

## Factors associated with outcome of acute encephalitis in children: a retrospective study of three referral hospitals

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### ABSTRACT

**BACKGROUND** Encephalitis is more frequent in children and has a poor outcome. There was no data on encephalitis in children in Indonesia, so this study was aimed to evaluate clinical presentation and diagnostic examination of children with acute encephalitis, and factors related to outcome.

**METHODS** This was a retrospective study of medical records between 2014 and 2018 in three referral hospitals in Jakarta and Tangerang. Clinical presentation at admission, cerebrospinal fluid analysis, neuroimaging, and electroencephalography (EEG) were documented. Outcome was determined at hospital discharge and classified as poor for severe neurological abnormalities at discharge or died. Logistic regression was used to evaluate associated factors with the outcome.

**RESULTS** A total of 190 children were included and most were age >1 year (71%). Most subjects presented with fever (90%) and seizures (87%). Of those who had seizures, 80% experienced generalized seizures. Focal neurological deficit was seen in 90 patients (47%). EEG was positive in 90% subjects (n = 27/30). Probable cases were found in 51% of all subjects. The mortality was 23%. Focal seizures (odds ratio [OR] = 3.305, 95% confidence interval [CI] = 1.122–9.742) and age >1 year (OR = 3.076, 95% CI = 1.388–6.803) were risk factors for a poor outcome.

**CONCLUSIONS** Acute encephalitis occurred most often in children aged >1 year. Fever and seizures were the most common symptoms. EEG was better than other examinations for confirming diagnosis of encephalitis. Focal seizures and age >1 year were associated with a three-fold increased risk for a poor outcome.

**KEYWORDS** child, encephalitis, risk factors, seizures

Encephalitis is inflammation of the brain parenchyma and frequently occurs in children under 5 years old. It may be caused by viruses, bacteria, fungi, parasites, autoimmune diseases, and inflammation after infection.<sup>1,2</sup> Most cases (65%) are of unknown etiology<sup>3–5</sup> and causes in Western countries are different from Asian countries,<sup>2,6–8</sup> with resultant differences in morbidity and mortality.<sup>1,5,8</sup> Some follow-

up studies showed that encephalitis can cause long-term morbidity that impairs development.<sup>9–12</sup>

Acute encephalitis is diagnosed using clinical, laboratory, electroencephalography (EEG), and radiological criteria without any histopathological evidence. Currently, there is no data about the clinical presentation and outcome of acute encephalitis in children in Indonesia. This study was aimed to describe

the clinical presentation, etiology, diagnosis, short-term outcome, and factors associated with outcome.

## METHODS

This retrospective study used data from medical records between January 2014 and October 2018 in three referral hospitals: Cipto Mangunkusumo Hospital (RSCM), Tangerang District Hospital (RSUT), and Fatmawati Hospital (RSUPF). RSCM and RSUPF are tertiary referral hospitals, while RSUT is a secondary referral hospital. The study was approved by the Ethical Committee of the Faculty of Medicine Universitas Indonesia (No: 766/UN2.F1/ETIK/2017).

Subjects were recruited consecutively based on the hospital and the latest data. Subjects were first recruited in RSCM, then RSUT, and finally RSUPF. Inclusion criteria used the International Classification of Diseases (ICD) X, and other ICD X codes (G03: meningitis due to other and unspecified causes, G04: encephalitis, myelitis, and encephalomyelitis, G05: encephalitis, myelitis, encephalomyelitis not classified elsewhere, A80-89: viral and prion infections of the central nervous system, B00.4: herpesviral encephalitis, B02.0: zoster encephalitis) with symptoms similar to encephalitis according to case definitions stated below.<sup>7</sup> The diagnosis of encephalitis was then reviewed and the cases were included if the major and minor clinical criteria applied.<sup>7</sup> Major criteria were: altered mental status (decrease or altered level of consciousness, lethargy, or personality changes) lasting  $\geq 24$  hours with no alternative identifiable causes. Minor criteria were: documented fever  $\geq 38^{\circ}\text{C}$  within 72 hours before or after admission; generalized or partial seizures not fully attributable to a pre-existing seizure disorder; new onset of focal neurologic findings; cerebrospinal fluid (CSF) leukocyte count of  $\geq 5$  cells/ml; abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset; abnormality of EEG that is consistent with encephalitis and not attributable to other causes. The subject was defined as “possible encephalitis” when one major and two minor criteria were met, and as “probable encephalitis” when one major and three minor criteria were met.<sup>7</sup> Data were excluded if the ICD X codes of the primary diagnosis were not fulfilled and if subjects had undergone a neurosurgical procedure due to previous neurological

problems (such as hydrocephalus, brain tumor, post ventriculoperitoneal shunt, or brain metastases).

