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Epilepsy Properties and Seizure Suppression in a Severe Motor and Intellectual Disabilities

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Abstract

***Purpose*: In hospitalized patients with severe motor and intellectual disabilities (SMID), we analyzed the association of the SMID class to factors such as the prevalence of epilepsy, frequency of seizures and number of concomitantly used anti-epileptic drugs (AEDs), and evaluated the usefulness of addition of the new AEDs (gabapentin, topiramate, lamotrigine and levetiracetam) to the treatment regimen. *Results*: The prevalence of epilepsy in the study population was about 60%. There were 39.5% who were free of epileptic seizures during the 6-year survey period and remained well-controlled with medication. As the SMID increased in severity, the frequency of seizures increased, the number of concomitantly used AEDs increased, and the tendency towards addition of new AEDs became more marked. About the use situation of new AED and old AED, this comparison revealed a tendency towards addition of a new AED when the seizures were poorly controlled in response to concomitant use of multiple old AEDs. The frequency of seizures and the number of concomitantly used AEDs were higher in patients with SMID of high severity than in those with SMID of low severity. Analysis of the time-course of the frequency of seizures before and after the addition of new AEDs revealed a significant reduction in the frequency of seizures following the addition of the new AEDs ($P > 0.001$). *Conclusions*: These results suggest that the new AEDs are useful in the management of SMID-associated epilepsy, because of their effect of reducing the frequency of SMID-associated seizures and their high tolerability.**

Keywords

Severe Motor and Intellectual Disabilities (SMID), Epilepsy, Anti-Epileptic Drugs (AEDs)

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1. Introduction

The concept of "Severe Motor and Intellectual Disabilities" (hereinafter called "SMID") resembles the global concept of "Profound Intellectual and Multiple Disabilities" ("PIMD") [1] and "Profound and Multiple Learning Disabilities" ("PMLD") [2]. SMID is "patient having severe mental disabilities and severe limbs disorder".

The number of patients with SMID in Japan is estimated to be about 40,000 - 50,000 [3]. SMID is caused by damage to the central nervous system (CNS) during the perinatal period or the growth period (infancy/early childhood), and the symptoms of SMID do not alleviate or disappear with age. Among the diverse clinical symptoms of SMID, CNS disorder-related paralysis or deformation, hypertonia, gastroesophageal reflux (GER) and respiratory failure are the most frequent. Aspiration pneumonia (arising from dysphagia), outbreak of infection (during prolonged hospital stay with other patients), etc. are secondary problems. In addition, a high rate of complication by epilepsy and the frequently intractable nature of epilepsy have also been pointed out [4], although the details remain to be clarified.

Until now, few large-scale epidemiological studies or other studies have been conducted on SMID in either Japan or overseas, and there are no reports of evidence-based medicine (EBM) for this condition [5].

We previously found a statistically significant association between the presence of SMID and the risk of epilepsy [6]. The present study was focused on investigation of the current status of epilepsy in SMID patients. The study was designed as a cross-sectional epidemiological study, involving statistical analysis of data, for the purpose of identifying 1) the features of SMID-associated epilepsy and 2) drug therapy for epilepsy beneficial in the management of SMID patients.

2. Methods

2.1. Patients Studied

Of the 115 patients with SMID admitted for a prolonged period (6 years) to the Japanese Red Cross Tokushima Hinomine Rehabilitation Center for People with Disabilities between January 1, 2010 and December 31, 2015, 81 patients (70.4%) receiving oral treatment with anti-epileptic drugs (AEDs) were enrolled in this study. Patients who had sustained damage at age 18 or over were not counted as cases of SMID and were excluded from this study. Patients with SMID who were admitted to the hospital during the study period but did not receive continued inpatient care were also excluded from the study.

2.2. Definition

Four AEDs approved in Japan in and after 2006, *i.e.* gabapentin (Sep. 2006), topiramate (Sep. 2007), lamotrigine (Dec. 2008) and levetiracetam (Sep. 2010), were classified as new AEDs, and the AEDs approved before that year were deemed as old AEDs [7].

Disability classification (rating of severity, with both intellectual and motor functions taken into account) used the Yokochi classification shown in (**Table 1**). Cases rated as A1-A3, B1-B3 and C1-C3 were counted as cases with SMID of high severity [8]. On the other hand, other SMID was classified as mild SMID of low severity.

2.3. Background of the Patients

The information on the following background variables of the patients was obtained from the medical records.

