Brain & Development 41 (2019) 618–624

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Early administration of vitamins B1 and B6 and L-carnitine prevents a second attack of acute encephalopathy with biphasic seizures and late reduced diffusion: A case control study

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Received 18 October 2018; received in revised form 26 February 2019; accepted 27 February 2019

Abstract

Background: Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most prevalent encephalopathy in Japanese children. AESD is characterized by a prolonged febrile seizure on day 1 followed by secondary seizures and MRI abnormality on days 4–6, resulting in high incidence of neurological sequelae. We aimed to clarify whether early administration of vitamins (vitamin B1, vitamin B6, and L-carnitine) would improve the clinical course of AESD.

Methods: We retrospectively reviewed 34 patients with acute encephalopathy who were admitted to our hospital between January 2009 and August 2016. Of the retrospectively registered 34 patients, 22 (65%) since 2011 were treated with the drug cocktail (prescription group) within 24 h of onset, whereas 12 (35%) before 2011 were not (non-prescription group). We compared clinical course, laboratory data, and MRI findings historically in both groups.

Results: The two groups did not differ in terms of laboratory findings except for blood lactate values. There were no differences between the two groups regarding duration of ICU admission, intubation, or the duration of seizures. Among the prescription group, two patients developed AESD while 20 had mild encephalopathy (single phasic). In contrast, seven patients in the non-prescription group developed AESD while five did not. The incidence of AESD was lower in the prescription group ($P = 0.004$). As for outcomes, the rate of developmental delay and epilepsy was significantly lower in the prescription group.

Conclusions: Our data suggested that early administration of vitamins would improve the clinical course of acute encephalopathy. Mitochondrial rescue and neuroprotection are thought to be responsible for the favorable results.

Keywords: Acute encephalopathy; AESD; Vitamin B1; Vitamin B6; L-Carnitine; Second attack

Abbreviations: ADEM, acute disseminated encephalomyelitis; AERRPS, acute encephalitis with refractory, repetitive partial seizures; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ANE, acute necrotizing encephalopathy; BTA, bright tree appearance; CPT-II, carnitine palmitoyl transferase II; GABA, gamma-aminobutyric acid; HSES, hemorrhagic shock and encephalopathy syndrome; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERS, mild encephalopathy with a reversible splenial lesion

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https://doi.org/10.1016/j.braindev.2019.02.015

1. Introduction

Acute encephalopathy is a breakdown of brain function usually following an infection in the absence of a direct inflammatory process in brain parenchyma, resulting in prolonged consciousness disturbance and/or seizures [1]. Acute encephalopathy has been reported worldwide, but occurs mainly in East Asia [1,2]. It has been reported that there were approximately one thousand cases of childhood viral encephalopathy in Japan during the three years 2007–2010 [2].

Although some genetic role is speculated, the precise pathological mechanism still remains unknown. Although acute encephalopathy is basically a heterogeneous syndrome involving variations in pathogens, clinical course, and brain image abnormalities, recent advances in brain imaging technology have enabled syndromic subdivision of encephalopathy. Some subdivisions have been established as a specific clinico-radiological encephalopathic syndrome, such as acute necrotizing encephalopathy, acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), and mild encephalopathy with a reversible splenial lesion [2]. Although nearly half of patients with acute encephalopathy still remain unclassified, these three syndromic subdivisions have clinical significance for acute phase treatment. Of these three syndromes, AESD is the most frequent syndrome and the prognosis of AESD is characterized by low fatality and a high incidence of neurological sequelae [2].

AESD is diagnosed with the following criteria: onset with seizures within about 24 h from the onset of fever (first attack), subsequent and transient improvement in consciousness and later occurrence of secondary seizures (second attack) on days 3–9 associated with MRI abnormality [3]. This MRI abnormality (reduction of diffusion coefficient in frontal or frontoparietal white matter) is one of the hallmarks of AESD diagnosis and is known as "bright tree appearance" (BTA) (Fig. 1). BTA is not observed in the early stage from onset, but it appears after 3–9 days. There is no earlier biomarker for the diagnosis. It is a major problem that early diagnosis of AESD at the stage of first attack is difficult.

