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Author Contributions

Conceived and designed the experiments: YO AOh MK KM. Performed the experiments: YT YK YMo YMi TH YY YYS NNB TA YSM KO TS AN HM FM KH TF MS KKI HH. Analyzed the data: MK YT YK TH YN HK AOk ST HN KB TY MM KM AOh. Contributed reagents/materials/analysis tools: MN JY MY. Wrote the paper: YO MK YK YT. Gave critical comments: AOk.

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Original article

Ketogenic diet therapy can improve ACTH-resistant West syndrome in Japan

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Abstract

Purpose: Ketogenic diet therapy (KD) has been used to treat children with refractory generalized epilepsy. We herein reported the efficacy of KD for West syndrome (WS) resistant to ACTH therapy. *Subjects:* Subjects, consisting of 6 patients (3 boys, 3 girls) with WS who continued to have epileptic spasms (ES) and hypsarrhythmia, received KD because other treatments including ACTH therapy failed to control WS. *Methods:* We retrospectively studied the clinical details of these patients and the efficacy of KD. *Results:* The mean age at the onset of epilepsy was 4 months (0–15 months). The underlying etiology consisted of lissencephaly, Down's syndrome, and focal cortical dysplasia. Hypsarrhythmia disappeared 1 month after the introduction of KD in 5 patients. The disappearance of ES was achieved in 2 patients, the frequency of ES episodes was 80% less in 3, and no change was observed in 1. Psychomotor development was promoted in 5 patients, along with improvements in ES and EEG. Gastrointestinal complications and lethargy, presumably caused by rapid ketosis, were reported as side effects in 3 patients during the first week of KD. Side effects including lethargy, anorexia, and unfavorable weight gain continued thereafter in these patients in spite of tolerance to KD. *Conclusion:* KD was effective for WS resistant to ACTH therapy, although gastrointestinal side effects should be considered when introducing KD to milk-fed infants.

Keywords: West syndrome; ACTH; Ketogenic diet; Gastrointestinal side effects

1. Introduction

West syndrome (WS) is considered the most common catastrophic epilepsy in infancy, and various treatment strategies ranging from antiepileptic-drug therapies to surgical procedures have been performed [1]. Although ACTH therapy is the first-line treatment for patients with WS in Japan, one or two antiepileptic drugs such as ZNS or high-dose vitamin B6 have been used prior to this therapy [2]. Ketogenic diet therapy (KD) has been used to mostly treat children with refractory generalized epilepsies in early or later childhood, i.e. Dravet syndrome, Doose syndrome, and Lennox-Gastaut syndrome, because it is commonly indicated to patients with refractory generalized epilepsy between 2 and 8 years old [3]. Because of differences in food culture in Japan, in which higher amounts of carbohydrates and lower amounts of fat are consumed than in western countries, and also the severe restriction of food in KD, pediatric neurologists do not currently recommend KD as a treatment option in Japan. On the other hand, it has recently been used as the initial treatment of WS in the United States as well as Korea, and good efficacy has been reported [4,5]. However, no studies have demonstrated a better response rate for the treatment of WS than that of ACTH therapy. Therefore, KD has not been promptly introduced when ACTH therapy

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is not effective in countries in which ACTH therapy is chosen as a first-line treatment, such as Japan. In this study, we examined the efficacy of and side effects associated with KD in patients with ACTH-resistant WS.

2. Subjects and methods

Subjects consisted of 3-year-old or younger children with WS in whom ketogenic milk/diet therapy was consecutively performed in our hospital between November 2011 and December 2012. Subjects were only included if they continued to have ES and a hypsarrhythmic EEG pattern satisfying the diagnosis of WS at the time when KD was introduced. We retrospectively investigated the underlying etiology, age at the onset of epilepsy, treatments before KD, age at the start of KD, efficacy, side effects, treatment period, and outcomes of the subjects.