The Glasgow coma scale (GCS) was evaluated at admission. Status epilepticus was defined as a seizure that lasted longer than 5 min, or recurrent seizures without improvement in the level of consciousness.<sup>13</sup> Focal neurological deficits consisted of focal symptoms at admission and focal seizures.<sup>14</sup> All these variables constituted the patient’s clinical presentation in this study.

The exploration of etiology was by CSF culture or polymerase chain reaction (PCR) when available. Leukopenia was defined as a blood leukocyte count of  $< 4,000$  cells/ $\mu\text{l}$ .<sup>14</sup> Pleocytosis in CSF was defined as a leukocyte count of  $\geq 5$  cells/ml.<sup>8</sup> Computed tomography (CT) scan or magnetic resonance imaging (MRI) was recorded from the interpretation by radiologists. EEG was defined as abnormal if any generalized or focal neurophysiology finding was noted.<sup>14</sup> The outcome was classified as poor and good. The patients who recovered or only had minimal symptoms at discharge (minimal concentration deficit, fatigue, and headache) were considered to have had a good outcome, while patients who still exhibited severe neurological abnormalities at discharge (spasticity, mental retardation, weakness, ataxia, seizures, aphasia, blindness, sensory impairment), or who died were considered to have had a poor outcome.<sup>1</sup>

### Statistical analysis

The sample size was calculated using comparison of two proportions and a minimum of 184 subjects was required for adequate statistical power. In bivariate analysis, the chi-square and Fisher’s exact tests were used for categorical variables. Mean differences were analyzed using the independent t-test or Mann–Whitney test. Factors with  $p < 0.25$  were included in the multivariate analysis, which includes age, loss of consciousness, level of consciousness, seizures, and hospitalization duration. Multivariate analysis was conducted using logistic regression with a value of  $p < 0.05$  considered as significant.

## RESULTS

From 905 subjects with appropriate ICD X codes, 190 were included in this study comprising 54 from RSCM, 98 from RSUT, and 38 from RSUPF. The subject recruitment pathway is shown in Figure 1. Patient

characteristics are described in Table 1. Probable encephalitis was more frequent in RSCM and RSUPF than in RSUT. In RSCM, focal neurological deficits and neurological abnormalities were frequently found. Many encephalitis patients in RSUT died. A total of 61% (100/190) of subjects had poor outcome and 23% (44/190) died.

