Paediatrica Indonesiana

VOLUME 43 July - August • 2003 NUMBER 7-8

Case Series

Electroencephalogram and clinical manifestations of Rett syndrome in children

ES Herini, MD; I Mangunatmadja, MD; Purboyo S, MD;
Hardiono D Pusponegoro, MD; Sunartini, MD

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.[1] The disorder almost exclusively affects females and is one of the most common causes of mental retardation.[2] 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.[3] 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. [4] EEG of RS raises much interest because of its unique feature and age-dependent change.[5] The EEG is usually normal or nonspecifically abnormal during stage I and early stage II of the disease. [6] Seizures of various types occur in one third of the patients, although virtually all have abnormal EEG. [1] Another authors wrote that most patients have either generalized convulsive, complex partial or simple motor seizure. [7] Recently, systematic mutation analysis on the critical region results in the identification of mutations in the methyl-CpG-binding protein 2 gene (MECP2). [2,8-10]

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

From the Departments of Child Health, Medical School, Gadjah Mada University, Yogyakarta (ES, S); University of Indonesia, Jakarta (IM, HDP) and Padjadjaran University, Bandung (PS).

Reprint requests to: ES Herini, MD, Department of Child Health, Medical School, Gadjah Mada University, Sardjito Hospital, Yogyakarta, Indonesia. Tel. 62-21-561616, Fax. 62-21-583745.

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.[11] 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 rhythmical 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) to 46 (-2SD)	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
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	CBZ

+: present; - : absent

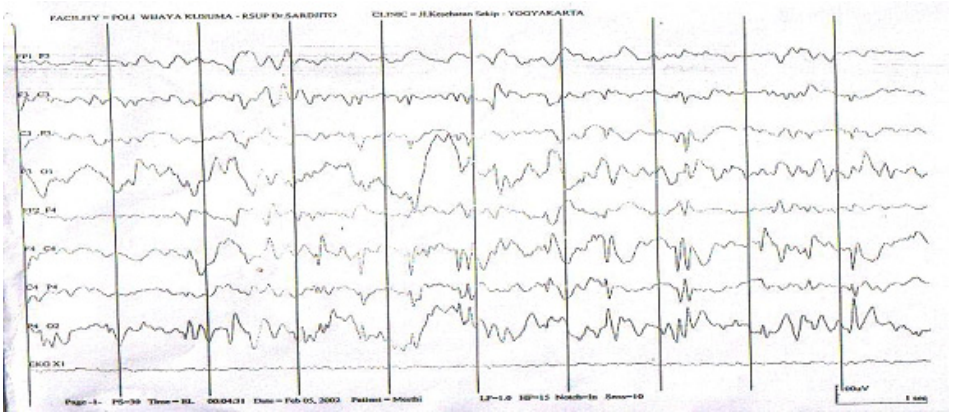

Figure 1. Case 1, 43 months. Spike slow wave in the right central (C4) and right parietal (P4) regions

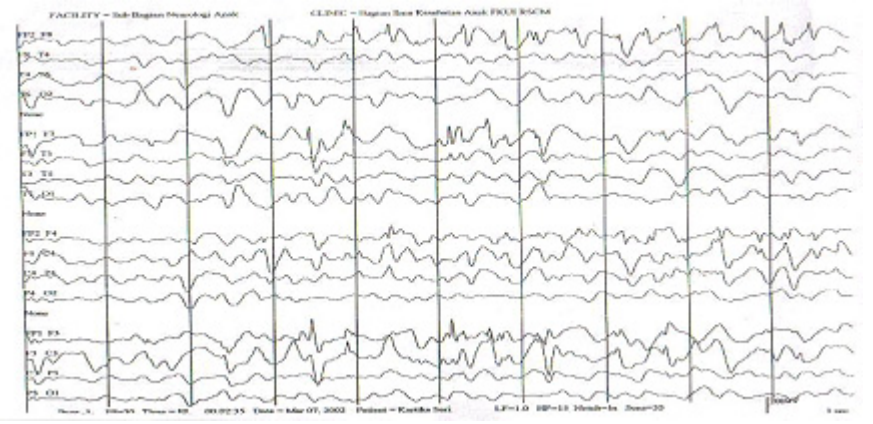

Figure 2. Case 2, 67 months,. Spike slow wave over left frontopolar (Fp1), right frontopolar (Fp2) regions, sharp slow discharge over right frontal (F4) region and slowing background activity. Calibration signal 1 second, 200 mV