Electroclinical outcomes with KD were evaluated based on improvements in the frequency of interictal EEG and ES episodes 1 and 3 months after the introduction of KD and also at the final follow-up. Improvements in EEG were visually assessed on both waking and sleep EEG, and graded as excellent (disappearance of both epileptic and non-epileptic abnormalities), good (resolution of hypsarrhythmia: some residual focal epileptic abnormalities or focal or diffuse slowing of background activity), and poor (no significant improvement). Concerning the ES frequency, the disappearance of ES was regarded as a complete response, an 80% or more reduction in the frequency of ES episodes as an excellent response, a 50–80% reduction as a good response, and a less than 50% reduction as no response. In contrast, a 50% or more increase in the frequency of seizures was regarded as aggravation.

A 3:1 (lipid:nonlipid) ketogenic milk formula (Meiji Dairies Corporation) or 4:1 ketogenic diet was used for the introduction and maintenance of KD. The protein requirement was calculated as 1.5–2 g/kg, and the calorie requirement was established as 80–90% of the energy requirement for infants. Water intake was not restricted. A fasting period of up to 6 h was employed, depending on the age of the subjects.

3. Results

KD was consecutively introduced to 6 patients (3 boys, 3 girls) during the study period. The mean age at the onset of epilepsy was 4 months (0–15 months). The underlying etiology consisted of lissencephaly ($n = 1$), Down's syndrome ($n = 1$), focal cortical dysplasia ($n = 1$), and unknown ($n = 3$). Regarding treatments prior to KD, ACTH therapy had been attempted in all 6, with no response being observed in 2, a partial response in 1 (50% reduction in ES only without EEG improvements), and a transient response in 3 (Table 1). In all 6 patients, at least 3 (average) or more antiepileptic drugs including high-dose vitamin B6 were administered without a response. Interictal EEG showed hypsarrhythmia in all patients at the time when KD was introduced.

The mean age at the start of KD was 23 months (9–40 months). The mean interval from ACTH therapy to the introduction of KD was 4 months (2–14 months). KD was initiated with the ketogenic formula in 4 patients including one who had received tube feeding through a nasogastric tube before the introduction of KD. A 4:1 ketogenic diet was introduced in the remaining 2 patients.

4. Electroclinical outcomes

Complete and excellent ES responses were achieved in 2 and 3 patients, respectively, 1 month after starting KD (Table 1). These responses were maintained at 3 months. Excellent and good EEG responses were obtained in one and 4 patients, respectively, at 3 months, while no significant improvement was observed in the remaining one patient. Psychomotor development appeared to be promoted in 5 patients, along with improvements in ES and EEG. KD had been maintained for 7.4 months on average at the final follow-up; however, despite complete and excellent ES responses as well as the resolution of hypsarrhythmia, it was discontinued in 3 subjects 6–8 months after its introduction because two patients showed poor weight gain and difficulty with eating orally, requiring the continuation of tube feeding, while the remaining patient continued to have lethargy and anorexia. At the final follow-up, two patients who discontinued KD showed the gradual aggravation of ES and EEG. The remaining one patient maintained a complete response.

5. Side effects

Lethargy and anorexia was transiently observed in all patients for a few days after the introduction of KD. Various degrees of gastrointestinal side effects including nausea and vomiting were also noted for a few days in the 5 patients who were introduced initially to the ketogenic milk formula (Table 1). One patient refused to take the 4:1 ketogenic diet 1 week after the introduction of KD, which necessitated a change from KD to the ketogenic milk formula through a nasogastric tube. This patient also developed gross hematuria due to a renal calculus during the 4:1 ketogenic diet, which required an increase in water supply through the tube and urinary alkalization by thiazide.

Mild lethargy and anorexia continued as the chronic side effects of KD in 2 patients taking the ketogenic milk formula who showed improvements in both ES and EEG. These two patients continued to require tube feeding of the ketogenic milk because they refused to

Table 1
Demographic data of the 6 patients.