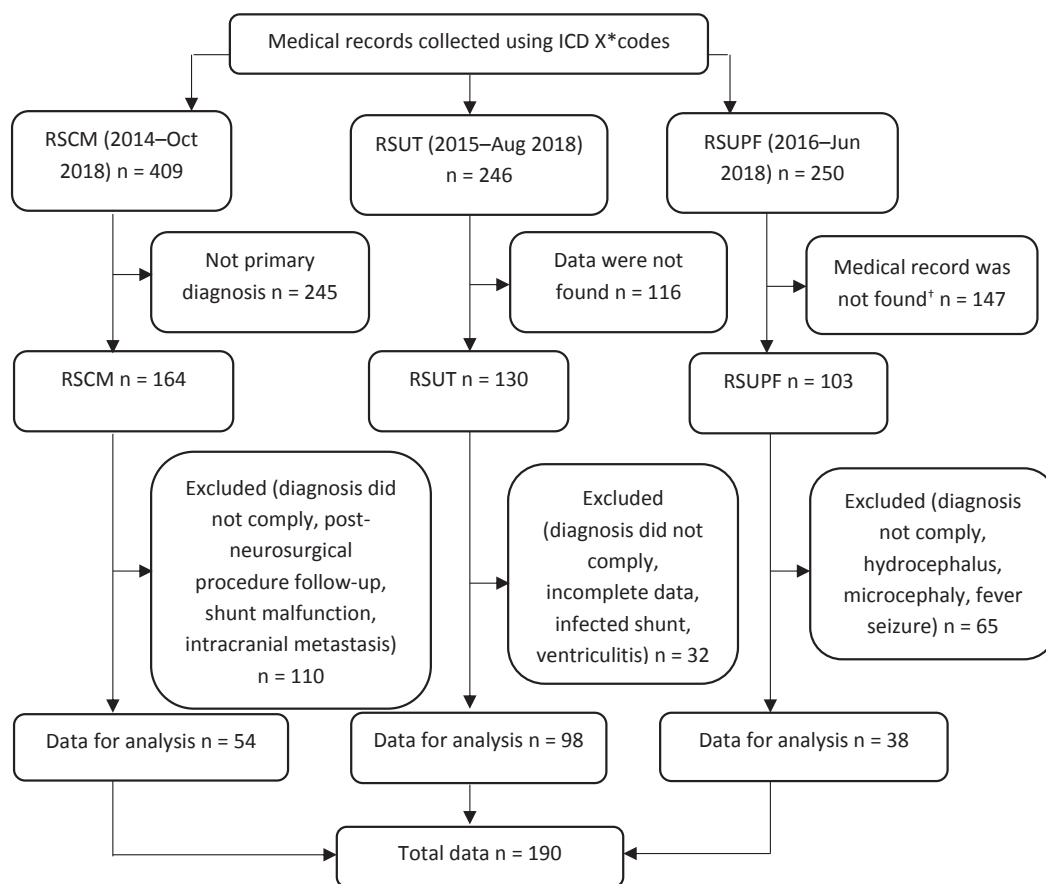
The risk factors for a poor outcome are described in Table 2. Poor outcome was noted more frequently in those with possible encephalitis, which occurred more often in RSUT, and thus RSUT contributed the highest mortality among the three referral hospitals. No difference was noted in the incidence of poor outcomes in those with possible or probable encephalitis, whereas a statistical difference was found in terms of mortality (Table 3). These results were not further analyzed due to limited sample size.

Two risk factors for poor outcome were age >1 year and focal seizures. Factors thought to be

associated with mortality were low GCS score, diagnostic criteria, duration of hospitalization, and leukopenia (Table 3).

Neuroimaging was performed in 106/190 (55.8%) subjects (CT scan in 92 and MRI in 14 patients; Table 1). Many subjects with poor outcome had multiple pathologies on CT scan, including brain atrophy, infarct, and brain edema. Poor outcome was noted in those who exhibited hypoxic-ischemic encephalopathy and brain atrophy on MRI.

Etiology was only investigated in 38 (20%) subjects (Table 4). Herpesvirus encephalitis was proven in two patients and one of them was also infected with tuberculosis diagnosed by PCR. Patients infected with tuberculosis or hyphae or *Bacillus* had poor outcomes. Among patients with herpes simplex virus encephalitis, poor outcome was noted in one patient. A total of 81% of subjects with poor outcomes had no etiologic agents found and five patients died.



**Figure 1.** Subjects recruitment pathway. ICD X=10th revision of the International Statistical Classification of Diseases and Related Health Problems; RSCM=Cipto Mangunkusumo Hospital; RSUT=Tangerang District Hospital; RSUPF=Fatmawati Hospital \*ICD X: G03: meningitis due to other and unspecified causes; B00.4: herpesviral encephalitis; G04: encephalitis, myelitis, and encephalomyelitis; B02.0: zoster encephalitis; A80-89: viral and prion infections of the central nervous system; G05: encephalitis, myelitis, encephalomyelitis not classified elsewhere; \*medical records data were not found due to backward pattern of sample collection using data from the latest year until sample size fulfilled