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.[3] 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[12] 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,[1,13,14] and approximately 80%-90% have epilepsy.[13,15] 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.[16] Although only two patients had epilepsy, all patients had abnormality in EEG. The EEG is almost abnormal,[7,14,17,18] shows slow background;[1,6] spikes are a common finding and are generally noted over the central,[17] central-temporal,[1,6] or central-parietal regions,[19] especially during sleep. In some patients, central of the

TABLE 2. EEG FEATURES

No	Case	Age (month)	Clinical Stage	Seizure	Epilepsy	Background activity	Epileptiform discharge
1.	PK	42	III	-	-	5-6 Hz with medium to high voltage and mixed 2-3 Hz.	Spike slow wave in the right central (C4) and right parietal (P4) regions.
2.	KS	66	III	+	General tonic clonic epilepsy	4-5 Hz with medium to high voltage and mixed 2-3 Hz.	- Spike slow discharge over left frotopolar (Fp1), right frontopolar (Fp2) regions and sharp slow discharge over right frontal (F4) region. - Slowing background activity
3.	M	48	III	+	- Febrile convulsion	5-6 Hz with medium to high voltage and mixed 2-3 Hz.	Spike and wave discharge were seen during the recording over left central (C3) and right central (C4) regions.
4.	FA	29	II	+	+ Partial seizure secondarily generalized	4-5 Hz with medium to high voltage and mixed 2-3 Hz.	Sharp wave discharge were seen during the recording over right frontotemporal (F8), right frontal (F4), right posterior temporal (T6), left posterior temporal (T5) and left frontotemporal (F7) regions.
5.	NWR	54	III	+	- Febrile convulsion	4-5 Hz with medium to high voltage and mixed 2-3 Hz.	Slowing background activity

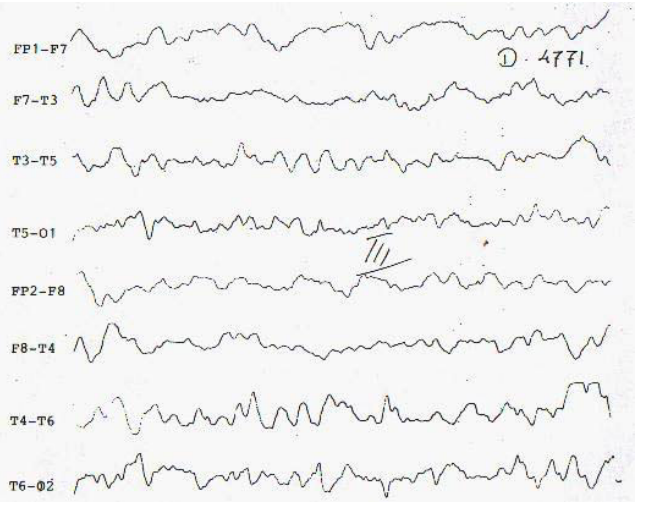

Figure 3. Case 5, 55 months. Slowing background activity. Calibration signal 1 second, 50 mV

spikes can be suppressed by stimulation of the hand or elicited by tapping the contralateral hand.[7] 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.[20]

Spike disappears with age and so may represent a dysfunctional phenomenon that is distinct from the underlying pathology.[1] 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.[6]

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, neurophysiological evidences are very important to decide of the stage of Rett disorder.

