Paediatrica Indonesiana

VOLUME 50 May • 2010 NUMBER 3

Original Article

Clinical characteristics and electroencephalography features of intractable childhood epilepsy – A case series

Irawan Mangunatmadja, Eva Devita Harmoniati

Abstract

Background The majority of epilepsy patients have good prognosis, but 10-40% will develop intractable epilepsy. Early identification of patients with risks of developing intractable epilepsy allows more intensive therapy to be performed.

Objective To study clinical characteristics and electroencephalography (EEG) features of intractable childhood epilepsy.

Methods We reviewed children with intractable epilepsy attending the Pediatric Neurology and Growth and Development Clinic in Child Health Department, Cipto Mangunkusumo Hospital from 2005-2008. EEG examination was performed in epilepsy patients who had consumed two or more antiepileptic drugs for at least 18 months but still experienced seizure at least once per month. Data of clinical characteristics were collected from the medical records and information provided by the parents.

Results There were 41 subjects. Age of onset between 0-1 year old was found in 50% subjects, neurological impairment in 80%, microcephaly in 50%, and abnormal neuroimaging in 14 of 24 subjects. Seizure manifestations were mostly generalized tonic clonic, tonic, myoclonic, and complex partial seizures. Abnormal EEG features were found in 88% subjects and the majority showed generalized slowing of the background activity. Focal and multifocal epileptiform activity was found in 31% and 28% subjects, respectively. Epileptiform activity was located mostly in the frontal and temporal lobe.

Conclusions Most patients with intractable epilepsy have age of onset before the age of 1 year. A substantial poportion of them have neurological impairment, microcephaly, abnormal neuroimaging, and abnormal EEG features. Seizure manifestation is mostly generalized seizure. Epileptiform activity in intractable childhood epilepsy is often found in the frontal and temporal lobe. **[Paediatr Indones. 2010;50:133-38]**.

Keywords: *intractable epilepsy, EEG, clinical characteristics, epileptiform activity*

Epilepsy is a disorder characterized by recurrent unprovoked seizure two times or more with an interval of more than 24 hours.[1-3] It is a common neurological problem occurring in 3-6/1000 children; 80% of patients become seizure free after having received antiepileptic drugs.[4] Several studies find that 10-40% of patients with epilepsy develop intractable epilepsy.[4-6] The predictors of intractable epilepsy can be determined from the clinical course of disease and diagnostic examination. Previous studies reports that 60-85% of intractable epilepsy patients have abnormal EEG features, and 51% patients have focal abnormality.[7,8] Berg *et al*[9] found focal slowing on the EEG as a strong predictor of intractability in epilepsy patients with nonidiopathic localization-related syndromes. In general, patients with epileptiform activity focus on the frontal and anterior temporal lobe tends to have lower remission rate compared to those with focus on the mid temporal lobe.[7]

Intractable epilepsy gives negative impact on social and psychological life of the patients, resulting in

From the Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Reprint request to: Irawan Mangunatmadja, Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jl. Salemba 6, Jakarta 10430, Indonesia. Tel. 62-21-3907742. Fax. 62-21-3907743.

failure in education and carrier opportunity. Cognitive ability could be impaired because of intractable seizure or chronic effects of antiepileptic drugs consumption.[5] Considering the negative impact of intractable epilepsy on patients' life, it is very important to identify patients at risk of developing intractable epilepsy as early as possible.

This study was performed due to limited study of clinical characteristics and EEG features of intractable childhood epilepsy, especially in Indonesia. The results of this study could be useful in predicting intractable epilepsy in newly diagnosed epilepsy patients, so that intensive management could be given earlier.

Table 1. Patient's characteristics (unless otherwise specified, N = 41)

Characteristics	n	%
Sex		
Male	24	58
Female	17	42
Age of onset		
0-1 yr	21	51
1-2 yr	6	15
3-4 yr	9	22
≥ 5 yr	5	12
Seizure frequency/month		
1-5	21	51
6-10	4	10
> 10	16	39
History of central nervous system infection		
Yes	2	5
No	39	95
History of status epilepticus		
Yes	16	39
No	25	61
Neurological impairment		
Yes	33	80
No	8	20
Microcephaly		
Yes	20	49
No	21	51
Seizure manifestations		
1 type	27	66
2 type	12	29
3 type	2	5
Abnormal neuroimaging (n=24)		
Yes	14	58
No	10	42
Number of antiepileptic drug		
2	27	66
3	9	22
> 3	5	12
EEG		
Normal	5	12
Abnormal	36	88

Methods

This was a case series of intractable epilepsy patients attending the Pediatric Neurology and Growth and Development Clinic, Cipto Mangunkusumo Hospital from September 2008-March 2009. We included all patients with intractable epilepsy aged below 18 years that still experienced seizure at least once a month and had consumed at least 2 antiepileptic drugs for at least 18 months. The exclusion criterion was intractable epilepsy patients with central nervous system congenital anomaly.