1) Basic information (age, sex, primary disease); 2) disability classification (Yokochi classification [9]); 3) epilepsy classification (classification of epilepsy, epilepsy syndrome and related paroxysmal disease (ILAE 1989)); 4) type of epileptic seizure (international classification of epileptic seizure (ILAE1981)); 5) frequency of epileptic seizure; 6) type and status of use of anti-epileptic drugs (AEDs). On variables which change with time, the values from the final measurements were adopted for the analysis.

2.4. Statistical Analysis

Statistical analysis was conducted on the survey data (primarily pertaining to SMID-associated epilepsy), including the data on "disability classification (Yokochi classification)", "number of concomitantly used AEDs",

Table 1. Yokochi classification (disability classification).

						<Intellectual development>
E6	E5	E4	E3	E2	E1	Do basic arithmetic
D6	D5	D4	D3	D2	D1	Read simple letters and figures
C6	C5	C4	C3	C2	C1	Understand simple colors and numbers
B6	B5	B4	B3	B2	B1	Understand simple words
A6	A5	A4	A3	A2	A1	No understanding words
Walk outdoor	Walk indoor	Locomote indoor	Sit	Roll over	No rolling	
		<Locomotion>				

"status of AED use" and "frequency of epileptic seizure". Furthermore, the time course of changes in the frequency of epileptic seizures during the six months period before the addition of a new AED(s) and the six months period after addition of a new AED(s) was analyzed statistically in 26 patients with SMID. In each test, $P < 0.05$ was regarded as denoting statistical significance.

2.5. Ethical Consideration

This study was carried out in compliance with the Ethical Guidelines on Epidemiological Studies (Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, August 16, 2007) after obtaining the approval of the Ethics Committee of the Japanese Red Cross Tokushima Hinomine Rehabilitation Center for People with Disabilities. The data collected from the medical records were managed in such a way as to not allow identification of any particular individual.

3. Results

3.1. Background of the Patients

The background variables of the patients are summarized in (**Table 2(a)**).

The patient age was 26.5 ± 8.3 years, and the percentages of males and females were 61.7% and 38.3%, respectively (slightly higher percentage of males). The primary disease was "cerebral palsy" in more than half (59.3%) of all the patients. All patients had the disease associated with organic disorders of the brain, such as cerebral hemorrhage aftereffects, epilepsy encephalopathic aftereffects, and meningitis aftereffects.

In the disability classification, 70.4% were rated as having SMID of high severity, thus indicting a high degree of disabilities.

The background variables of the patients in relation to the epilepsy are shown in (**Table 2(b)**). In regard to the classification of epilepsy, a high percentage (58.0%) of the patients was rated as "symptomatic-localized".

The type of epileptic seizure was partial seizure in 28.4%, generalized seizure in 33.3% and a mixture of the two types in 30.9% of the patients. In more detailed analysis of the type of seizure, partial seizure was classified as complex partial seizure in 40.0%, secondary generalized seizure in 55.4% and simple partial seizure in only 4.6% of the patients. Generalized seizure was mostly classified as tonic seizure (35.4%) or tonic-clonic seizure (30.4%), and rarely as myoclonus or cataplexy. The frequency of seizures during the six-year survey period was 3.7 ± 7.9 attacks/month. Patients who remained free of seizures during the six-year period accounted for the highest percentage (39.5%). In total, the percentage of patients experienced seizures was higher than that of seizure-free patients, and 9.9% had 30 attacks or more per month (equivalent to one attack or more/day on average).

The background variables of the patients in relation to the AEDs prescribed are shown in (**Table 2(c)**).

The number of AEDs used was 2.3 ± 1.1 (mean ± SD). The most frequently used number of concomitantly used AEDs was 2 (32.1%), followed by 1 (28.4%). Among the AEDs used, old AEDs accounted for a very large proportion (86.1%). The percentages of the individual AEDs used were as follows; valproate sodium (VPA): 28.9%; phenobarbital (PB): 11.8%; carbamazepine (CBZ): 11.2%. Among the AEDs used that were used independently, that is, without any other AED, VPA was the most frequently used. Among the cases who received

Table 2. (a) Background of the patients; (b) background of the patients in epileptic seizure; (c) background of the patients in relation to the AEDs.

