Paediatrica Indonesiana

VOLUME 45 September - October • 2005 NUMBER 9-10

Original Article

The Epilepsies of Rett Syndrome in Indonesia

E.S. Herini, MD; Sunartini H, MD; I. Mangunatmadja, MD; Purboyo S, MD; Hardiono D. Pusponegoro, MD

ABSTRACT

Objective This study aimed to evaluate various types of seizures, EEG findings, and last evolution of epileptic seizures found in children with Rett Syndrome (RTT).

Methods A case series of ten female subjects from Sardjito Hospital, Yogyakarta; Cipto Mangunkusumo Hospital, Jakarta; and Hasan Sadikin Hospital, Bandung from February 2001-April 2004. Diagnosis of RTT was established using necessary and supportive criteria by the RTT Diagnostic Criteria Work Group and epilepsy was diagnosed according to clinical and EEG findings.

Results The age during initial diagnosis of RTT ranged from 2 years 6 months - 10 years 2 months (average: 4 years 6 months). The diagnosis of epilepsy, on the other hand, was established from 2 years - 5 years 10 months (average: 3 years 8 months). All subjects (10/10) had abnormal EEG results. Eight out of ten had epileptiform discharge; the remaining had slowing background activity. The average age of initial seizure onset was 18 months. Five were diagnosed as epileptic subjects. Febrile convulsions were the most common initial seizure. General tonic clonic seizure was major type of seizure which manifested in 2 subjects.

Conclusion All EEG results showed abnormality, although seizure did not appear. Five out of ten subjects experienced epilepsy **[Pediatr Indones 2005;45:203-206]**.

Keywords: *Rett Syndrome, EEG, epilepsy*

Epileptic seizures have been reported to occur in one-third of children with Rett Syndrome (RTT).[1-3] Partial and generalized seizures, psychomotor (complex partial) and focal motor seizures may be experienced by RTT females.[1,4] Kerr reported that seizures occurred in 75-80% of classical cases and approximately 50% continue to experience epileptic seizures.[5] Many events, presumed to be seizures, however, did not have electroencephalograms (EEGs) connected during video-EEG monitoring, which suggests the possibility of non epileptic mechanisms. Almost all RTT females have abnormal EEG results.[3] EEG epileptiform activity is almost uniformly present at diagnosis.[6] EEGs show slow background and prominent central temporal spikes. By the age of 10 years, these spikes eventually disappear and such activity tends to diminish, representing a dysfunctional phenomenon that is distinct from underlying pathology.[2,4] True petit mal epilepsy (regular, 3 per second spike and wave) has not yet been reported.[5] Extensive monitoring has indicated that the occurrence of epileptic seizures in RTT is likely overestimated, although actual seizures may be overlooked.[4] Seizures usually appear in rapid destructive stage or second stage, and pseudo stationary stage or third stage. With the progression of the disorder, epileptic seizures, similar to that of EEG spikes, are likely to disappear. This is known as the late motor deterioration stage, in which the EEG commonly shows diffuse slowing.[4,7]

Presented at The 8th Asian and Oceanian Congress of Child Neurology in India on October 7-10, 2004

From the: Department of Child Health, Medical School, Gadjah Mada University, Sarjito Hospital, Yogyakarta, Indonesia (ESH, SH); Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo hospital, Jakarta, Indonesia (IM, HDP); Department of Child Health, Medical School, Padjadjaran University, Hasan Sadikin Hospital, Bandung, Indonesia (PS).

Reprint request to: E S Herini, MD, Department of Child Health, Medical School, Gadjah Mada University, Sarjito Hospital, Jl. Kesehatan No.1, Yogyakarta, Indonesia. Tel: 62-274-587333/561616; Fax: 62-274-583745.

Methods

This was a case series conducted in the Outpatient Clinic at the Child Health Department, Sardjito Hospital, Yogyakarta; Cipto Mangunkusumo Hospital, Jakarta; and Hasan Sadikin Hospital, Bandung, Indonesia, 10 female subjects with RTT were enrolled. Clinical diagnosis of RTT and stage (I, II, III, or IV) were confirmed according to diagnostic criteria for RTT (**Table 1**).[7] Subjects' ages at initial examination were 2-10 years (average 4 years to 6 months). The age during the last visit ranged from 3 years 8 months to 11 years.