The parents were asked to fill in an informed consent and interviewed about the patients history of illness. Additional data of clinical characteristics were collected from the medical records. The patients were asked to stop consuming antiepileptic drugs from the night until the morning before the EEG examination was performed.

Variables investigated were type and frequency of the seizure, number and type of drugs, and clinical characteristics (age of onset, neurological impairment, microcephaly, abnormal neuroimaging, history of central nervous system infection, and history of status epilepticus). Data were processed using the SPSS v. 13 program and presented in textular and tabular manner. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, University of Indonesia.

Results

There were 41 subjects who agreed to participate in this study, 24 males and 17 females, ranging in age from 20 months-17 years old, with the mean age 8 years old. In 51% subjects the age of onset was between 0-1 year old. The complete characteristics of the subjects are depicted in **Table 1.** In this table we can see that history of status epilepticus was noted in 39% of subjects and history of central nervous system infection was positive in only 5% of subjects. It is important to note that neurological impairment was found in 80% subjects consisted of cerebral palsy, mental retardation, global developmental delay, delayed speech, and hemiparesis.

Neuroimaging study such as computed tomography (CT-scan) or magnetic resonance imaging (MRI)

was performed in only 24 subjects and 14% of them showed abnormal features. Our subjects showed CT scan features of cerebral atrophy, calsification, infarct, mielination disorder, fluid collection, corpus callosum disgenesis, and gliosis.

The types of seizure are shown in **Table 2**. The majority (65%) showed generalized seizure, consisted of absence (3%), atonic (3%), tonic clonic (24%), tonic (21%), and myoclonic (14%). Complex partial seizure was the most focal seizure found in our study.

Table 2. Seizure manifestations of intractable epilepsy patients

Seizure manifestations (n=41)	Total* (n=58)	%
Generalized		
Tonic clonic	14	24
Tonic	12	21
Myoclonic	8	14
Atonic	2	3
Absence	2	3
Focal		
Clonic/Tonic	5	9
Focal secondary generalized	5	9
Complex partial	10	17

Note *: there were 14 subjects with > 1 types of seizures

Table 3. EEG features of intractable epilepsy patients (ictal and interictal)

EEG Features	Total	%
Normal	5	12
Abnormal	36	88
Background activity		
Normal	1	3
Hypofunction	35	97
Epileptiform activity		
Not found	7	19
Focal	11	31
Multifocal	10	28
Generalized	4	11
Focal+Generalized	4	11

The EEG findings are summarized in **Table 3**. Normal EEG features was found in 12% subjects and abnormal in 88%. Slowing of the background activity was found in 85% consisted of generalized and focal slowing of the background activity each found in 80% and 20% subjects, respectively. One subject with abnormal EEG showed normal background activity.

There was 33 interictal EEG features from 36 abnormal EEG found, but epileptiform activity was not found in 7 subjects. Focal and multifocal epileptiform activity was found in 11 and 10 subjects, respectively. Epileptiform activity was mostly found in the frontal (42%) and temporal lobe (26%).

Subjects with epileptiform activity in the frontal, parietal lobe, and generalized epileptiform activity showed few types of seizure, comprising of generalized seizure, complex partial seizure, and focal secondary generalized. Subjects with epileptiform activity in the temporal lobe showed generalized seizure, focal secondary generalized, complex partial seizure and simple partial seizure. Subjects with epileptiform activity in the central region and the occipital lobe showed generalized and complex partial seizure.

Discussion

Intractable epilepsy develops from a chronic epileptogenesis process that is triggered by insults to the brain such as central nervous system infection, hypoxia, tumor, etc. Based on the epileptogenesis theory, insults occuring in the first year of life will cause neuronal damage that could trigger the epileptogenesis process.[12] Our study found age of onset in 51% (95% CI 36 to 66) subjects were between 0-1 year old. The same results were also found in previous studies and was statistically significant as predictors of intractability.[4,8,9,11]

Table 4. Localization of epileptiform activity on the EEG and seizure manifestations of intractable epilepsy patients

Localization of epileptiform activity	Seizure manifestations				
	Focal n	Complex partial n	Focal secondary generalized n	Generalized n	Total n (%)
Generalized					
Focal	-	1	3	8	12 (11)
Frontal	-	8	9	26	43 (42)
Temporal	2	2	3	20	27 (26)
Occipital	-	1	-	6	7 (7)
Parietal	-	2	1	7	10 (10)
Central	-	1	-	3	4 (4)