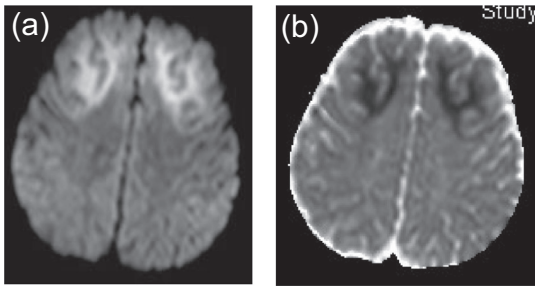

Fig. 1. Typical bright tree appearance with frontal predominance is shown in a patient with AESD. Shown here are (a) diffusion weighted imaging (DWI) and (b) apparent diffusion coefficient (ADC). Abnormal hyperintensity in DWI associated with a decreased ADC suggested cytotoxic edema.

The current treatment for AESD is mainly empirical supportive therapy with poor supportive evidence; it includes immunosuppression, anti-oxidative therapy, and hypothermia therapy, as well as systemic management and seizure control [1]. There was no solid evidence for the efficacy of treatments for AESD [1]. A preliminary study of the beneficial effect of early vitamin B6 (administration within 3–36 h after early seizure) for AESD was reported in 2009 [4]. In this report, Ishii et al. [4] found that the cases with administration of vitamin B6 showed a better clinical course (reduced rate of late seizures) than cases without administration. Being inspired by the report, we have started to try early vitamin B1, vitamin B6, and L-carnitine from 2011 aimed at mitochondrial rescue and excitotoxicity relief for patients with acute encephalopathy.

The present study aims to examine the role that early administration of vitamin B1, vitamin B6, and L-carnitine plays in preventing a second attack in the biphasic course of AESD.

2. Methods

We defined acute encephalopathy based on criteria that were reported [1] as follows: acute onset of severe and sustained impairment of consciousness mostly following an infection. Characteristic clinical features include altered mental status that continued over 24 h (Japan coma scale, over 20; Glasgow coma scale, under 10 or 11), and seizures or focal neurologic signs. In addition to these core features of acute encephalopathy, AESD was diagnosed with the criteria described above in the Introduction.

First, we retrospectively reviewed the clinical course of patients with acute encephalopathy between January 2009 and August 2016. Historically, early administration of vitamin B1, vitamin B6, and L-carnitine for all patients with acute encephalopathy started in 2011. The exclusion criteria included cases with underlying diseases, central nervous system inflammation, brain images nonspecific for AESD, and an interval longer than 24 h between the onset of disease and hospital admission. The exclusion criteria were adopted to examine the early effects of vitamin B1, vitamin B6, and L-carnitine in homogeneous groups without neurological abnormalities before onset.

There were 118 patients with acute encephalopathy as an initial diagnosis who were admitted or transferred from regional hospitals (Fig. 2). Of the 118 patients, 62 cases with abnormal MRI findings other than BTA typical for AESD on brain MRI were excluded, for example, AERRPS (acute encephalitis with refractory, repetitive partial seizures), MELAS (mitochondrial