**Table 1.** Patient's characteristics

Variable	RSCM, n (%) (N = 54)	RSUT, n (%) (N = 98)	RSUPF, n (%) (N = 38)	Total, n (%) <sup>*</sup>	Data <sup>†</sup>	p
Age (years)					190	<b>0.031</b>
≤1	9 (17)	36 (37)	10 (26)	55 (29)		
>1	45 (83)	62 (63)	28 (74)	135 (71)		
Gender					190	0.428
Male	29 (58)	56 (57)	17 (45)	102 (54)		
Female	25 (42)	62 (43)	21 (55)	88 (46)		
Incidence of poor outcome					175	<b>0.016</b>
Possible	19 (36)	57 (58)	9 (37)	85 (49)		
Probable	34 (64)	41 (42)	15 (63)	114 (51)		
Level of consciousness	53 (98)	93 (95)	36 (95)	182 (96)	190	0.594
GCS <7	5 (10)	8 (8)	4 (11)	17 (9)	185	0.894
GCS ≥7	45 (90)	89 (92)	34 (89)	168 (91)		
Seizure	47 (87)	88 (90)	30 (79)	165 (87)	189	0.181
Type of seizure					160	<b>0.005</b>
Generalized	31 (65)	70 (85)	27 (90)	128 (80)		
Focal	17 (35)	12 (15)	3 (10)	32 (20)		
Status epilepticus	12 (22)	40 (41)	9 (24)	61 (52)	120	<b>0.031</b>
Fever	44 (81)	94 (96)	32 (84)	170 (90)	188	<b>0.028</b>
Focal neurological deficit	38 (70)	36 (37)	16 (42)	90 (47)	190	<b>&lt;0.001</b>
Outcome					164	0.288
Poor	33 (69)	55 (60)	12 (50)	100 (61)		
Good	15 (31)	37 (40)	12 (50)	64 (39)		
Mortality	11 (20)	27 (28)	6 (16)	44 (23)	190	0.393
Fever duration before admission (days), median (min–max)	5 (1–60)	4 (1–30)	4 (1–30)	4 (1–60)	163	0.333 <sup>‡</sup>
Hospitalization duration (days), median (min–max)	9 (1–33)	7 (1–47)	10 (1–35)	9 (1–136)	184	<b>0.026<sup>‡</sup></b>
Leukopenia	3 (6)	2 (2)	4 (11)	9 (5)	189	0.107
Pleocytosis ≥5/mm <sup>3</sup>	23 (64)	10 (24)	3 (75)	36 (44)	81	<b>0.001</b>
Examined subjects/total	36 (67)	41 (42)	4 (10)			
Protein CSF (g/dl), median (min–max)	25 (5–885)	279 (24–19.460)	60 (27–259)	85 (5–19.460)	74	<b>&lt;0.001<sup>‡</sup></b>
EEG abnormal	19 (95)	5 (83)	3 (75)	27 (90)	30	0.396
Examined subjects/total <sup>§</sup>	20 (37)	6 (6)	4 (10)			
CT scan abnormal	16 (67)	27 (73)	25 (81)	68 (74)	92	0.497
Examined subjects/total <sup>§</sup>	24 (44)	37 (38)	31 (82)			
MRI abnormal	8 (80)	0 (0)	3 (75)	11 (78)	14	1
Examined subjects/total <sup>§</sup>	10 (18)	0 (0)	4 (10)			

RSCM=Cipto Mangunkusumo Hospital; RSUT=Tangerang District Hospital; RSUPF=Fatmawati Hospital; GCS=Glasgow coma scale; CSF=cerebrospinal fluid; EEG=electroencephalography; CT=computed tomography; MRI=magnetic resonance imaging

<sup>\*</sup>Percentage was counted from available data (<sup>†</sup>); <sup>‡</sup>available data for analysis, missing data = total subjects–available data; <sup>‡</sup>statistically analyzed using Kruskal–Wallis, otherwise: chi-square; statistically significant if  $p < 0.005$ ; <sup>§</sup>examined subjects/total is number of examined subjects per total available subjects from the hospital

