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Original Article

A study of oxidative stress and the newer antiepileptic drugs in epilepsy associated with severe motor and intellectual disabilities

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Abstract

Background: Patients with severe motor and intellectual disabilities (SMID) are those who have both severe intellectual disabilities and severe physical disabilities. Intractable epilepsy is often associated with SMID. The purpose of this study was to elucidate the relationship between epilepsy associated with SMID and oxidative stress, and to clarify the safety and efficacy of the newer antiepileptic drugs (newer AEDs), lamotrigine and levetiracetam.

Methods: This study was conducted in 27 SMID patients with epilepsy who were treated with the newer AEDs. The patient characteristics and the safety and efficacy of the newer AEDs were investigated. The reactive oxygen metabolite (d-ROM) and biological antioxidant potential (BAP) levels were measured as indicators of the degree of oxidative stress. The relationship between the investigation results (the patient characteristics, and the safety and efficacy of the newer AEDs) and the results of measurements of the d-ROMs/BAP were analyzed.

Results: All the patients who discontinued the newer AEDs had abnormal plasma d-ROM levels. In addition, all the patients who developed adverse events also had abnormal d-ROM levels. Furthermore, there was a trend toward a lower response rate in patients with higher plasma d-ROM levels.

Conclusion: The results of this study suggested that d-ROM levels are useful for predicting the safety and efficacy of the newer AEDs (lamotrigine, levetiracetam) in SMID patients with intractable epilepsy. Therefore, d-ROMs could be important biomarkers for determining the safety and efficacy of drug therapy in SMID patients with epilepsy.

Keywords: antiepileptic drugs; children with disabilities; epilepsy; oxidative stress

1. Introduction

The disease entity of severe motor and intellectual disabilities (SMID) is characterized by the presence of both severe intellectual disabilities and severe physical disabilities, and the concept of SMID is similar to the globally recognized concepts of "profound intellectual and multiple disabilities" (PIMD)[1] and "profound and multiple learning disabilities" (PMLD).[2]

There are an estimated 40,000−50,000 SMID patients in Japan.[3] SMID is a condition in which the central nervous system is damaged during the developmental stages in the perinatal period and infancy, and the primary disease or symptoms do not bate with age. In a previous study, we demonstrated a statistically significant association between SMID and epilepsy, which suggests that epilepsy is one of the characteristic manifestations of SMID.[4] Although the older antiepileptic drugs (older AEDs) have long been used in drug therapy for epilepsy in Japan, newer antiepileptic drugs (newer

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AEDs) have received approval and been introduced in the market one after another since 2006. However, there have been few reports exclusively addressing the efficacy of these drugs against epilepsy associated with SMID. Furthermore, although Tanuma et al[5] conducted an investigation on the relationship of SMID with respiratory disturbance and oxidative stress based on measurement of plasma 8-hydroxy-2′-deoxy-guanosine (8-OHdG), there are no reports of studies on the relationship between epilepsy associated with SMID and oxidative stress. Therefore, we conducted this study to clarify the usefulness and safety of the newer AEDs for epilepsy in patients with SMID using oxidative stress markers, namely, the oxidative stress [plasma levels of reactive oxygen metabolites (d-ROMs)] and antioxidant activity [biological antioxidant potential (BAP)] levels.

Table 1
Background of patients ($n = 27$).

Sex	Male	20 (70.8)
	Female	7 (29.2)
Age (y)	Average ± SD	27.0 ± 7.3
	Maximum	39
	Minimum	10
	Median	27.0
Main disease	Cerebral palsy	12 (44.4)
	Hypoxia encephalopathic aftereffects	3 (11.1)
	Epileptic encephalopathy aftereffects	3 (11.1)
	Cerebral hemorrhage aftereffects	2 (7.4)
	Lissencephaly	2 (7.4)
	CFC syndrome	1 (3.7)
	Acute encephalopathic aftereffects	1 (3.7)
	Theophylline encephalopathic aftereffects	1 (3.7)
	Meningitis aftereffects	1 (3.7)
	Dentatorubral-pallidoluysian atrophy	1 (3.7)
Renal damage	Available	0
	None	27
Liver damage	Available	0
	None	27
Comorbidities[a]	Available	0
	None	27
The number of use AEDs	1 agent	0 (0.0)
	2 agents	1 (3.7)
	3 agents	12 (44.4)
	4 agents	12 (44.4)
	5 agents ≤	2 (7.4)
Use of old AEDs[b]	Valproate sodium (VPA)	21 (32.3)
	Phenobarbital (PB)	8 (12.3)
	Zonisamide (ZNS)	8 (12.3)
	Phenytoin (PHT)	6 (9.2)
	Clonazepam (CZP)	6 (9.2)
	Carbamazepine (CBZ)	5 (7.7)
	Clobazam (CLB)	4 (6.2)
	Ethosuximide (ESM)	3 (4.6)
	Nitrazepam (NZP)	2 (3.1)
	Clorazepete dipotassium	1 (1.5)
	Acetazolamide	1 (1.5)

Data are presented as *n* or *n* (%).
AEDs = antiepileptic drugs; CFC = cardio-facio-cutaneous; SD = standard deviation.
[a] Hypertension, diabetes, hyperlipidemia, kidney disease, infectious disease.
[b] There is overlap in a value ($n = 65$).

2. Methods

2.1. Patients

Among the SMID patients who were hospitalized and treated at the Japanese Red Cross Tokushima Hinomine Rehabilitation Center for People with Disabilities, Tokushima, Japan between January 1, 2009 and December 31, 2015, 27 who manifested epilepsy and had been initiated on treatment with the newer AEDs were included in this study. After obtaining consent from the parents for this clinical study, random samples were collected from these patients.

2.2. Drugs evaluated

Two drugs, lamotrigine (LTG) and levetiracetam (LEV),[6,7] which are AEDs that received approval for use in Japan in and after 2006 and are highly recommended worldwide, were evaluated as the newer AEDs. AEDs that had received approval for clinical use prior to 2006 were defined as the older AEDs.

2.3. Items investigated

Medical records were investigated to collect the following characteristics of the patients: sex, age, primary disease, having organ disorder, and the number and types of used AEDs.

Table 2
Continuation rate and safety of LTG and LEV.

Drug continuation rate	LTG	LEV
No. of cases	11	16
Withdrawal No. of cases	2 (18.2)	3 (18.8)
(Withdrawal reason)		
Safety (adverse event)		
Drug rash	1 (9.1)	0
Mood change/edema	0	1 (6.3)
Exacerbation of the seizure	0	1 (6.3)
Efficacy		
Seizure No. of times immutability	1 (9.1)	1 (6.3)
Adverse event[a]	**LTG**	**LEV**
No. of cases of the adverse event expression	2 (18.2)	4 (25.0)
No. of cases of the adverse event expression	2 (18.2)	5 (31.2)
(total) (Contents of adverse events)		
Psychiatric disorders		
Mood change	0	1 (6.3)
Nervous system disorders		
Exacerbation of the seizure	0	1 (6.3)
Somnolence	1 (9.1)	2 (12.5)
Skin & subcutaneous tissue disorders		
Drug rash	1 (9.1)	2 (12.5)
General disorders and administration site conditions		
Edema	0	1 (6.3)

Data are presented as *n* or *n* (%).
LEV = levetiracetam; LTG = lamotrigine.
[a] Withdrawal number of cases by adverse event: LTG 1 (9.1%), LEV 2 (12.5%).

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