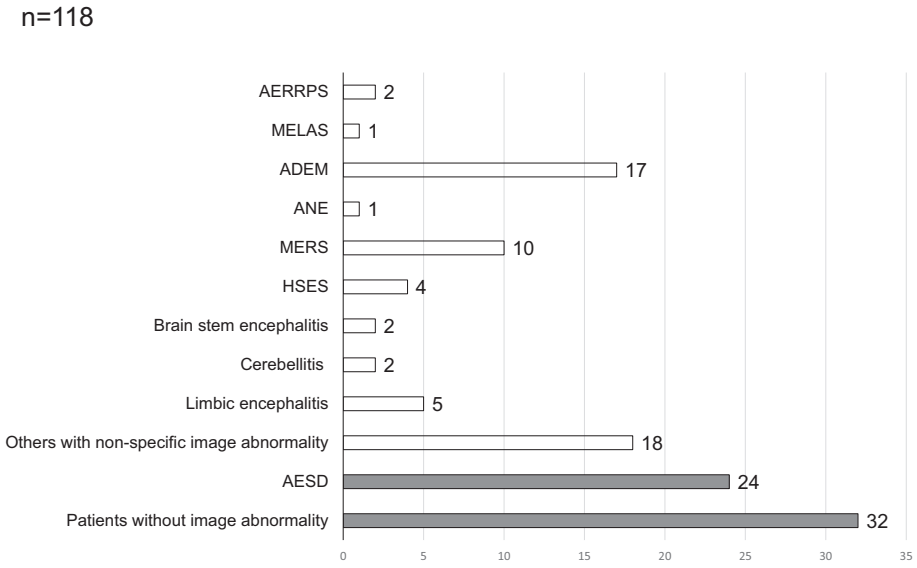

Fig. 2. Diagnostic classification of 118 cases with acute encephalopathy. Of the 118 patients, 62 cases (white bars) had abnormal MRI findings other than bright tree appearance (BTA) typical for AESD. The category "Others with non-specific image abnormality (white bar labeled '18 patients')" indicates those patients not belonging to a specific encephalopathy syndrome. Abbreviations: AERRPS, acute encephalitis with refractory repetitive partial seizures; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; ADEM, acute disseminated encephalomyelitis; ANE, acute necrotizing encephalopathy; MERS, mild encephalopathy with a reversible splenial lesion; HSES, hemorrhagic shock and encephalopathy syndrome; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion.

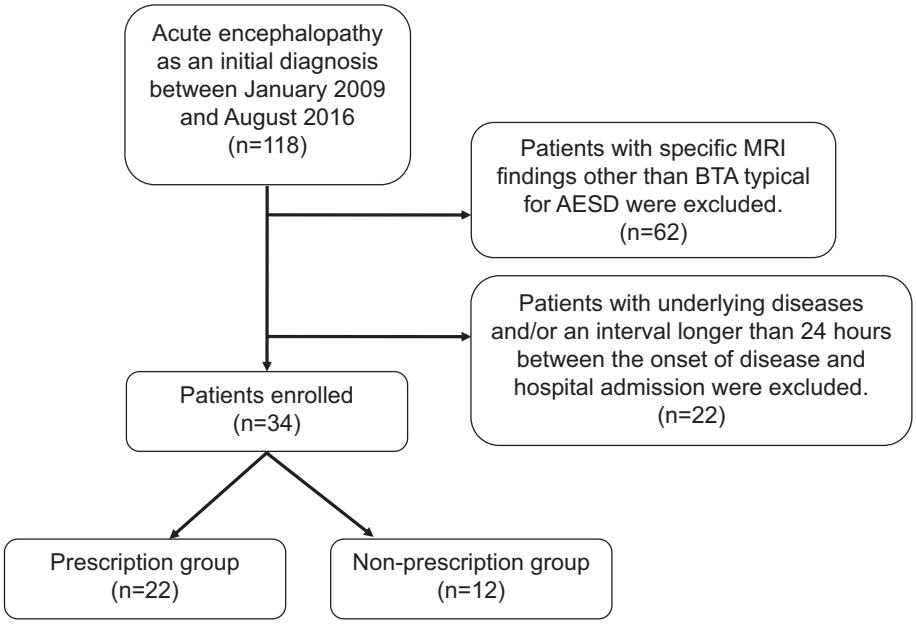

Fig. 3. Thirty-four enrolled patients and exclusion criteria. The prescription group was administered vitamins B1 and B6 and L-carnitine within 24 h of onset and the non-prescription group was not.

encephalopathy, lactic acidosis, and stroke-like episodes), and ADEM (acute disseminated encephalomyelitis) (Fig. 3). Of the remaining 56 patients, we further excluded 22 cases with underlying diseases and/or an interval longer than 24 h between the onset of disease and hospital admission (Fig. 3). As a result, 34 patients were enrolled in the present retrospective study.

Of 34 patients with acute encephalopathy, 22 (65%) were treated with vitamin B1, vitamin B6, and L-carnitine (prescription group) within 24 h of onset, whereas 12 (35%) were not (non-prescription group)

(Fig. 3). Because vitamin treatment started in 2011, we could compare both groups historically. We administered vitamin B1 (100 mg/day), vitamin B6 (20 mg/kg/day), and L-carnitine (30 mg/kg/day) within 24 h from the onset for a duration of 10 days.

Age, sex, pathogens, laboratory data, clinical forms, treatments, and sequelae (developmental delay and epilepsy) were retrospectively reviewed using medical records. Regarding developmental delay, 32 patients were classified into two groups, namely, the developmental delay group having obvious decline in motor function or intelligence and the non-developmental delay group without neurological deficit at the final follow-up. The incidence of epilepsy was also compared in the two groups. We were not able to follow up two (one in each group) out of 34 patients regarding developmental delay and epilepsy in a long-term course.

The study protocol was approved by the institutional ethics committee of the National Center for Child Health and Development on March 9, 2017 (examination number 1414).