**Table 2.** Factors related to encephalitis outcome

Variable	Bivariate analysis		Multivariate analysis		
	Poor outcome, n (%)	Good outcome, n (%)	<i>p</i>	OR (95% CI)	<i>p</i>
Age (years) (N = 164)			<b>0.008</b>	3.076 (1.388–6.803)	<b>0.006</b>
≤1	22 (45)	27 (55)			
>1	76 (67)	37 (33)			
Male gender (N = 164)	53 (62)	33 (38)	0.857		
Loss of consciousness (N = 164)	98 (62)	60 (38)	<b>0.210*</b>	2.154	0.468
Level of consciousness (N = 160)			<b>0.059</b>		0.066
GCS <7	14 (82)	3 (18)			
GCS ≥7	84 (59)	59 (41)			
Fever (N = 163)	91 (61)	58 (39)	0.773		
Seizure (N = 163)	87 (62)	54 (38)	0.523		
Type of seizure (N = 137)			<b>0.096</b>	3.305 (1.122–9.742)	<b>0.03</b>
Focal	21 (75)	7 (25)			
Generalized	63 (58)	46 (42)			
Status epilepticus (N = 105)	34 (61)	22 (39)	0.429		
Focal neurological deficit (N = 164)	51 (62)	31 (38)	0.749		
Incidence of poor outcome (N = 158)			0.85		
Possible	35 (61)	22 (39)			
Probable	62 (61)	39 (39)			
Fever duration before admission (days), median (min–max) (N = 144)	4 (1–60)	5 (1–60)	0.298 <sup>†</sup>		
Hospitalization duration (days), median (min–max) (N = 161)	7 (1–33)	11 (1–47)	<b>0.005</b>	0.959	0.107
Pleocytosis ≥5/mm <sup>3</sup> (N = 71)	19 (58)	14 (42)	0.814		
Abnormal CT scan (N = 74)	35 (62)	21 (38)	0.347		
Abnormal MRI (N = 12)	4 (44)	5 (56)	1*		
Abnormal EEG (N = 27)	19 (76)	6 (24)	1*		
Case of abnormal EEG (N = 24) <sup>‡</sup>					
Diffuse slowing	5 (100)	0 (0)	0.28*		
Focal slowing/seizure	14 (74)	5 (26)	1*		
Leukopenia <4,000 cells/μl (N = 163)	6 (86)	1 (14)	<b>0.250*</b>	1.411	0.99

OR=odds ratio; CI=confidence interval; GCS=Glasgow coma scale; CT=computed tomography; MRI=magnetic resonance imaging; EEG=electroencephalography

All statistical analysis were using chi-square, except \*Fisher exact test; <sup>†</sup>Mann–Whitney test, <sup>‡</sup>only 24 subjects had data availability for the outcome. Statistically significant if *p*<0.05; included in the multivariate analysis if *p*<0.25

Abnormal neurologic findings at discharge (Table 5) were spasticity (34%, 22 subjects; 5 subjects with combination with other neurologic abnormalities such as delayed development, aphasia, and involuntary movement), epilepsy (16%), involuntary movements (9%, 6 subjects), mild motor impairment (9%, 6 subjects), behavioral disorders (9%, 6 subjects).

## DISCUSSION

Some clinical findings found to be frequent in children with encephalitis were decreased level consciousness (96%), fever (90%), seizures (87%), and focal neurological deficit (47%). This finding was in line with the Californian encephalitis project whose inclusion criteria were similar.<sup>15</sup> Children older than

**Table 3.** Bivariate analysis of mortality

Variable	Died, n (%)	Survived, n (%)	p
Age (years) (N = 190)			0.51
≤1	11 (20)	44 (80)	
>1	33 (24)	102 (76)	
Male gender (N = 190)	23 (22)	79 (78)	0.83
Loss of consciousness (N = 190)	44 (24)	138 (76)	0.202*
Level of consciousness (N = 185)			<b>0.018</b>
GCS <7	8 (47)	9 (53)	
GCS ≥7	36 (21)	132 (79)	
Fever (N = 188)	41 (24)	129 (76)	0.374*
Seizure (N = 189)	38 (23)	127 (77)	0.81
Type of seizure (N = 160)			0.11
Generalized	33 (26)	95 (74)	
Focal	4 (12)	28 (88)	
Focal neurological deficit (N = 190)	16 (18)	74 (82)	0.095
Status epilepticus (N = 120)	13 (21)	48 (79)	0.173
Diagnosis (N = 190)			<b>0.001</b>
Possible	26 (37)	44 (63)	
Probable	18 (16)	96 (84)	
Fever duration before admission (days), median (min–max) (N = 163)	3 (1–30)	5 (1–60)	0.051 <sup>†</sup>
Hospitalization duration (days), median (min–max) (N = 184)	2 (1–17)	11 (1–47)	<b>&lt;0.001<sup>†</sup></b>
CSF pleocytosis ≥5/mm <sup>3</sup> (N = 81)	7 (19)	29 (81)	0.294
Abnormal CT scan (N = 74)	33 (59)	23 (41)	0.506
Abnormal MRI (N = 14) <sup>‡</sup>	0 (0)	11 (100)	
Abnormal EEG (N = 30)	0 (0)	27 (100)	
Leukopenia <4,000 cells/μl (N = 189)	6 (67)	3 (33)	<b>0.006*</b>