Case No.	Gender	Onset age of epilepsy (months)	Age at the last follow-up	Underlying disorders	Response to ACTH	Antiepileptic drugs used before KD	Seizure types before KD	Seizure frequency (/day)	Age at the introduction of KD (months)	Interval between ACTH and KD (months)	EEG improvements at 3 months	Seizure improvements at 3 months	Seizure and EEG status at the final follow-up	Complications		Development
														<1 week	1 week<	
1	M	2	25	Unknown	Transient electroclinical response by the first and second ACTH trial and none by the third ACTH trial	VPA, TPM, NZP, LTG	ES	1–3S (5–30 times)	17	3	Good	Excellent	Good EEG and seizure improvement after stopping KD, infrequent spike (Lt FTP)	Excessive ketosis: urinary stone	Refusal to drink or eat	Promoted
2	F	2	26	Lissencephaly	Transient clinical response for 10 months	PB, VB6, VPA, ZNS, CLB, LTG, LEV	ES, GTS	6–7S (50 times)	20	5	Good	Excellent	Diffuse slow spike-and wave appeared in EEG	Transient vomiting, hypoK	Vomiting	Promoted
3	F	2	24	Unknown	Transient clinical response for 3 months by the first ACTH trial and none by the second ACTH trial	VPA, ZNS, NZP, TPM, Bit B6	ES	1–11S (3–50 times	20	12	Good	Excellent	Good and excellent improvement was maintained	Transient vomiting	Refusal to drink ketogenic milk	Promoted
4	F	3	50	Suspect of slowly progressive degenerative disease	No electroclinical response	Vit. B6, γglb, ACTH (twice), VPA, TPM, CZP, LTG, CLB, LEV, GBP	ES	10S (70 times)	40	24	Poor	Poor	Poor	Lethargy	Lethargy, low thyroxin (T4) level	No change
5	M	4	18	Down's syndrome	No electroclinical response	VPA, CZP, ZNS	ES	10S (50 times)	9	2	Excellent	Complete	Complete and excellent improvement was maintained after stopping KD	Transient vomiting	Chronic diarrhea	Promoted
6	M	7	21	Cortical dysplasia	Transient clinical response	ZNS, TPM, NZP, VPA, LTG, VB6	ES	5S (10 times)	14	6	Good	Excellent	Good EEG and seizure improvement after stopping KD, spike (bil F)	None	Weight gain, poor water intake	Promoted

Abbreviations: KD, ketogenic diet; ES, epileptic spasms; GTS, generalized tonic seizures; S, series; hypoK, hypokalemia.

take the milk orally. KD was discontinued 3 months after its introduction in one patient due to lethargy, poor weight gain, and insufficient improvements in ES and hypsarrhythmia. All 6 patients required tube feeding at some point during KD due to gastrointestinal problems including refusal of oral intake.

6. Discussion

Even though the food culture in Japan was traditionally opposite to KD because it was rich in carbohydrates and low in fat, KD had been actively employed to treat children with refractory generalized epilepsy during the 1970s and 80s. Tajima et al. used KD to treat 51 patients, and revealed that 8 and 3 patients achieved excellent and good improvements, respectively, 2 years after KD had been introduced [6]. Oguni et al. reported the results of KD in 54 patients with refractory epilepsy between 1984 and 2007 according to the epileptic syndrome classification. They concluded that the most effective epileptic syndrome, in terms of the response rate achieved by KD, was a transient state from West to Lennox-Gastaut syndrome, followed by severe myoclonic epilepsy in infants and Doose syndrome beyond the 1 year follow-up [7].

The indication of the KD trial has been extended worldwide to infantile spasms due to development of the ketogenic milk formula. Kossoff et al. compared the effectiveness of ACTH therapy with that of KD in patients with infantile spasms and emphasized the long-term safety and efficacy of KD [8]. Although the efficacy of ACTH therapy 1 month after starting the treatments was slightly better than that of KD in their study, the incidence of side effects and recurrence rates were higher with ACTH therapy.