All subjects underwent EEG examinations, although they did not experience seizure. We evaluated seizure types, EEG findings, and the last evolution of epileptic seizures by history taking and medical records. Epilepsy classifications were based on that of epileptic seizures.[8]

Results

Out of 10 subjects with RTT, 3 were in clinical stage II, 7 were in stage III, but none were in stage I and IV (**Table 2**). The age during diagnosis ranged from 2 years 6 months - 10 years 10 months (average 4 years 6 months). Seven out of 10 subjects had seizures; 3 experienced epilepsy, 2 had simple febrile seizure and epilepsy, and 2 others had simple febrile seizure only. Five out of 10 subjects were diagnosed with epilepsy; two with generalized tonic clonic seizures, 1 with partial seizure secondarily generalized, 1 with myoclonic epilepsy, and another with absence epilepsy. Febrile convulsions were the most common type of initial seizure, while the major type of seizure was general tonic clonic seizure (4/10). Seizure onset was 8 months - 5 years 10 months (average 1 year 6 months). The diagnosis of epilepsy was established at 2 years - 5 years 10 months (average 3 years 8 months). The types of epilepsy were generalized tonic clonic seizure, absence, partial seizure secondarily generalized, and myoclonic epilepsy. All subjects (10/10) had abnormal EEG results. EEG results in eight subjects exhibited epileptiform discharge and the remaining showed slowing background activity only.

Six out of 10 subjects received anti epileptic therapy. Three of them were given one anti epileptic drug only and the remainders were administered double drug. Five subjects received carbamazepine, two were given phenobarbital, and the others received valproic acid.

TABLE 1. DIAGNOSTIC CRITERIA FOR RETT SYNDROME

Necessary criteria
1. Apparently normal prenatal and perinatal period
2. Apparently normal psychomotor development through the first 6 months up to 18 months
3. Normal head circumference at birth
4. Deceleration of head circumference at birth, deceleration of head growth between the age of 5 months and 4 years
5. Loss of acquired purposeful hand skills between the age of 6 and 30 months, that is temporarily associated with communication dysfunction and social withdrawal.
6. Development of severely impaired expressive and receptive language and the presence of apparent, severe psychomotor retardation
7. Stereotypic hand movements such as hand wringing/squeezing, clasping/tapping, mouthing and "washing"/rubbing automatisms appearing after purposeful hand skills are lost
8. Appearance of gait apraxia and truncal apraxia/ataxia between 1 and 4 years
9. Diagnosis tentative until 2 to 5 years of age
Supportive criteria
1. Breathing dysfunction
2. EEG abnormalities
3. Seizures
4. Spasticity, often associated with muscle wasting and dystonia
5. Peripheral vasomotor disturbances
6. Scoliosis
7. Growth retardation
8. Hypotrophic, small feet

TABLE 2. THE EPILEPSIES OF RETT SYNDROME

No.	The age at diagnosis of RTT	The stage of RTT	The age at diagnosis of epilepsy	Seizure onset	Type of seizure	Therapy
1.	2Y6M	II	--	--	--	CBZ
2.	5Y5M	III	2Y6M	2Y6M	GTCS	PB, CBZ
3.	4Y1M	III	--	8M	Simple febrile seizure	–
4.	4Y6M	III	--	6M	Simple febrile seizure	Vitamin B6
5.	5Y5M	III	--	13M	Simple febrile seizure	PB
			5Y10M	5Y10M	GTCS	VA
6.	10Y2M	III	5Y	5Y	Absence	No treatment, seizure disappeared spontaneously after 6 months
7.	2Y8M	II	--	--	--	–
8.	2Y8M	II	--	--	--	–
9.	3Y3M	III	3Y2M	6M	Simple febrile seizure	CBZ, VA
				3Y2M	Partial seizure secondarily generalized	Free of seizure 1 year ago
10.	4Y	III	2Y	2Y	Myoclonic epilepsy	CBZ

GTCS = generalized tonic clonic seizures
CBZ = carbamazepine; PB = phenobarbital; VA = valproic acid

Based on the types of epilepsy, one patient was diagnosed as absence (Case 6). She did not receive anti epileptic drug; nevertheless, the seizure disappeared spontaneously after 6 months. On the other hand, one patient did not develop seizure. We continuously gave carbamazepine to improve alertness and thought.