2.1. Statistical methods

For statistical analysis, we used the Fisher's exact test to compare the results of the duration of ICU admission, intubation, the number of seizures, and prevention of AESD between the prescription group and non-prescription group. The Mann-Whitney *U* test was applied to the proportions of categorical variables (such as age), and laboratory data between the groups. Significant differences were defined as $P < 0.05$ in the conditional analysis. All statistical analysis was conducted using Microsoft Excel® (version 2016).

3. Results

In the prescription group (n = 22), patient age ranged from 0 to 35 months (median 8 months), and in the non-prescription group (n = 12), patient age ranged from 11 to 27 months (median 20.5 months). Sex ratio between the two groups was not significant.

A shown in Fig. 4, the trigger pathogens in both groups were diverse and no specific trend was observed. These were comparable with the results of a nation-wide epidemiological survey of acute encephalopathy in Japan [2].

The two groups did not differ significantly in terms of the laboratory findings (aspartate amino transferase, alanine amino transferase, creatine kinase, blood urea nitrogen, creatinine), except for the blood lactate values, as shown in Table 1. There were no significant differences between the two groups regarding ICU admission, intubation, or the duration of seizures (Table 2). Both groups equally received edaravone and glucocorticoid pulse therapy in the same regimen, which is regarded as empirically effective for acute encephalopathy [1,5,6].

Concerning the outcome, among the prescription group two patients developed AESD while 20 had mild encephalopathy (single phasic). In contrast, seven patients in the non-prescription group developed AESD while five did not. Thus, the rate of AESD was significantly lower in the prescription group ($P = 0.004$) (Fig. 5). As for outcomes, in the prescription group only one of 21 patients had developmental delay, whereas in the non-prescription group four out of 11 patients had developmental delay. The rate of developmental delay was significantly lower in the prescription group ($P = 0.037$) (Table 2). In the prescription group, one of 21 patients developed epilepsy, whereas in the non-prescription group, five of 11 patients developed epilepsy. The rate of epilepsy was significantly lower in the prescription group ($P = 0.011$) (Table 2). The range of follow-up periods and the most recent follow-up age are shown in Table 2.

4. Discussion

The most important finding of the present study is that early administration of vitamins B1 and B6 and L-carnitine could prevent a second attack of AESD, leading to milder clinical manifestations and better outcomes.

Although the pathological mechanism of acute encephalopathy is not clearly known, three basic mechanisms were suggested [1], that is, (1) metabolic derangement associated with mitochondrial energy failure, (2) a systemic cytokine storm and vasogenic brain edema, and (3) excitotoxicity and delayed (apoptotic) neuronal death [7]. The three pathological conditions are interrelated, and the relative contributions of each mechanism differ in each syndrome. High levels of glutamate accumulating in the intercellular space may cause neuronal cell damage, e.g., during prolonged seizures, ischemia, trauma, or neurodegeneration by an unknown mechanism [8,9]. This condition is referred to as excitotoxicity. Excitotoxic neuronal damage is predicted to play an important role in the pathogenesis of AESD because proton MR spectroscopy showed that the glutamine/glutamate complex was elevated during the acute phase of AESD [7]. A growing imbalance of excessive glutamate-driven excitation and reduced gamma-aminobutyric acid (GABA)-mediated inhibition might cause glial swelling and the resulting brain edema observed in AESD [7]. Vitamin B6 acts as a coenzyme of glutamate decarboxylase and activates the transformation of glutamate into GABA, leading to reduced excitotoxity. Vitamin B6 as used in our study probably had a neuroprotective effect against excitotoxity.