GCS=Glasgow coma scale; CSF=cerebrospinal fluid; CT=computed tomography; MRI=magnetic resonance imaging; EEG=electroencephalography  
 Statistical analysis was using chi-square, except: \*Fisher exact test; <sup>†</sup>Mann–Whitney test; statistically significant if  $p < 0.05$ ; <sup>‡</sup>only 11 subjects had data availability for the mortality

1 year of age had more severe clinical presentations at admission, such as low GCS, status epilepticus, focal neurological deficit, and leukopenia but less seizures and fever. Refractory status epilepticus can be a prognostic factor for poor outcome, such as longer hospitalization, poor outcome associated with epilepsy, but not with mortality.<sup>13</sup> Uncontrolled seizures might indicate a severe cortical injury. In this study, children with status epilepticus had poorer outcome. Lee et al<sup>16</sup> also stated that status epilepticus was related to epilepsy post-encephalitis in patients monitored for 6 years. Seizures in our study were more common (87%) compared with recent studies (42.7–73%).<sup>5,13,15–18</sup> Seizures were also reported to be higher in prevalence when MRI abnormalities were also considered.<sup>18</sup>

There were more neurologic abnormalities at discharge in children presenting with a focal neurological deficit at admission (55% versus 29%,  $p = 0.001$ ). Focal deficit was related to poorer outcome at hospital discharge.<sup>14</sup> Klein et al<sup>5</sup> found 70% of children with focal deficit had persisting neurologic abnormalities at discharge. We found focal seizures increased the risk for poor outcome 3-fold compared with generalized seizures. Parenchymal brain injury may have happened in focal seizure. Our study found spasticity and epilepsy as the most frequent neurological abnormalities at discharge. Focal neurologic symptoms indicate severe brain injury (such as a cerebral infarct), thus imposing a higher risk of neurological complications, such as epilepsy or motor impairment.<sup>8,19</sup>

**Table 4.** Distribution of neuroimaging findings among subjects

Neuroimaging pathology	n	n available with outcome	Poor outcome	Good outcome
<b>CT scan</b>				
Focal/diffuse hypodensity	15	11	7	4
Brain atrophy	11	10	8	2
Subdural hygroma	3	1	0	1
Meningitis	4	2	2	0
Suspected encephalitis	7	5	2	3
Cerebral edema	15	14	8	6
Hypodensity + hyperdensity + subdural hygroma + brain atrophy + calcification	1	1	1	0
Infarct + edema	2	2	2	0
Meningitis or meningoencephalitis	1	1	0	1
Hypodensity + atrophy	3	2	2	0
Others	6	6	4	2
<b>MRI</b>				
Acute disseminated encephalomyelitis	1	0	0	0
Hypoxic-ischemic encephalopathy	1	1	1	0
Brain atrophy	1	1	1	0
Encephalitis	5	5	2	3
Meningitis	1	0	0	0
Infarct	2	2	0	2
<b>Etiology</b>				
Sterile/undetected	24	21	17	4
<i>Staphylococcus</i>	4	4	2	2
HSV	2	2	1	1
<i>Bacillus</i>	2	2	2	0
<i>Enterococcus faecalis</i>	1	0	0	0
<i>Acinetobacter</i>	1	1	0	1
<i>Escherichia coli</i>	1	1	0	1
<i>Streptococcus</i>	1	1	0	1
Hyphae (contaminated)	1	1	1	0
Tuberculosis	1	1	1	0

CT=computed tomography; MRI=magnetic resonance imaging; HSV=herpes simplex virus

Limited resources for performing diagnostic workup meant the diagnosis was categorized as possible and probable encephalitis using criteria from Venkatesan et al.<sup>7</sup> Most were probable cases (51%). Mortality was higher in possible cases diagnosed in RSUT, which had further limitation of resources to support the clinical diagnosis of encephalitis and a higher number of subjects with age <1 year old.

