ONLINE FIRST

ORIGINAL ARTICLE

Correlation between Hearing Loss with Acute Encephalitis Syndrome in Indonesian Children

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doi: 10.22442/jlumhs.2023.00973

ABSTRACT

OBJECTIVE: The study aimed to correlate hearing loss and clinical characteristics in children following Acute Encephalitis Syndrome.
METHODOLOGY: This cross-sectional study was conducted in the pediatric neurology outpatient clinic and audiology outpatient clinic of Dr. Soetomo Hospital Surabaya from August 2018 to January 2019. Written informed consent was obtained from parents before the study. Cases of AES with ages three months to 18 years were included. Age, fever, seizures, decreased consciousness and brain edema were analyzed. Hearing loss was evaluated by using Otoport Automated Auditory Brainstem Response (ABR). Statistical analysis was done by using the Fisher Exact test.
RESULTS: A total of 25 children were enrolled in the study, 60 % male and 52% aged < 12 months. There was a diagnosis of meningoencephalitis in 52% of patients, and hearing loss occurred in 5 patients. Age, fever, seizure, decreased consciousness and brain edema were evaluated as clinical characteristics of hearing loss. Fever > 39°C ($p = 0{,}046$), seizure ≥ 30 minutes ($p = 0{,}038$) and decreased consciousness (Glasgow Coma Scale (GCS) ≤ 8) ($p = 0.002$) were significantly correlated with hearing loss in AES.
CONCLUSION: Fever, seizure and decreased consciousness correlated with hearing loss in children with AES.

KEYWORDS: Acute Encephalitis Syndrome, Children, Consciousness, Disease, Hearing loss, Infection

INTRODUCTION

One of Indonesia's significant health pediatric problems is Acute Encephalitis Syndrome (AES). AES is a set of clinical symptoms and signs of febrile disease accompanied by an acute mental status alteration and new onset of seizures. Several different viruses, bacteria, spirochetes, fungus, parasites, toxins etc could cause it[1,2]. The term could refer to meningitis, encephalitis or meningoencephalitis. AES could occur as epidemics or non-epidemics (sporadic)[3]. The etiology in most encephalitis cases (65%) is unknown[4]. Based on a systematic review of non-epidemic studies conducted in children, they reported a minimum incidence of 10 per 100.000[3]. Surveillance conducted by Ompusunggu S 2008[5] study reported 1.496 AES cases from 15 hospitals in six provinces in Indonesia.

AES may cause neurological complications such as hearing loss[6]. It could be detected immediately after exposure to infection[7]. Sensorineural hearing loss was the most common complication in children with intracranial infection[7,8]. Hearing loss in children associated with AES is a constellation of many risk factors that affect its prognosis.

Several studies demonstrated clinical characteristics that affect hearing loss. Those are age, fever, seizure, decreased consciousness and brain edema in radiologic imaging[9-11]. Those factors remained controversial. A study conducted in three hospitals in Jakarta and Tangerang also reported that the most common clinical findings in children with encephalitis were decreased level of consciousness, fever, seizure, and focal neurological deficit[4]. Some have provided positive results, while others have not.

Nevertheless, up to this date, the number of studies on clinical characteristics for hearing loss in post-AES children is limited. The hearing evaluation was uncommon following AES children; no previous study on clinical characteristics for hearing loss in post AES children were recorded. The study aims to correlate hearing loss and clinical features in children following AES.

METHODOLOGY

This cross-sectional study was conducted at Dr. Soetomo Hospital, Surabaya, Indonesia. Data were collected from pediatric neurology outpatient clinic medical records. The study was conducted from August 2018 to January 2019. Written informed consent was obtained from parents before the study. A case of AES is described as acute onset of febrile disease accompanied by a binding mental status alteration (including confusion, disorientation or coma) and new onset of seizures (excluding simple febrile seizure)[1,2]. Clinical characteristics analyzed were age, fever, seizure, decreased consciousness and brain edema. The patients were excluded if there was a history of head trauma, cyanotic congenital heart disorders, severe intracranial neurological abnormalities, neuromuscular disorders and developmental disorders. All patients in this study were evaluated for hearing function using the Otoport Automated Auditory Brainstem Response (ABR) system connected to the electrode. The result was categorized as refer or pass. Refer mean that the patient could not hear below 60 dB, and it's classified as hearing loss. Pass mean normal hearing.

Fisher Exact test and category SPSS ver. 23.0 (SPSS Inc., Chicago, IL, USA) were used for statistical analysis. Statistical significance was considered at a *P*-value of < 0.05.

RESULTS

Thirty-six patients participated in this study; eleven dropped out (Three patients were not in good condition, and eight refused to perform hearing function evaluation). Twenty-five patients were enrolled in this study (**Table I**). The mean age of the subject was 26.04 ± SD 30.07 months.