In this study, KD was performed in 6 patients with ACTH-resistant WS. Marked clinical and EEG improvements were observed in 5, which demonstrated the efficacy of KD over that of ACTH therapy at least in these patients. The resolution of hypsarrhythmia was achieved in 5 of the 6 patients even though complete seizure control was only obtained in 2 patients. Since hypsarrhythmia is considered to be electrographic status epilepticus and responsible for catastrophic psychomotor deteriorations in this syndrome, the effectiveness of KD appeared worthwhile even when complete seizure control was not achieved.

The chronic side effects of KD generally include vitamin deficiencies, growth disorders, bone-system diseases, dyslipidemia, and renal calculi. Serious side effects such as cardiomyopathy and arrhythmia have rarely been reported. In this study, we noted complications related to KD initiated during infancy, which has rarely occurred in children older than this age range. Marked lethargy and gastrointestinal side effects, mainly nausea and vomiting, was frequently observed with an increase in blood ketone levels and transient parental fluid infusions being required in half of cases, although KD was tolerated within 1–2 weeks. However, various degrees of refusal to take KD or milk were observed thereafter in all patients. Thus, tube feeding was transiently or chronically required to maintain KD. This may have been due to gastric irritation because of the ketogenic milk, which contained a high level of medium-chain triglycerides (MCT), and also the poor taste of the milk or diet. This has been reported previously for classical KD in children and attempts have been made to overcome these issues by improving the diet composition and fine-tuning. KD should generally provide a ketone ratio of 4:1 (classical) because of difficulties in maintaining sufficient ketosis over a long period of time. However, Seo et al. suggested that a ketone ratio of 3:1 was more favorable than 4:1 for the treatment of infantile spasms, considering not only effectiveness, but also side effects [9]. In this study, favorable ketosis was achieved with the 3:1 ketogenic diet in all patients after switching 4:1 to 3:1 KD. Therefore, in milk-fed infants, KD can be introduced with 3:1 ketogenic milk. However, ketogenic formulated milk generally contains a high level of MCT, which induces persistent gastric symptoms such as nausea and vomiting; therefore, it can be difficult to increase the milk volume to meet calorie demands. Under these conditions, mixing with a liquid state 3:1 ketogenic diet using a mixer or replacing ketogenic milk with that containing a lower MCT composition may be needed.

Kang et al. compared ketogenic diet therapies for infantile spasms between two treatment periods, 6–8 months and 2 years. They reported that similar long-term effects were obtained, although the incidence of side effects was lower in 6–8 month treatment period [10]. In this study, we also discontinued KD 6 and 8 months after the introduction of KD in 2 patients, respectively, despite excellent clinical and EEG improvements because of the continuation of lethargy and poor weight gain.

7. Conclusion

In conclusion, KD was effective for WS resistant to ACTH therapy, although the consideration of gastrointestinal side effects is necessary when introducing KD to these infants. A better tolerated and more palatable ketogenic diet and milk specialized for milk-fed infants is needed.

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Original article

Study of epileptic drop attacks in symptomatic epilepsy of early childhood – Differences from those in myoclonic-astatic epilepsy

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Abstract

Objectives: We studied epileptic drop attacks (EDA) in symptomatic epilepsy of early childhood by means of video-polygraphic recordings and compared clinico-electrical differences in EDA among patients with idiopathic myoclonic-astatic epilepsy (MAE).

Subjects and methods: Subjects consisted of 21 children with symptomatic epilepsy and 20 with idiopathic MAE whose EDA were documented at an age between 7 months and 6 years. The seizure types causing EDA as well as other demographic data were compared between the two epilepsy types.

Results: A video-polygraphic study captured a total of 188 EDA (median: 8) in patients with symptomatic epilepsy and 182 EDA (median: 7) in those with idiopathic MAE. In the former, EDA were caused by epileptic spasms (ES) corresponding to generalized biphasic slow discharges, sharp-and-slow wave complexes, or the flattening of ongoing background activity in 15 patients, atonic seizures associated with runs of generalized spike-and-wave complexes in four patients, and myoclonic-atonic seizures in the remaining two patients. The mode of occurrence of EDA in ES was periodic clustering in eight of 15 patients. Interictal EEG revealed generalized irregular multiple spikes-and-waves with focal or multifocal accentuations. Sixteen idiopathic MAE patients had myoclonic-atonic seizures while the remaining four had myoclonic-flexor seizures, all corresponding to generalized high amplitude spikes or polyspike-and-wave complexes and occurring singly.