EEG was abnormal in 90% of examined cases, CT scan in 74%, and pleocytosis of CSF in 44%. EEG have been reported to be abnormal in 87–96% of children with encephalitis, but the findings were not

specific.<sup>8,20,21</sup> In a previous study, pleocytosis was found in 53.7% patients.<sup>13</sup> DuBray et al<sup>15</sup> used a cut-off of >10 cells/mm<sup>3</sup> as a factor predicting poor outcome of acute encephalitis, and clinical recovery was more common in patients with pleocytosis. None of the radiological examinations nor CSF analyses were associated with poor outcome in our study, which is similar to Rismanchi et al.<sup>22</sup>

Neuroimaging descriptions considered to be consistent with acute encephalitis (focal or diffuse inflammation) were hypodensity on CT scan or signal abnormalities on MRI.<sup>13</sup> Klein et al<sup>5</sup> found that

**Table 5.** Abnormal findings at discharge

Variable	n (%)
Spasticity	17 (27)
Epilepsy	10 (16)
Involuntary movement	6 (9)
Behavioral problem	6 (9)
Mild motor problem	6 (9)
Aphasia	3 (5)
Hemiparesis	3 (5)
Apathetic	2 (3)
Spasticity + delayed development	2 (3)
Spasticity + aphasia	2 (3)
Severe clinical condition (not specified)	2 (3)
Paraparesis + aphasia	1 (2)
Paraparesis + behavioral problem	1 (2)
Hydrocephalus	1 (2)
Spasticity + involuntary movement	1 (2)
Delayed development	1 (2)

abnormalities suggesting cerebral edema, cortical and subcortical focal hypodensity, and torcular enhancement were significantly higher in patient with neurological deficit at discharge. In our study, 74% of evaluated cases had abnormal CT scan findings of which hypodensity, cerebral edema, and brain atrophy were the most frequent (Table 4). Another study showed hypodensity in only 2.7% of cases and edema in 5.4%.<sup>13</sup> Focal abnormalities or any abnormalities on neuroimaging have been found to be a predictor of poor outcome,<sup>5,14</sup> and in our study, 11 out of 14 cases had abnormal MRI findings. MRI has been shown to be abnormal in 50% of subjects with encephalitis in acute settings and was superior to CT scan which was abnormal in only 23%.<sup>23</sup> Focal hyperintensity on MRI combined with an abnormal EEG had better predictive value than EEG alone, so MRI is indicated for children with focal neurological deficit, intractable seizures, focal spikes on EEG, and focal or continuous generalized delta waves.<sup>14</sup>

EEG findings considered to be important are focal slowing or diffuse epileptiform discharge.<sup>5</sup> In our study, 90% of children with encephalitis had abnormal findings on EEG which was similar to a previous study (92%)<sup>5</sup> that found diffuse slowing in 82% of cases, and focal slowing in 45%. Meanwhile, we found only 7 children (26%) with diffuse slowing (but only 5 out of 7 had availability for outcome analysis), whereas 74%

had focal slowing and/or focal epileptiform discharges. Continuous generalized delta waves were associated with poor outcome in one study,<sup>14</sup> while another<sup>13</sup> found focal abnormalities were more frequent. In our study, 5 out of 7 patients who had diffuse patterns had poor outcome, in comparison with 14 out of 20 patients with focal patterns.

Pathogenic etiologies found in our study were different with those found in other studies in Taiwan,<sup>14</sup> Sweden,<sup>8</sup> and Vietnam.<sup>24</sup> Etiologies were not detected in 63% of subjects in our study which was higher than in Sweden (52%),<sup>8</sup> Taiwan (57%),<sup>14</sup> and California (48,9%),<sup>15</sup> but lower than the Klein et al<sup>5</sup> study (76%). In the United States, only 50% of cases had the etiology identified in clinical settings.<sup>2,25</sup> The most frequent etiologies in the latter study were tic-borne encephalitis virus, enterovirus, respiratory syncytial virus, varicella zoster virus, and influenza virus (A and B). In Taiwan, *Mycoplasma pneumoniae* (31%) and enterovirus (46%) were the most frequent, similar to the DuBray et al's study.<sup>14,15</sup> We only found herpes simplex encephalitis in 2 cases (5.3%), similar to the number found by Wang et al,<sup>14</sup> Fowler et al,<sup>8</sup> and Rautonen et al.<sup>17</sup> Studies from Thailand in 1996–1998 and Vietnam mentioned that dengue virus and Japanese encephalitis virus were the most prevalent findings.<sup>3,24</sup>