Status epilepticus is thought to be associated with intractability because it causes cerebral hypoxia, hypoglicemia, hypercarbia, progressive lactate and respiratory acidosis leading to irreversible neuronal damage.[13-15] History of status epilepticus in our study was found in 39% (95% CI 24 to 54) subjects. Kwong et al[8] found 22.1% symptomatic intractable epilepsy patients and 8.5% cryptogenic epilepsy patients had history of status epilepticus. Other studies found history of status epilepticus was more common in the intractable epilepsy patients but showed no statistical significance.[4,11,16]

History of central nervous system infection is one of the etiologies of symptomatic epilepsy, commonly found in tropical countries besides perinatal asphyxia. Previous study in Hong Kong and India found 18-24% intractable epilepsy patients had a history of central nervous system infection.[4,8] Our study only found two subjects from total 41 subjects with history of intractable epilepsy. The minimal number of subjects with a history of central nervous system infection in our study maybe due to the limited number of patients who survived and had epilepsy as their sequels.

Destructed brain tissue due to infection during the third trimester or the perinatal period, hypoxic ischemic encephalopathy, metabolism disorder such as aminoaciduria or hypothyroid will result in microcephaly.[18,19] In our study, there were 49% (95% CI 34 to 64) subjects with microcephaly and 51% subjects with normal head circumference. Ko et al[16] in the United States found microcephaly in only 6.3% intractable epilepsy patients. Although the frequency of microcephaly was higher than that in the control group but it didn't show statistical significance as a predictor of intractability.[16] Studies performed in developed countries showed small frequency of microcephaly due to better health facilities and environment that will lead to minimal case exposed to etiology of secondary or acquired microcephaly.

Neurological impairments in intractable epilepsy patients can result from chronic consumption of antiepileptic drugs, epilepsy itself, underlying brain lesion, or combinations of those factors.[20] This implies that abnormal neurological status in epilepsy patients can be present in the early phase of the disease or develops after several years of the disease course when the epilepsy becomes intractable.

Our study found 80% (95% CI 68 to 93) subjects with abnormal neurological status consisted of cerebral palsy, mental retardation, hemiparesis, global developmental delay, and delayed speech. Previous studies found similar results and showed statistical significance as a factor associated with intractability.

Predictors of intractable epilepsy could also be determined from diagnostic examinations such as neuroimaging study and EEG. Our study found abnormal neuroimaging in 14 of 24 subjects with 95% confidence interval between 38 to 78. Patients with normal neuroimaging may have disorder such as ion channelopathies, changes in neurotransmitter receptor, and reactive autoimmunity that do not show major structural abnormality.

Previous study showed approximately 50-60% intractable epilepsy patients with abnormal MRI or CT scan and was statistically significant.[11,16] Different results were reported by Berg et al[9] that only found 20.3% of epilepsy patients with abnormal neuroimaging. This is maybe due to the population based study performed by Berg et al compared to hospital based study performed by other investigators.

Abnormal EEG features were found in 88% (95% CI 78 to 98) subjects. Patients with age of onset in the early childhood frequently showed abnormal EEG features compared to epilepsy patients with age of onset in adulthood. Eighty five (95% CI 74 to 96) percent subjects showed slowing of the background activity. Study by Ko et al[16] found similar results, 73.6% intractable epilepsy patients had abnormal background activity. There were 80% (95% CI 67 to 93) subjects that showed generalized slowing of the background activity and 20% subjects showed focal slowing. Ko et al[16] reported different results, generalized and focal slowing of the background activity were found in 49.3% and 30.6%, respectively. This difference was probably due to difference in the source of EEG used in these two studies. Our study used the last EEG performed, so there might be more negative impact of the disease itself or the chronic effect of antiepileptic drugs to the brains' background activity.

Epileptiform activity was found in 29 of 36 subjects with abnormal EEG features. Thirty one percent subjects showed focal epileptiform activity and 28% subjects showed multifocal epileptiform activity, previous study also found similar results.

Epileptiform activity was mostly found in the frontal (42%) and temporal lobe (26%). Contrary to the results reported by Ko et al[16] that only found 15.3% epileptiform activity in the frontal lobe. Dheona et al reported that 20% of intractable epilepsy patients showed epileptiform activity in the temporal lobe.[6] This difference maybe due to difference in sample size and possibility that epileptiform activity in the frontal lobe sometimes showed normal result.

Subjects with epileptiform activity in the frontal lobe showed complex partial, focal secondary generalized, and generalized seizure. Subjects with epileptiform activity in the temporal lobe showed all type of seizure that were in accordance with the International League Against Epilepsy 1981 seizure classification.[21] Our study found 14 from 41 subjects with multiple types of seizure. Previous studies found 9-12% intractable epilepsy patients experienced multiple types of seizure. This difference was probably due to difference in sample size and study design performed.