Discussion

RTT is a x-linked dominant neurodevelopmental disorder, caused by mutations in the methyl-CpG binding protein-2 (MECP2) gene of RTT, and have been diagnosed in a large number of females worldwide.[9,10] Seizures are supportive criteria for RTT, and tend to appear in early childhood in almost 80% RTT. [7] In this study, we found seven out of 10 subjects who experienced seizure; five were diagnosed with epilepsy. Seizure may prove to be a difficult complication which the median age of initial onset was 4 years. Generalized tonic clonic seizures are predominant, and partial complex seizures are the next most common type.[6] Barrera *et al* [11] reported that the symptomatology is in decreasing order i.e., tonic, generalized clonic, partial, absence and myoclonic seizures; half of them had more than one type of seizure. The onset of epilepsy in our study was similar to that of Barrera *et al*,[11] which reported that the age of initial seizure was between 18 months and 7 years 8 months (median 4 years 5 months) from 17 RTT females. The median age of initial seizure onset in our study was similar with the onset reported in other studies.

The type of seizure reported most predominant in other studies is also generalized tonic clonic seizures, although our study only had a small number of subjects. Four subjects experienced simple febrile seizure; however we do not know whether this had correlation with RTT.

Atypical variants of RTT have been reported. Among these subjects are those with absence of early

normal development, lack of subsequent deterioration, and early, uncontrolled seizures. EEG epileptiform activity is almost uniformly present at diagnosis, although this tends to diminish after age 10 years.[6]

The EEG demonstrates poorly organized background with frontal central spikes that are accentuated during sleep.[12,13] Epileptiform discharge in RTT females appear with or without seizures.[6] The occurrence of epilepsy in our study was different from that of Steffenburg *et al*, [14] which reported that history of epilepsy was present in 94% of RTT subjects. This is due to the difference in age range of which in our study was from 2 years 6 months - 10 years 2 months; while in their study was 5 to 55 years, where the onset of epilepsy is approximately 4 years old.

In RTT treatment, seizures should be controlled by anticonvulsant agents such as valproic acid, phenobarbital, carbamazepine, etc.[15] In our study, seizures were successfully controlled using carbamazepine, phenobarbital, and valproic acid also. Managing epilepsy in RTT subjects is not difficult. Some literatures report that no specific therapy for seizures have been proven to be effective, however others report that the administration of carbamazepine and ketogenic diet have been helpful.[6]

Conclusion

All EEG results showed abnormality, although seizure did not appear. Five out of 10 subjects experienced epilepsy. The percentage of epilepsy in RTT depends on the age of subjects studied.

References

1. Glaze DG. Neurophysiology of Rett Syndrome. Ment Retard Dev Disabil Res Rev 2002;8(2):66-71.
2. Naidu S. Rett Syndrome: A disorder affecting early brain growth. Ann Neurol 1997;42(1):3-9.
3. Menkes JH. Heredodegenerative diseases. In: Menkes JH, Sarnat HB, editors. Child neurology. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 171-239.
4. Niedermeyer E, Silva FL. Degenerative disorder of the central nervous system. In: Niedermeyer E, Silva FL, editors. Electroencephalography basic principles, clinical applications, and related fields. 3rd ed. Baltimore: Williams & Wilkins; 1993. p. 365-6.
5. Kerr A. Annotation: Rett syndrome: Recent progress and implications for research and clinical practice. J Child Psychol Psychiatry 2002;43(3):277-87.
6. Swaiman KF, Dyken PR. Degenerative diseases primarily of gray matter. In: Swaiman KF, Ashwal S, editors. Pediatrics neurology principles and practice. 3rd ed. St. Louis: Mosby; 1999. p. 833-48.
7. The Rett Syndrome Diagnostic Criteria Work Group. Diagnostic criteria for Rett Syndrome. Ann Neurol 1988;23:425-8.
8. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489.
9. Huppke P, Held M, Laccone F, Hanefeld F. The spectrum of phenotypes in female with Rett syndrome. Brain Dev 2003;25(5):346-51.
10. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett Syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG-binding protein 2. Nat Genet 1999;23:185-8.
11. Nieto-Barrera M, Nieto-Jimenez M, Diaz F, Campana C, Sanchez ML, Ruiz del Portal L, *et al*. Clinical course of epileptic seizures in Rett's Syndrome [abstract]. Rev Neurol 1999;28(5):449-53.
12. Singer HS, Naidu S. Rett Syndrome "We'll keep the genes on for you". Neurology 2001;56:582-5.
13. Moser HW, Naidu S. The discovery and study of Rett Syndrome. In: Capute AJ, Accardo PJ, editors. Developmental disabilities in infancy and childhood. Baltimore: Brookes; 1991. p. 325-33.
14. Steffenburg U, Hagberg G, Hagberg B. Epilepsy in a representative series of Rett Syndrome [abstract]. Acta Paediatr. 2001;90(1):34-9.
15. Haslam RHA. The nervous system. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson's textbook of pediatrics.16th ed. Philadelphia: WB Saunders; 2000. p.1793-866.