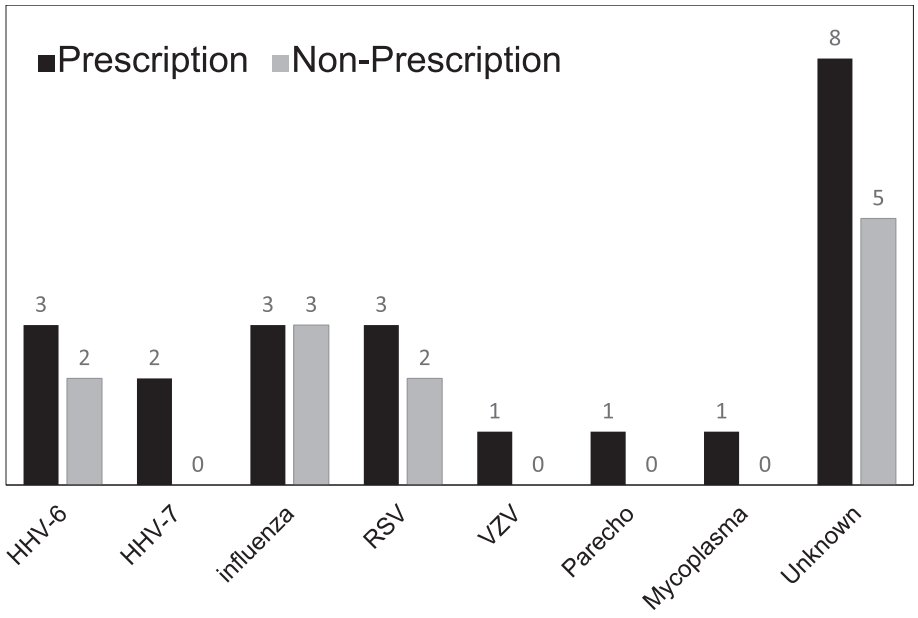

Fig. 4. Pathogens associated with acute encephalopathy in the prescription and non-prescription groups.

Table 1
Comparison of laboratory data between the prescription and non-prescription groups.

	Prescription (n = 22)		Non-Prescription (n = 12)		
Parameter	Median	Range	Median	Range	*P*
Aspartate amino transferase (U/L)	45.5	(25–4887)	53.5	(24–261)	0.678
Alanine amino transferase (U/L)	20.5	(9–3915)	23	(10–94)	0.471
Creatine kinase (U/L)	149.5	(50–4917)	194	(60–5610)	0.665
Blood urea nitrogen (mg/dL)	11.7	(4.0–31.8)	11.1	(6.4–19.2)	0.885
Creatinine (mg/dL)	0.3	(0.19–0.89)	0.3	(0.18–0.58)	0.540
Lactate (mmol/L)	2.5	(0.7–16.0)	1.3	(0.8–4.0)	0.020*

* Indicates statistical significance.

Table 2
Comparison of treatments and outcomes between the prescription and non-prescription groups.

	Prescription (n = 22)		Non-prescription (n = 12)		*P*
Age at onset, median months (range)	8	(0–35)	21	(11–27)	0.009*
Male, *n* (%)	15/22	(68)	8/12	(67)	0.928
Observation period, median days (range)	549	(4–1987)	1217	(38–3114)	0.023*
Final observed age, median years (range)	4.5	(2–11)	7.0	(2–11)	0.106
ICU admission, *n* (%)	21/22	(95)	11/12	(92)	0.588
Intubation, *n* (%)	16/22	(73)	10/12	(83)	0.402
Seizure >30 min, *n* (%)	20/22	(91)	9/12	(75)	0.225
Developmental delay, *n* (%)	1/21	(5)	4/11	(36)	0.037*
Epilepsy, *n* (%)	1/21	(5)	5/11	(45)	0.011*

* Indicates statistical significance.

Vitamin B1 is an important cofactor that is necessary to maintain the functional integrity of cells in the brain. It is involved in processes associated with the metabolism of lipids, glucose, amino acids, and neurotransmitters [10]. The active form of vitamin B1 is required for the proper functioning of major enzyme systems in mitochondria and elsewhere [11]. Vitamin B1 as used in our study probably had a mitochondrial rescue function.

L-carnitine plays an important regulatory role in the transport of long-chain free fatty acids in mitochondria and it also has anti-oxidative activity [12]. L-carnitine as used in our study might have reduced nerve damage as a

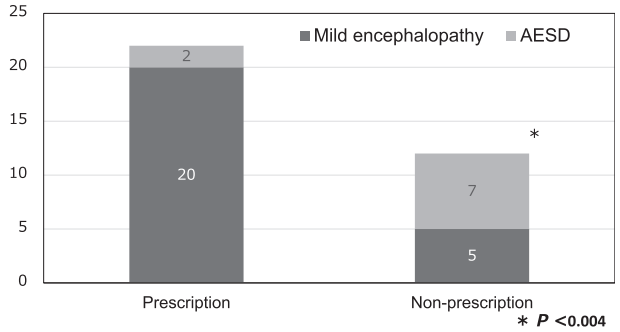

Fig. 5. Comparison of AESD between the prescription and non-prescription groups. The rate of AESD was significantly lower in the prescription group.

mitochondrial rescue agent and through antioxidant action [13].