Seizure manifestations in majority subjects were generalized seizure consisted of generalized tonic clonic (24%), tonic (21%), and myoclonic (14%). The most common focal seizure in our study was complex partial seizure, occurring in 17% subjects. Similar with our study results, Ko et al[16] also found generalized seizure as the most common seizure manifestations in intractable epilepsy patients. Contrary to our study results, other studies found focal seizure as the most common seizure manifestations in intractable epilepsy patients.[8,9] This maybe due to multiple seizure type classified separately from focal and generalized seizure, resulting in impression that the focal seizure is more common than the generalized seizure.

Our study showed that age of onset between 0-1 year old, neurological impairments, microcephaly, abnormal neuroimaging study, and slowing of the background activity on the EEG are commonly found in intractable epilepsy patients. Epileptiform activity is mostly found in the frontal and temporal lobe. These results are consistent with the results of previous studies on predictors of intractable epilepsy. Unfortunately, we cannot conclude these characteristics studied as predictors of intractability due to the study design performed. We suggest a prospective cohort or case control study to determine these clinical characteristics and diagnostic study results as predictors of intractable epilepsy.

Based on this study, pediatricians should think of the possibility of intractable epilepsy in newly diagnosed epilepsy patients accompanied by those clinical characteristics and diagnostic study results mentioned above. Intensive management can be given as early as possible to prevent the development of intractable epilepsy. One important action is to increase antiepileptic dose as soon as there is no response of seizure control after therapy is given and close observation is warranted.

As a conclusion, intractable epilepsy patients show age of onset between 0-1 year old, neurological impairment, microcephaly, abnormal neuroimaging, and abnormal EEG features with generalized slowing of the background activity. Seizure manifestation is mostly generalized seizure. Epileptiform activity in intractable childhood epilepsy is often found in the frontal and temporal lobe.

References

1. Johnston MV. Seizures in childhood. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson textbook of pediatrics. 17th ed. Philadelphia: Saunders, 2004; p.1993.
2. Jensen FE, Privitera MD, Shields WD. Evolving directions in the management of epilepsy. Clinician. 2002;20:6-9.
3. Paolicchi JM. Epilepsy in adolescents: diagnosis and treatment [homepage on the internet]. [cited 2005 Apr 6]. Available from: http://www.dcmsonline.org.
4. Chawla S, Aneja S, Kashyap R, Mallika V. Etiology and clinical predictors of intractable epilepsy. Pediatr Neurol. 2002;27:186-91.
5. Chabolla DR. Medically refractory seizures [homepage on the internet]. [cited 2005 Apr 6]. Available from: http://www.dcmsonline.org.
6. Sheth RD. Epilepsy surgery presurgical evaluation. Neurol Clin Am. 2002;20:1195-1215.
7. Singhvi JP, Sawhney IM, Lal V, Pathak A, Prabhakar S. Profile of intactable epilepsy in a tertiary referral center. Neurol India. 2000;48:351-6.
8. Kwong KL, Sung WY, Wong SN, So KT. Early predictors of medical intractability in childhood epilepsy. Pediatr Neurol. 2003;29:46-52.
9. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children. A prospective study. Neurology. 2001;56:1445-52.

10. Camfield P, Camfield C. The frequency of intractable seizure after stopping aeds in seizure-free children with epilepsy. Neurology. 2005;64:973-5.
11. Akhondian J, Heydarian F, Ali Jafari S. Predictive factors of pediatric intractable seizures. Arch Iranian Med. 2006;9:236-9.
12. Acharya JN. Recent advances in epileptogenesis. Curr Science. 2002;82:679-88.
13. Stafstrom CE. Back to basic: the pathophysiology of epileptic seizure: a primer for pediatricians. Pediatr Rev. 1998;19:342-51.
14. Sirven JI, Waterhouse C. Management of status epilepticus. Am Fam Physician. 2003;68:469-76.
15. Young GM. Pediatrics, status epilepticus [homepage on the internet]. [Updated 2008 Jul 18, cited 2009 Mar 17]. Available from: http://www.emedicine.com. .
16. Ko TS, Holmes GL. EEG and clinical predictors of medically intractable childhood epilepsy. Clin Neurophysiol. 1999;110:1245-51.
17. Engel J. Causes of human epilepsy. In: Engel J, editor. Seizures and epilepsy. Philadelphia: F.A. Davis Company, 1989; p.112-30.
18. Purugganan OH, Adam HM. Abnormalities in head size. Ped Rev. 2006;27:473-6.
19. Rios A. Microcephaly. Pediatr Rev. 1996;17:386-7.
20. Beckhung E, Uvebrant P. Motor and sensory impairment in children with intractable epilepsy. Epilepsia. 1993; 34:924-9.
21. Commission on Classification and Terminology of The International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. In: Wyllie E, editor. The treatment of epilepsy: principles and practice. 2nd ed. Pennsylvania: Williams & Wilkins,1997; p.367-75.