Conclusion: EDA often seen in young children with symptomatic epilepsy were most frequently caused by flexor type ES and rarely by myoclonic-atonic seizures, a hallmark seizure type of MAE. In a clinical setting, the occurrence of periodic clusters and independent focal or multifocal accentuations of generalized spike-and-wave complexes in interictal EEG may indicate EDA caused by ES.

Keywords: Epileptic drop attacks; Epileptic spasms; Myoclonic-atonic seizures; Atonic seizures; Symptomatic epilepsy; Early childhood

1. Introduction

Epileptic drop attacks (EDA) are one of the most pharmacoresistant epileptic seizure types due to the potential risk of serious injuries to patients, especially after the age of late infancy when young children acquire the ability to sit, stand, and walk. EDA cause a sudden loss in postural control, which results in a fall onto the ground without warning, followed by the almost immediate resumption of an upright position [1]. Falling mechanisms appear to differ depending on the epileptic seizure type, i.e. atonic seizures, myoclonic seizures, myoclonic-atonic seizures, generalized tonic (axial) seizures, complex partial seizures, and epileptic negative

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myoclonus [2]. They have often been observed in well-defined epileptic syndromes, such as Lennox–Gastaut syndrome (LGS), idiopathic myoclonic–astatic epilepsy (MAE), and frontal and temporal lobe epilepsy [3–7]. Previous studies reported that axial or flexor spasms were the most frequent cause of EDA in older children and adults with LGS or symptomatic generalized epilepsy, who also had generalized tonic seizures and atypical absence seizures [11,12]. On the other hand, we found that EDA in young children with idiopathic MAE, one of the unique idiopathic childhood-onset epilepsy syndromes during early childhood, were caused by either atonic, myoclonic-atonic, or myoclonic-flexor seizures [2,9]. Thus, the seizure types that most often cause EDA in infants and young children with epilepsy other than idiopathic MAE have yet to be clarified, which may cause difficulties when making a differential diagnosis from idiopathic MAE [8–10]. In the present study, we retrospectively compared the clinical and video-polygraphic characteristics of EDA during early childhood between patients with symptomatic epilepsy who manifested with EDA as the main seizure type and those with idiopathic MAE.

2. Subjects and methods

Subjects were retrospectively recruited from approximately 1100 patients who consecutively underwent ictal video-EEG between 1980 and 2010 at Tokyo Women's Medical University, and satisfied the following criteria: (1) onset age of EDA from 7 months to 6 years of age; (2) repeated EDA as the cardinal symptom that were recorded at least twice with video-polygraph between 7 months and 6 years of age; (3) evidence of a symptomatic etiology based either on developmental delays or neurological abnormalities before the onset of epilepsy or structural/functional cerebral abnormalities as demonstrated by brain magnetic resonance imaging (MRI)/single photon emission computed tomography (SPECT).

We also recruited patients with idiopathic MAE whose EDA were captured at least twice during the study period in order to characterize differences in EDA between the two epilepsy types. The diagnosis of idiopathic MAE was made based on the criteria of 1989 international classification of epilepsies and epileptic syndromes, satisfying criteria (1), (2) and the absence of criteria (3).

Video-polygraphic EDA findings were retrospectively reviewed and the exact seizure types according to the 1981 seizures classification system were identified in each patient [13]. Ictal video-EEGs were analyzed by the two authors (Drs. Itoh and Oguni) and the final decisions for determining the types of seizures and EEG patterns were made by the agreement of these two authors. The following demographic data were also analyzed; ages at the onset of epilepsy and EDA, clinical and EEG findings of EDA, development before the onset of epilepsy, associated seizure types, neuroimaging findings, chromosomal and genetic studies, responses to the treatment, and outcomes.