(a)

SMID n = 115	n (%)
Use AEDs	
Use	81 (70.4)
None	34 (29.6)
SMID which uses AEDs n = 81	
Basic information	n (%)
Age (years)	
Average ± SD	26.7 ± 8.3
Median	27
Maximum	39
Minimum	15
Sex	
Male	50 (61.7)
Female	31 (38.3)
Primary disease	
Cerebral palsy	48 (59.3)
Cerebral hemorrhage aftereffects	6 (7.4)
Epilepsy encephalopathic aftereffects	6 (7.4)
Acute encephalopathic aftereffects	3 (3.7)
Meningitis aftereffects	2 (2.5)
Lissencephaly	2 (2.5)
Lowe syndrome	2 (2.5)
CFC syndrome	1 (1.2)
Shaken Baby Syndrome	1 (1.2)
Schizencephaly	1 (1.2)
others	9 (11.1)
Disability classification	n (%)
Yokochi classification	
A1-A3, B1-B3, C1-C3 (high severity)	57 (70.4)
Others (low severity)	24 (29.6)

(b)

Epilepsy classification			n (%)		n (%)
Classification of epilepsy*		Symptomatic-localization-related	47 (58.0)	Symptomatic	76 (93.8)
		Symptomatic-generalized	29 (35.8)		
		Idiopathic-localization-related	0 (0)	Idiopathic	0 (0)
		Idiopathic-generalized	0 (0)		
		Unclassifiable	5 (6.2)		
Type of epileptic seizure**	**Outline**	partial	23 (28.4)		
		generalized	27 (33.3)		
		Partial + generalized mix	25 (30.9)		

Continued

		Unclassifiable	6 (7.4)		
		Partial (total n = 65)			
		Simple partial	3 (4.6)		
		Complex partial	26 (40.0)		
		Secondarily generalized	36 (55.4)		
		Generalized (total n = 79)			
	Details	Clonic	7 (8.9)		
		Tonic	28 (35.4)		
		Tonic-clonic	24 (30.4)		
		Absence	15 (19.0)		
		Myoclonic	3 (3.8)		
		Atonic	2 (2.5)		
Frequency of epileptic seizure			n (%)		n (%)
		Average ± SD	3.7 ± 7.9		
	Average	Median	0.4		
		Maximum	52.5		
		Minimum	0		
Seizure number of times/month (Jan. 2010-Dec.2015)		0	32 (39.5)	Seizure (−) in 6 year	32 (39.5)
		0.1 - 0.9	13 (16.0)		
		1 - 4.9	6 (7.4)		
	Details	5 - 9.9	17 (21.0)	Seizure (+) in 6 year	49 (60.5)
		10 - 19.9	3 (3.7)		
		20 - 29.9	2 (2.5)		
		30≤	8 (9.9)		

*Classification of epilepsy, epilepsy syndrome and related paroxysmal disease (ILAE1989); **International classification of epileptic seizure (ILAE1981).

(c)

AEDs			**n (%)**		**n (%)**
		1	23 (28.4)	Monotherapy	23 (28.4)
		2	26 (32.1)		
		3	19 (23.5)		
		4	11 (13.6)	Combination	58 (71.6)
The number of the use AEDs		5	1 (1.2)		
		6	1 (1.2)		
		Average ± SD	2.3 ± 1.1		
	Average	Median	2		
		Maximum	6		
		Minimum	1		
Use of AEDs (total n = 187)	**Outline**	New AED	26 (13.9)		
		Old AED	161 (86.1)		

Continued

Details	Valproate sodium (VPA)	54 (28.9)	
	Phenobarbital (PB)	22 (11.8)	
	Carbamazepine (CBZ)	21 (11.2)	
	Zonisamide (ZNS)	16 (8.6)	
	Levetiracetam (LEV)	15 (8.0)	New AED***
	Phenytoin (PHT)	14 (7.5)	
	Lamotrigine (LTG)	11 (5.9)	New AED***
	Clonazepam (CZP)	10 (5.3)	
	Clobazam (CLB)	8 (4.3)	
	Others	16 (8.6)	
Monotherapy (n = 23)	VPA	11 (47.8)	
	CBZ	6 (26.1)	
	PB	3 (13.0)	
	PHT	1 (4.3)	
	ZNS	1 (4.3)	
	CZP	1 (4.3)	
Combination (n=58)	VPA + PB	4 (6.9)	
	VPA + CBZ	3 (5.2)	
	VPA + PHT	2 (3.4)	
	VPA + ZNS	2 (3.4)	
	Others	47 (81.0)	

***New AED which was used in this study, other AED was classified in Old AED.

multiple AEDs, the frequency of use was high in the order of VPA-PB > VPA-CBZ.