Our study found the mortality was higher than previous studies from other countries that showed a range of mortality of 3–15%.<sup>17,26</sup> This may be because of lower GCS at admission in our study. Previous studies showed the risk factors for mortality were younger age, low GCS, focal neurological deficit, and neuroimaging abnormalities.<sup>5,14–16</sup> Younger age is associated with immature function of the substantia nigra, action of gamma-aminobutyric acid, vulnerability of younger microglia to hypoxic-ischemic activation, therefore the neuron would be more easily excitable.<sup>27</sup> Our study found younger age was a protective factor. Fowler et al<sup>9</sup> also found age >5 years old had two times the risk of persistent symptoms after encephalitis. Daxboeck et al<sup>28</sup> also showed children with older age had poorer outcome in encephalitis due to *Mycoplasma pneumoniae*. This may be because of greater inflammatory responses in older age, with pleocytosis and higher CSF protein levels. Low GCS, status epilepticus, focal neurological deficit, and leukopenia were also more frequent in the older age group. Unidentified etiology may have contributed to poorer outcome and higher mortality since it



contributed to suboptimal treatment. Unfortunately, limited facilities in these three hospitals contributed to this. A cohort study in a single center in Australia showed there were only 39% confirmed encephalitis cases in children and most were autoimmune.<sup>20</sup> Unfortunately, that examination is yet to be developed in Indonesia and it may have contributed to the unknown etiology in this study. We only recorded outcome at hospital discharge. Fowler et al<sup>9</sup> stated that almost 50% of encephalitis patients experienced persistent neurologic symptoms at discharge, such as personality disorder, developmental delay, and cognitive disorders.<sup>22</sup> Most children have an incomplete recovery at discharge and may fully recover after 6–12 months.<sup>2,9,10</sup> The majority of patients after acute encephalitis with residual neurologic symptoms at discharge eventually improved.<sup>9,10</sup> On the other hand, DuBray et al<sup>15</sup> did not find much a clinical improvement in 12 months after discharge. In Taiwan, 25% of subjects had a poor outcome after 5 months follow-up due to epilepsy, delayed development, mental retardation, behavioral and emotional problems, learning difficulties, neuropathy, motor weakness, and speech disorders.<sup>14</sup> Other long-term studies have also reported permanent neurological disorders, such as paresis with motor impairment, delayed development, behavioral changes, and moderate to severe learning difficulties.<sup>11,17,29</sup> Future neuropsychology assessment at school entry was suggested because of the possibility of having significant cognitive impairment, attention deficit hyperactivity disorder, and learning difficulties at follow-up during school years even though the children with encephalitis were considered as having a good outcome at discharge.<sup>12</sup>

Limitations of this study include those related to sample selection. We used encephalitis codes in the ICD X, and several other diagnostic codes related to encephalitis. There was a possibility of “missed” codes, due to manually defined code selection. Incomplete data in the medical record were seizure characteristics, fever duration before admission, unstandardized level of consciousness, presence of focal neurological deficit, and poorly described neurological abnormality that persisted at discharge. As a result, the sample size was not similar for each variable; hence, bivariate and multivariate analysis should be cautiously interpreted. This study also did not evaluate the long-term outcome, which could change over time.<sup>9,10,12,14,15</sup> This was the first study of encephalitis in children in Indonesia

and can serve as a baseline profile for diagnosis and management of suspected cases in order to choose the most appropriate test for different settings despite financial limitations.

In conclusion, children with acute encephalitis were mostly >1 year old and most commonly presented with fever and seizures. Abnormal EEG findings were the most useful diagnostic tool. Focal seizures and age >1 year were risk factors for poor outcome. Further long-term study (including neuropsychiatry assessment) for at least one year after onset should be conducted to fully assess the outcomes related to encephalitis. Improvements are needed in documentation, so that better depiction of the burden and prognosis of encephalitis in Indonesia can be achieved.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

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