Recent studies suggested that secondary mitochondrial dysfunction is related to the pathological mechanism of various types of acute encephalopathy with the thermolabile phenotype of carnitine palmitoyl transferase II (CPT II) variation, particularly in Japan [14,15]. This thermolabile variant causes mitochondrial ATP utilization failure during periods of high fever. The ATP demand is so high in infants that a thermolabile CPT II variant-induced ATP reduction might lead to susceptibility to encephalopathy in children [14]. CPT II is an enzyme localized on the mitochondrial inner membrane that removes fatty acids from carnitine. In this situation, vitamin B1 and L-carnitine can be a treatment for metabolic disorders related with CPT II. The real CPT II deficiency and thermolabile CPT II variants associated with encephalopathy are different entities, but there is also a common basic mechanism for both entities. The L-carnitine administration for CPT II deficiency is also listed in the guidelines of the Japanese Society for Inherited Metabolic Diseases [16].

The thermolabile CPT II variant F352C is one of the predisposing factors for acute encephalopathy in Japan, although acute encephalopathy develops with various factors involved. We cannot easily clarify the carnitine level in emergency situations on the day of onset. Considering the various effects of carnitine and its lack of side effects, we believe its administration to be worthwhile.

Of the various trigger pathogens, HHV-6 was the most common pathogen in AESD, followed by influenza virus [2]. Because there was no significant difference between both groups in our study as to herpes viruses including HHV-6, HHV-7, and VZV (the prescription group: 6/22; the non-prescription group: 2/12; $P = 0.69$), we believe this does not significantly affect the therapeutic effect or outcome. Regarding other pathogens, because the number of patients was so small, we could not draw any definite and reliable conclusions.

The blood lactate value at admission was higher in the prescription group than in the non-prescription group. The precise etiology of the difference in blood lactate in both groups could not be clarified from our own data. Although blood lactate concentrations are affected by several factors, we presumed that the lactate elevation in our patients, especially in the prescription group, might be ascribed to prolonged seizure with high fever at onset (the possibility of secondary mitochondrial dysfunction). Seizures, regardless of their origin, represent excessive rapid energy demand in the brain, leading to secondary mitochondrial dysfunction. Because the mean age of the prescription group (8 months) was younger than that of the non-prescription group (21 months), we can speculate that the seizure burden severely affected the younger group (prescription group), resulting in lactate elevation, although seizure duration in both groups did not differ. An important noteworthy point here is that this younger group received vitamin B1, vitamin B6, and L-carnitine therapy and that this therapy might have prevented the second seizure episode. We believe that seizure susceptibility was lowered in the prescription group, and that the outcome was improved. On the other hand, in the non-prescription group, although the seizure burden was not large (that is, not severe as reflected in blood lactate level), the susceptibility to seizure remained high and the second seizure occurred.

Omata et al. [17] reported that early treatment within 24 h with vitamin B1, vitamin C, biotin, vitamin E, coenzyme Q_{10}, and L-carnitine (a mitochondrial drug cocktail) was effective as a mitochondrial rescue and antioxidant therapy. They reported that there was no significant difference in AESD incidence between the treated and untreated groups. However, they found that the outcomes were significantly better in the early treatment group. Their treatment protocol did not include vitamin B6. Vitamin B6 has the function of reducing excitotoxicity, which is believed to cause the neuronal damage of AESD. Taken together, it is possible that the use of vitamin B6 contributed most to the decrease in the incidence of AESD in our study.

Ishii et al. [6] reported in a preliminary study about the beneficial effect of early vitamin B6 administration (within 3–36 h after early seizures) for AESD in 2009. They found that the cases with administration of vitamin B6 showed a better clinical course (reduced rate of late seizures) than cases without administration, despite the fact that all cases had subcortical white matter lesions on MRI. Compared to vitamin B6 dose (20 mg/kg/day) in our protocol, their dose of vitamin B6 was low (1.0–1.5 mg/kg/day). If a larger dose of vitamin B6 is administered early, lesions on MRI might be prevented, as in our cases.

Our study has several limitations. It is a retrospective analysis and the number of patients was small. It is a

single-center study specific to our population and possibly not generalizable to other cases. Different ages of both groups and different observation periods can reflect selection bias. There is no significant difference for the other items. Additional research is needed to determine whether the treatment is suitable in multiple centers and it is necessary to accumulate a group of patients with similar ages and observation periods.