3.2. Relationship between the Disease Severity and Each Factor

The results are graphically represented in (**Figure 1**).

The frequency of epileptic seizures was significantly higher in the cases with SMID of high severity than in the cases with SMID of low severity (P = 0.048). The number of concomitantly used AEDs was significantly higher in the cases with SMID of high severity cases than in the cases with SMID of low severity (P = 0.02).

3.3. Relationship between the Disease Severity and the Use of AED Situation ("New AED Addition Group" and "Old AED Alone Group")

The results are shown in (**Figure 2**).

"New AED addition group" were more severe SMID than mild SMID. However, there was not the significant difference (P = 0.25).

3.4. Comparison between AED ("New AED Addition Group" and "Old AED Alone Group") and Each Factor

The results are shown in (**Figure 3**).

"New AED addition group" significantly had much seizure number of times (P < 0.001). Furthermore, there was significantly much number of the combination of AED (P < 0.001).

3.5. Changes in the Frequency of Seizures after the Addition of a New AED(s)

The results are shown in (**Figure 4**).

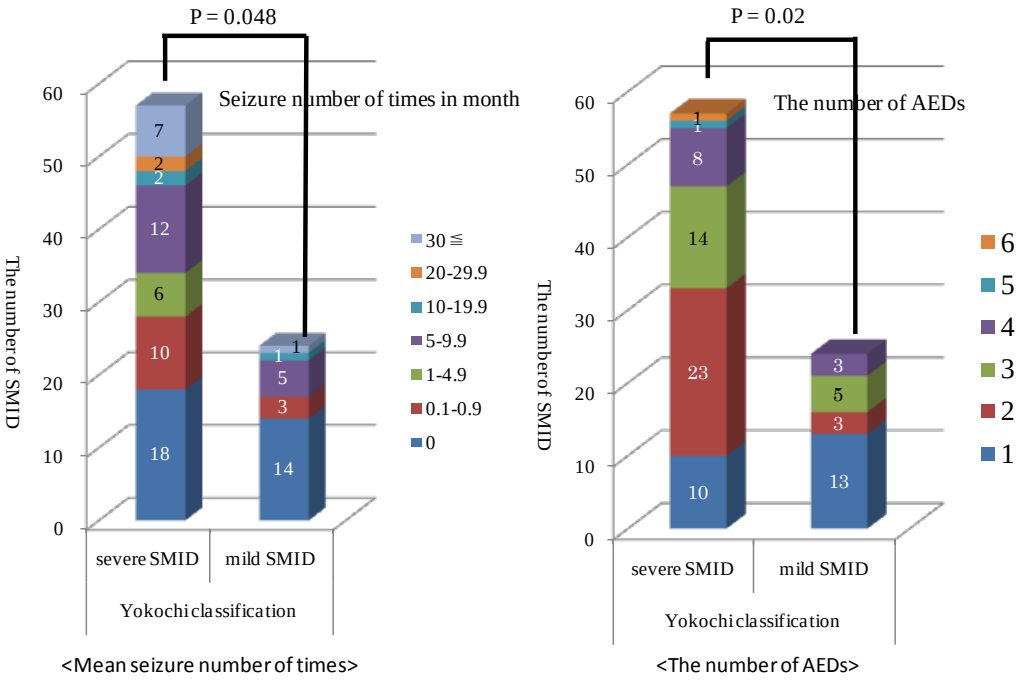

Figure 1. Relations of disease severity and each factor (Mann-Whitney U test).