Table I: Baseline Characteristics of the Patients

Characteristics	Number
Sex	
Male	15 (60%)
Female	10 (40%)
Age	
3 - ≤ 12 months	12 (48%)
> 12 months	13 (52%)
Residence	
Surabaya	15 (60%)
Outside Surabaya	10 (40%)
Weight (Mean ± SD) (kg)	13.74 ± 9.26
Height (Mean ± SD) (cm)	82.7 ± 19.35
Nutritional Status	
Severe	1 (4%)
Moderate	4 (16%)
Well-nourished	14 (56%)
Overweight/Obese	6 (24%)
Axilla temperature (°C)	
>40	4 (16%)
≤40	21 (84%)
Hemoglobin level (Mean ± SD) (g/dL)	11.85 ± 1.46
White blood cell (Mean ± SD) (µL)	13014.8 ± 4080.35
Cerebrospinal Fluid Culture	
S. epidermidis	3 (3%)
S. hominis	1 (1%)
S.viridans	1 (1%)
E. coli	2 (2%)
Steril	18 (72%)
Diagnosis	
Meningitis	6 (24%)
Encephalitis	7 (28%)
Meningoencephalitis	12 (48%)
Length of stay (Mean ± SD) (day)	12.8 ± 7.38

The results of ABR are shown in five subjects (**Table II**).

Table II: Clinical characteristics of AES patient with ABR result hearing loss

Number	Age (months)	Fever (°C)	Seizure (minutes)	Consciousness (GCS)	Brain edema	Diagnosis
1	14	>39	<30	>8	Yes	Meningitis
2	12	>39	<30	≤8	Yes	Meningitis
3	4	>39	≥30	≤8	Yes	Meningoencephalitis
4	24	>39	≥30	≤8	No	Meningitis
5	15	>39	≥30	≤8	Yes	Meningoencephalitis

The statistical analysis showed that fever, seizure and decreased consciousness were significantly correlated with hearing loss following AES (**Table III**).

Table III: Clinical characteristics correlation between groups

		Hearing Loss (REFER) n = 5		No Hearing Loss (PASS) n = 20		P
		N	%	N	%	
Age (months)	3 - ≤ 12	3	(25)	9	(75)	0.608
	> 12	2	(15.384)	11	(84.616)	
Fever (°C)	> 39	5	(35.714)	9	(64.286)	0.046*
	≤ 39	0	(0)	11	(100)	
Seizure (minute)	≥ 30	3	(60)	2	(40)	0.038*
	< 30	2	(10)	18	(90)	
Decrease of Consciousness	≤ 8	4	(80)	1	(20)	0.002*
	> 8	1	(5)	19	(95)	
Brain edema	Yes	4	(30.769)	7	(63.636)	0.096
	No	1	(7.143)	13	(92.857)	

*p<0.05, statistically significant with Fisher exact test

DISCUSSION

AES can be classified as meningitis, encephalitis, and meningoencephalistis[12]. The etiology of AES varies based on geographical location and season[13]. Various causes, such as viruses, bacteria, parasites or fungi, can cause AES**.** Japanese Encephalitis (JE) is one of AES causes from viral etiology[14,15]. Japanese Encephalitis Virus (JEV) can cause symptomatic or asymptomatic infection infections[16,17]. Organisms that can be caused encephalitis and meningitis some of them are *E.Coli, Group B streptococcus, Streptococcus pneumonia,* and *Neisseria meningitides*[18].

Acute encephalitis is a common cause of mortality and neurodevelopmental problems in children[19]. Furthermore, AES is suspected of causing hearing loss. This study showed remarkable clinical characteristics for hearing loss following AES children. Although studies about the correlation between clinical features of children with AES and hearing loss are minimal, we specify to analyze clinical characteristics that affect hearing loss following AES children.

This study indicates that age is insignificant as a clinical characteristic for hearing loss following AES children. This result supports a study by Karanja BW 2013[10] that shows similar results. Although not related, age is probably a risk factor for hearing loss following AES children because of its closeness to immune immaturity. Immune system immaturity causes pathogens can penetrate the blood-brain barrier when bacteremia occurs. Bacterial surface proteins such as CbpA in *S. pneumonia* an Opc, Opa, and PilC in *N. meningitidis* are responsible for the invasion of the blood-brain barrier[11]. The expansion of meningeal and inflammatory infection from subarachnoid space into the ear through the cochlear duct and internal auditory results in labyrinthitis and organ damage resulting in deafness. Components of bacterial wall stimulate the release of cytokines TNF-c and IL-1 triggering severe inflammation. This process expands from subarachnoid space into the ears through the cochlear duct and internal auditory canal, resulting in labyrinthitis, organ damage, and hearing loss[20,21]. Young children are more susceptible to severe infections due to immune system immaturity and brain development.

