusion, epileptic spike discharge with or without clinical seizures was found in almost all of RS patients. These paroxysmal discharges tended to start in centroparietal to temporal areas followed by fron-
tal area, suggesting the process and sequences of the
cortical involvement. Compelling clinical, neurophysi-
ological evidences are very important to decide of the
stage of Rett disorder.

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