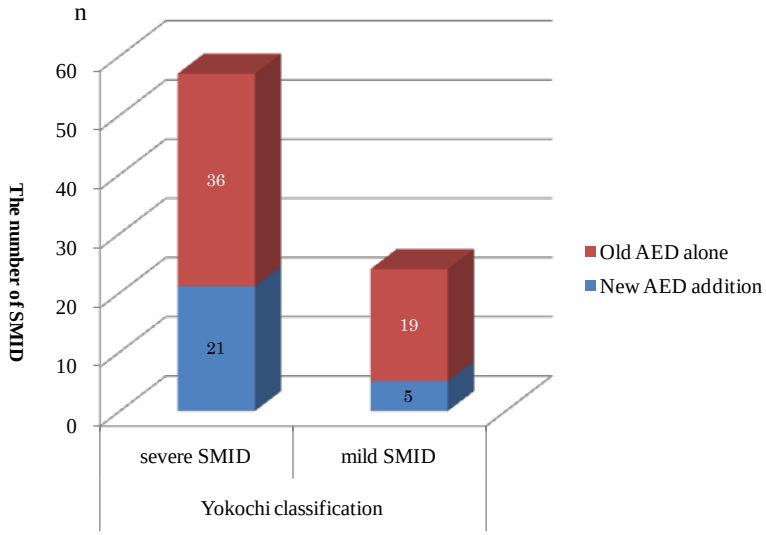

Figure 2. Relations of disease severity and AEDs (New AED addition group and Old AED alone group) P = 0.25 (Chi-squared test).

In the analysis of the mean monthly frequency of seizures during the six months period before the addition of a new AED(s) and the six months period after the addition of a new AED(s), the frequency of seizures was significantly lower after the addition of a new AED(s) than before in most patients ($P < 0.001$).

4. Discussion

In recent years, the treatment of epilepsy has advanced markedly, thanks to the development of new anti-epileptic drugs, surgical intervention, etc. With these developments, there has been an increase in the number of cases among SMID patients in which the seizures can be adequately controlled through precise diagnosis and treatment. Hospitalized patients with SMID can receive treatment under satisfactory settings for epilepsy treatment

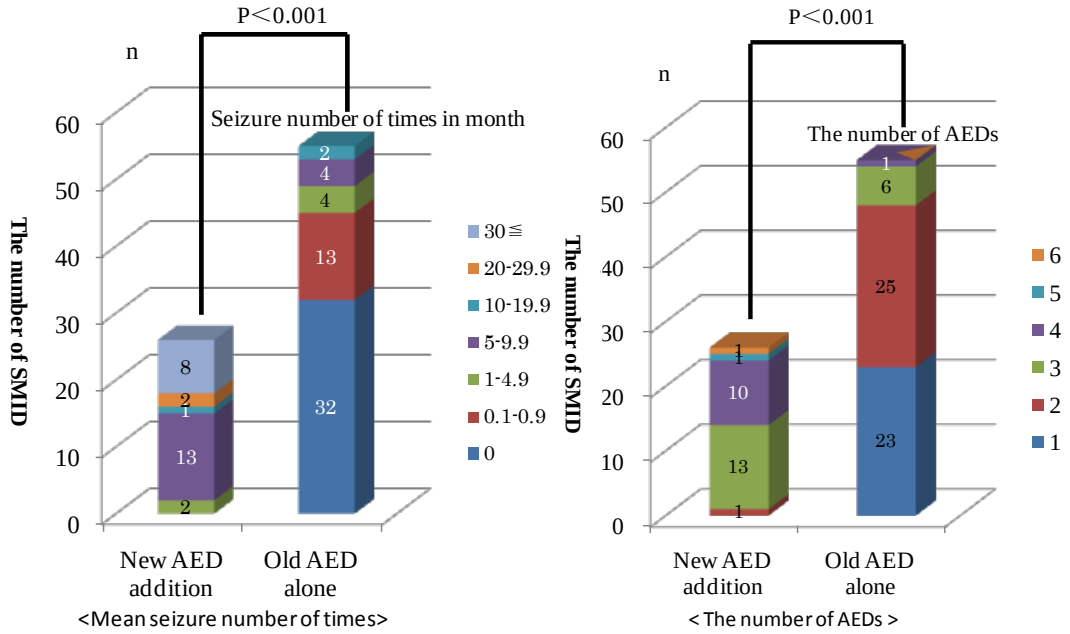

Figure 3. Comparison between use AEDs (New AED addition or Old AED alone) and each factor (Mann-Whitney U test).