5. Conclusions

Our data suggested that early administration of vitamin B1, vitamin B6, and L-carnitine prevented a second AESD attack and resulted in a milder clinical course. The vitamin B1, vitamin B6, and L-carnitine combination might function in mitochondrial rescue and neuroprotection, leading to a more favorable outcome.

Acknowledgements

We wish to thank the medical editors from the Division of Education for Clinical Research at NCCHD for editing this manuscript. This study was supported by NCCHD 30-32 awarded to K.O.

References

[1] Mizuguchi M, Yamanouchi H, Ichiyama T, Shiomi M. Acute encephalopathy associated with influenza and other viral infections. Acta Neurol Scand Suppl 2007;186:45–56.
[2] Hoshino A, Saitoh M, Oka A, Okumura A, Kubota M, Saito Y, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. Brain Dev 2012;34:337–43.
[3] Takanashi J, Oba H, Barkovich AJ, Tada H, Tanabe Y, Yamanouchi H, et al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 2006;66:1304–9.
[4] Ishii C, Noda M, Oda A, Ishikawa R, Oba K, Narui K, et al. Trial administration of pyridoxal phosphate to 9 AEFCSE cases. J Jpn Soc Emerg Pediatr 2009;8:35–41.
[5] Okumura A, Mizuguchi M, Kidokoro H, Tanaka M, Abe S, Hosoya M, et al. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev 2009;31:221–7.
[6] Takanashi J, Taneichi H, Misaki T, Yahata Y, Okumura A, Ishida Y, et al. Clinical and radiologic features of encephalopathy during 2011 E coli O111 outbreak in Japan. Neurology 2014;82:564–72.
[7] Takanashi J, Tada H, Terada H, Barkovich AJ. Excitotoxicity in acute encephalopathy with biphasic seizures and late reduced diffusion. AJNR Am J Neuroradiol 2009;30:132–5.
[8] Arundine M, Tymianski M. Molecular mechanisms of calcium-dependent neurodegeneration in excitotoxicity. Cell Calcium 2003;34:325–37.
[9] Guerriero RM, Giza CC, Rotenberg A. Glutamate and GABA imbalance following traumatic brain injury. Curr Neurol Neurosci Rep 2015;15:27. https://doi.org/10.1007/s11910-015-0545-1.
[10] Abdou E, Hazell AS. Thiamine deficiency: an update of pathophysiologic mechanisms and future therapeutic considerations. Neurochem Res 2015;40:353–61.
[11] Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. Chem Biol Interact 2006;163:94–112.
[12] Glatstein M, Bonifacio Rino P, de Pinho S, Scolnik D, Pivko-Levi D, Hoyte C. Levocarnitine for the treatment of valproic acid-induced hyperammonemic encephalopathy in children: the experience of large, tertiary care pediatric hospital and a Poison center. Am J Ther 2017. https://doi.org/10.1097/MJT.0000000000000706.
[13] Silva-Adaya D, Perez-De La Cruz V, Herrera-Mundo MN, Mendoza-Macedo K, Villeda-Hernandez J, Binienda Z, et al. Excitotoxic damage, disrupted energy metabolism, and oxidative stress in the rat brain: antioxidant and neuroprotective effects of L-carnitine. J Neurochem 2008;105:677–89.
[14] Kubota M, Chida J, Hoshino H, Ozawa H, Koide A, Kashii H, et al. Thermolabile CPT II variants and low blood ATP levels are closely related to severity of acute encephalopathy in Japanese children. Brain Dev 2012;34:20–7.
[15] Shinohara M, Saitoh M, Takanashi J, Yamanouchi H, Kubota M, Goto T, et al. Carnitine palmitoyl transferase II polymorphism is associated with multiple syndromes of acute encephalopathy with various infectious diseases. Brain Dev 2011;33:512–7.
[16] The Japanese Society for Inherited Metabolic Diseases, supervising editor. Newborn mass screening disease practice guidelines 2015. Shindan To Chiryo Sha, Tokyo, 2015; p. 164–73 (in Japanese)
[17] Omata T, Fujii K, Takanashi J, Murayama K, Takayanagi M, Muta K, et al. Drugs indicated for mitochondrial dysfunction as treatments for acute encephalopathy with onset of febrile convulsive status epileptics. J Neurol Sci 2016;360:57–60.