Nevertheless, they have higher neurogenesis ability than older children and adults, so they have more ability to regenerate brain tissue[8]. Children over five years old are twice as likely to have persistent symptoms after encephalitis[4]. This theory might explain why young children have fewer neurological complications than older children.

Our study demonstrates that fever has significant clinical characteristics for hearing loss following AES children. It is assumed that fever in AES children is associated with the host response to pathogenic bacteria and its products, such as endotoxin and inflammatory factors that penetrate the blood-brain barrier that triggers inflammatory response[8]. Cell wall lipopolysaccharide from gram-negative and peptidoglycan from gram-positive bacteria trigger an inflammatory response. These substances induce inflammatory mediators production by astrocytes, glia, and endothelial cells such as TNF-α, IL-1, IL-6, IL-8, macrophage induced protein 1 and 2, and other mediators such as nitric oxide, MMP-1 and MMP-2, and prostaglandine[8]. Furthermore, high fever occurs, causing hair cell damage and nerve in inner ear or cochlea, resulting in sensorineural deafness[20,21].

In our finding, seizure for more than 30 minutes has significant clinical factors for hearing loss following AES in children. The precise correlation between seizure and hearing loss in AES children remains unknown. However, a seizure is suspected to be associated with neuronal damage, and thus, it has the exact cause of sensorineural hearing loss. Nerve damage is multifactor causes such as bacterial toxins, cytotoxic products from immune cells and pathological process of intracranial complications[8,10]. Another theory suggests that toxins released by bacteria and inflammatory mediators as the host response to the infection trigger

neuron cell apoptosis. For example, pneumolysin, released by S. pneumonia and MMP, which are inflammatory mediators, cause necrosis of the cerebral cortex. Furthermore, nerve damage causes hearing loss[11,20]. According to Santoso LA 2020[4] study result, risk factors for poor outcomes in patients with acute encephalitis were focal seizure and age > 1 year old. Poor outcome in that study means patients still have severe neurological abnormalities at discharge, such as death, sensory impairment, spasticity, mental retardation, ataxia, blindness, seizures, aphasia, and weakness.

We also identified decreased consciousness (GCS<8) as a significant clinical characteristic for hearing loss following AES in children. Besides damage in the level of neurons, it is also presumed that decreased consciousness is associated with increased intracranial pressure. It results from toxic mediators release and interstitial edema due to changes in blood-brain barrier permeability. In addition, exudates also cause damage to the vestibulocochlear nerve, cochlea, and labyrinth, thus resulting in sensorineural hearing loss. Moreover, lipopolysaccharide from the cell wall is also suspected of causing sterile labyrinthitis, perineuritis, and vestibulocochlear damage[20,21]. Hearing loss following AES children and decreased consciousness probably has the same cause, damage in the neuron level. Low GCS is frequently found in children in the older age group[4].

Although it is suspected that brain edema has a correlation with bacterial toxin and inflammatory mediators release, thus reflecting neuron damage which probable cause hearing loss. In our study, it turns out different results. In some existing literature, it is found that in post-meningitis patients, there is abnormal ossification in the left ear cochlea and cochlea ossification in the left and right ear[22]. In another finding, brain edema is uncommon. It is assumed that brain edema associated with the central nervous system and meninges inflammation causes disturbances in meningeal blood vessels, thus impairing blood flow.

Furthermore, vascular impairment causes mixed cerebral edema, interstitial edema due to cerebral fluid resorption impairment at arachnoid villi and vasogenic edema due to increasing hematomeningeal barrier permeability[23,24]. Despite that pathophysiologic, the direct correlation between brain edema and hearing loss remains unknown. An animal study demonstrated when the brain inflamed during meningitis, it releases pro-inflammatory cytokines such as IL-6 and leukocyte recruiting protein (ICAM). It suggests that pro-inflammatory cytokines cause brain edema and hearing loss due to neuronal damage in pre and post synapse nerve[25].

Our study has limitations that must be considered. It was only evaluated once when the patient attended to pediatric neurology outward clinic. Thus, it can not simultaneously investigate the correlation among those clinical characteristics for hearing loss following AES children. Ideally, the patient should be checked twice, once when admitted to the hospital ward, and the second one when they attended the outward clinic.

CONCLUSION

Fever, seizure, and decreased consciousness were correlated with hearing loss following AES children. Although expected can provide prediction, the direct connection between these three factors and hearing loss incidents is still uncertain. Further animal and clinical studies of risk factors and hearing loss in following AES children should help reveal the direct connection and the most influential risk factors following AES children.

Ethical permission: This study was approved by the Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya number 0399/KEPK/VII/2018.
Conflict of Interest: No conflict of interest.
Financial Disclosure / Grant Approval: No external funding was obtained from any source, and the institute and authors provided all the expenses/resources for the study.

Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Gunawan PI: Concept, design, data collection, analysis, statistics, writing manuscript and editing.
Polanunu MR: Concept, design, data collection, analysis, statistics, and manuscript writing.

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