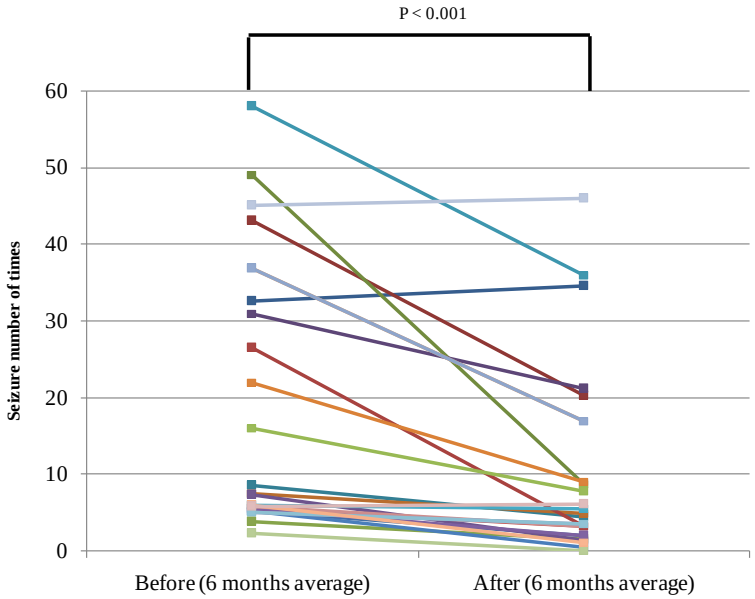

Figure 4. Changes in the frequency of seizures after the addition of a new AED (n = 26) (paired t-test).

(e.g., availability of diagnosis by physicians familiar with clinical neurology, periodic electroencephalography and blood drug level measurement, medication control by medical staff and so on). However, even at present, there are still intractable cases where sufficient control of the seizures is difficult despite treatment with appropriately selected AEDs. Under such circumstances, the present study was undertaken to analyze the prevalence of epilepsy, frequency of seizures and associated factors (number of concomitantly used AEDs, etc.), and the disability class in hospitalized patients with SMID. The efficacy of the new AEDs were evaluated as well.

The prevalence of epilepsy was 70.4%, close to the rate previously reported for SMID patients and markedly higher than the rate (0.09% - 5.7%) [10] in the general population. We may thus estimate that epilepsy is a characteristic feature of the disease seen in SMID patients.

When the epilepsy in the SMID patients was classified using the existing classification of epilepsy, epilepsy syndrome and related paroxysmal disease (ILAE1989), the epilepsy was symptomatic in all the cases and there was no case of idiopathic epilepsy. This result is consistent with the primary disease of the patients studied, suggesting that SMID is complicated by epilepsy due to some organic disorders of the brain. This seems to be a major characteristic of the epilepsy seen in SMID patients.

In this study, the types of epileptic seizures seen in SMID patients were classified in accordance with the international classification of epileptic seizure types (ILAE1981). According to this classification, secondary generalized seizure was the most frequent type of partial seizure and tonic seizure was the most frequent type of generalized seizure. According to the report on the types of seizures by W. Allen and Hauser, complex partial seizure was the most frequent type of partial seizure, and tonic-clonic seizure was the most frequent type of generalized seizure. The percentage of partial seizures other than simple/complex seizure was less than 10% [11] according to their report, differing greatly from the results of the present study. We may thus estimate that a high percentage of secondary generalized seizures is a characteristic of the epileptic seizure types seen in SMID patients.

During the six-year survey period, successful suppression of seizures was not obtained in 60.5% of the study patients when judged in accordance with the domestic criteria [12]. This indicates that epilepsy which develops in children with SMID of high severity is significantly intractable. The time of onset of brain disorders associated with SMID is often in the fetal period to infancy/early childhood, resulting in the lack of normal brain development in these patients. Furthermore, it seems that persistence of epilepsy increases the severity of the seizures with time, leading to progression of the brain disorders and thereby a higher potential for the development of seizures, making the seizures intractable. The basic step of drug therapy for epilepsy is that the symptoms of a seizure should be described in detail to the physician in charge. However, considering that such clarity of expression is difficult for SMID patients and that the presence of seizures may be sometimes overlooked because of the limited medical staff available, it is plausible to imagine that many of the seizures are not counted. Therefore, we cannot rule out the possibility that the status of epilepsy control in SMID patients is poorer than that revealed by this survey and that the actual frequency of seizures is higher than that revealed in this study.

The number of concomitantly used AEDS was 2.3, on average. It was 2 in the highest percentage of patients (32.1%), 1 in 28.4% and 3 in 23.5% of the patients. This result is consistent with the mean at other facilities providing care for severely sick children (2.19 - 2.4 AEDs) [3] [5]. The number of concomitantly used AEDs for secondary epilepsy, etc., in adults with cerebrovascular disease has been reported to be 1.6 - 2.0, with the percentage of single AED users exceeding 50% [13] [14]. When compared to such a report, the number of concomitantly used AEDs for patients with SMID-associated epilepsy in the present study tended to be larger. The larger number of concomitantly used AEDs may be explained if we consider that patients during infancy or early childhood often have intractable epilepsy syndromes such as Ohtawara syndrome (early infantile epileptic encephalopathy with suppression burst: EIEE) and West syndrome. Another possible factor is the difficulty in selecting optimum drugs, because identification of the type of seizure in individual cases is not easy.