References

1. Naidu S. Rett Syndrome: a disorder affecting early brain growth. Ann Neurol 1997;42:3-9.
2. Hoffbuhr K, Devaney JM, LaFleur B, Sirianni N, Scacheri C, Giron J, *et al*. MECP2 mutations in children with and without the phenotype of Rett syndrome. Neurology 2001;56:1486-95.
3. Percy A, Gillberg C, Hagberg B and Engerström IW. Rett syndrome and the autistic disorders. In: Budensteiner JB, editor. Neurology clinics. Philadelphia: W.B. Saunders Company; 1990. p. 659-76.
4. Percy AK. Progressive dementia associated with other neurologic abnormalities. In: Beng BO, editor. Principles of child neurology. New York: Mc Graw Hill; 1996. p. 1469-93.
5. Nomura Y. Neurophysiology of Rett Syndrome. Brain & development 2001;23: S50-7.
6. Hahn JS, Tharp BK. Neonatal and pediatric electroencephalography. In: Clinical neurology. New York: Churchill Livingstone; 1999. p. 81-127.
7. Fisch BJ. Fisch Spehlmann's EEG Primer. Basic principles of digital and analog EEG. Amsterdam: Elsevier; 1999. p. 301-2.
8. Auranen M, Vanhala R, Vosman M, Levander M, Varilo T, Hietala M, et al. MECP2 gene analysis in classical Rett syndrome and in patients with Rett-like features. Neurology 2001;56:611-7.
9. Inui K, Akagi M, Ono J, Tsukamoto H, Shimono K, Mano T, *et al*. Mutational analysis of MECP2 in Japanese patients with atypical Rett syndrome. Brain & Development 2001;23:212-5.
10. Gotoh H, Suzuki I, Maruki K, Hirasawa K, Sasaki N. Magnetic resonance imaging and clinical findings examined in adulthood studies on three adults with Rett syndrome. Brain & Development 2001;23:S118-21.
11. The Rett Syndrome Diagnostic Criteria Work Group. Diagnostic criteria for Rett syndrome. Ann Neurol 1988;23:425-8.
12. Ashwal S. Congenital structural defects of the brain. In: Levene MI, Chervenak FA, Whittle MJ, Bennett MJ, Punt J. Fetal and neonatal neurology and neurosurgery. 3rd ed. London: Churchill Livingstone; 2001. p. 199-236.
13. Edelson SM. Rett Syndrome. Center for the Study of Autism, Salem, Oregon. 1999 [cited 2002 March 3]. Available from: URL: http://www.autism.org/rett.html.
14. Menkes JH. Heredodegenerative disease. In: Menkes JH and Sarnat HB editors. Child neurology 6th ed. Philadelpia: Lippincott Williams & Wilkins; 2000. p. 171-239.
15. Oldfors A, Sourander P, Armstrong DL, Percy AK, Engerstrom IW, Hagberg BA. Rett Syndrome: cerebellar pathology. Pediatr Neurol, 1990;6:310-4
16. Haslam RHA. The nervous system. In: Behrman RE, Kliegman RM, Jenson HB, editors. Textbook of pediatrics. Philadelphia: WB Saunders; 2000. p.1793-1866.
17. Naidu S, Niedermeyer E. Degenerative disorders of central nervous system. In: Niedermeyer E, Silva FLD, editors. Electroencephalography. Basic Principles, clinical applications, and related fields. Baltimore: Williams & Wilkins; 1993. p. 351-71.
18. Swaiman KF, Dyken PR. Degenerative diseases primarily of gray matter. In: Swaiman KF and Ashwal S, editors. Pediatric neurology principles & practice. St Louis: Mosby; 1999. p. 833-48.
19. Blume WT, Kaibara M. Role of the electroencephalogram in some pediatric neurological problems. In: Blume WT, Kaibara M, editors. Atlas of pediatric electroencephalography. Philadelphia: Lippincott-Raven; 1999. p. 361-71.
20. Moser HW and Naidu S. The discovery and study of Rett Syndrome. In: Capute AJ and Accardo PJ editors. Developmental disabilities in infancy and childhood. Baltimore: Paul H Brookes; 1991. p. 325-33.