Following the finding that a larger number of AEDs were used in SMID patients, we compared the total number of concomitantly used AEDs between patients receiving the new AED and those who were receiving only the older AEDs. This comparison revealed that the new AEDs tended to be added in cases showing inadequate control of seizures with multiple old AEDs. An increase in the number of concomitantly used AEDs is associated with risks such as: 1) drug interactions; 2) increase in the incidence of adverse reactions; and 3) inability to pinpoint which of the AEDs is proving effective. Under the recent trend of recommending simpler drug therapy, with the use of a single drug as far as possible instead of carelessly increasing the number of concomitantly used drugs [14].

The AEDs used in this study were similar to those reported for epilepsy associated with non-SMID disease by Yamada *et al*. [15]. Because patients with SMID often develop generalized seizures or mixed-type seizures, it seems that VPS has been used as the drug of first choice in accordance with the NICE Guidelines [16]. Other than this drug, PB tended to be used in a high percentage of patients. The frequent use of PB may be based on the expectation of the muscle relaxant activity of this drug for the control of contractures and hypertonia unique to SMID, the objective for PB use thus differing from that in epilepsy patients in general.

The relationships between the disability classification (Yokochi classification) and each factor were also analyzed. The analysis revealed that as the severity of the disability increased, the frequency of seizures increased, the number of concomitantly used AEDs became higher and the new AEDs tended to be added to the treatment.

These findings seem to be associated with 1) evidence of difference in the nature of epilepsy between SMID-free individuals and patients with SMID, which is characterized by extremely low intellectual and motor function levels and 2) the magnitude of damage to the brain during functional development of the CNS. As another characteristic of SMID-associated epilepsy, carry-over of epilepsy from infancy/early childhood to adulthood is often seen, and the frequency of seizures in such cases will probably rise as the brain disorder tends to become worse with age.

In the analysis of the time-course of the frequency of seizures before and after the addition of a new AED(s) in 26 patients, the frequency of seizures decreased after the addition of the new AED(s) in most cases. Thus, the new AEDs were shown to be capable also of suppressing intractable epileptic seizures such as SMID-associated seizures. The reason of such a result is because new AED has new action mechanism (e.g., Glutaminic acid release restraint function, bind to synaptic vesicle protein 2A, and the adjustment of the neurotransmitter acts). As a result, in new AED, it was suggested that it was drug which was useful for SMID intractable epilepsy more.

In regard to the drugs defined as new AEDs in the present study, there are numerous reports demonstrating the usefulness of these drugs, in terms of their high efficacy when used for the treatment of epilepsy in general [17]-[19]; however, there are scarcely any reports on the usefulness of these new AEDs for SMID-associated epilepsy. The results of the present study, undertaken under such circumstances, suggest that the new AEDs may be useful in drug therapy for intractable epilepsy associated with SMID.

This study involves limitations. Since SMID is a collective term used for various diseases and syndromes, rather than representing a single disease, its clinical symptoms can change over time and follow diverse courses. For this reason, it is difficult to characterize the tendency of SMID in a clear-cut manner. Furthermore, the present study covered only a proportion of SMID patients receiving inpatient care in Japan, and did not cover those patients who remained at home. For this reason, the findings of this study may not apply to all patients with SMID, PIMD and PMLD. Accumulation of data from further cases and verification of such data are desirable from now on.

5. Conclusions

The present study revealed some characteristics of SMID-associated epilepsy and the trends in its relationship to the use of new AEDs.

At present, epileptic seizures in SMID patients are quite difficult to control, and it is difficult to say that the patients and their guardians are satisfied with the current care. Frequent onset or persistence of severe epileptic seizure will undoubtedly serve as a factor for the start of a negative spiral of events (accumulation of brain nerve damage, reduction in the QOL, etc.). The present survey and analysis suggests that the new AEDs will be useful in the control of SMID-associated epilepsy. We believe that from now on, new AEDs should be used proactively, beginning in the early stages of treatment, rather than as a “last resort”.

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