EDA were defined as patients, while either standing or sitting, that suddenly became incapable of maintaining an erect posture, dropped onto the ground, and recovered instantaneously to the previous position. EDA sequences were confirmed at least twice by a video-polygraphic examination. Details of the video-polygraphic recordings were described elsewhere [14]. All EDA were analyzed in slow motion and in the frame-by-frame video replay mode.

The developmental or intelligence quotient (DQ or IQ) was assessed by the Japanese Tsumori-Inage infant developmental scale or modified Binet IQ scale, respectively, at the first visit to our hospital. Development was estimated at the first visit according to DQ values and the acquisition of developmental milestones if the DQ or IQ test was not performed, and subsequently classified into a normal ($DQ \geqslant 80$), borderline ($80 > DQ \geqslant 70$), mild ($70 > DQ \geqslant 60$), moderate ($60 > DQ \geqslant 30$), and severe delay ($30 > DQ$). Delays in development prior to the onset of epilepsy were estimated according to the history of acquired developmental milestones.

The proposed protocol was approved by the Ethics Review Board of Tokyo Women's Medical University.

2.1. Statistical analyses

The chi-squared test and *t*-test were employed to compare the results between two variables. Fisher's exact test was used when the expected number was less than 5. A comparison between more than three variables was performed using the chi-squared test with cross tabulation. We employed the Bonferroni correction to calculate *P* values to adjust for multiple testing. A *P* value of <0.05 was regarded as significant.

3. Results

There were 21 patients with symptomatic epilepsy and 20 patients with idiopathic MAE who successfully underwent the ictal video-polygraph of EDA and fulfilled the criteria. They comprised 10 boys and 11 girls, and 13 boys and 7 girls, respectively. Demographic data were described in Tables 1 and 2.

3.1. Clinical and EEG analyses of EDA

3.1.1. EDA in symptomatic epilepsy

Video-polygraphic examinations showed sudden dropping of the body onto the ground either from standing or sitting positions and immediate recovery in all 21

Table 1
Clinico-electrical findings of 21 patients with epileptic drop attacks.

Case No.	Gender	Underlying disorder	Present age (y: mo)	Onset age of epilepsy (y: mo)	Delay in development prior to the onset of epilepsy	Onset age of DA (y: mo)	Age at study (y: mo)	Development at the first visit	Other associated seizure types	Interictal EEG abnormality		Clinical characteristics of DA	Frequency of DA	Number of DA analyzed by polygraph	Ictal EEG pattern	DA occurrence	Brain MRI	99mTc-HM-PAO brain SPECT	Effect of ACTH	Other effective treatment	Outcome			Follow-up period (y: mo)
										GSW	Localized SW										Seizures	Epileptic EEG abnormality	Intelligence	
1	F	21 trisomy	9:0	2:1	+	2:1	2:8	Mo (DQ 36)	AA	+	Rt-F	Flexor type ES	0–4/day	4	Generalized biphasic HVS	S	Delay in myelination	Lt-T, basal ganglia↓	Ex	–	N	N	S	6:4
2	F	Unknown	8 :5	0:7	–	0:8	0:8	N (DQ 80)	–	+	–	Flexor type ES	10–20/day	4	GSW	S	Minimal atrophy	R > L	Ex	–	N	N	N (IQ 98)	7:9
3	M	Unknown	9:5	1:1	–	1:5	3 :0	Mo	GTS	+	–	Flexor type ES	10–20/day	20	Generalized biphasic HVS	C/S	N	Bil. F, LT↓	Ex	–	N	Rt-PO	S	6:5
4	F	Cerebral infarction due to CHD	21:1	2:0	+	2:0	3:8	B	GTCS	+	Rt-O	Flexor type ES	10>/day	8	GSW	S	Atrophy in Rt-O	Rt-O↓	ND	VPA+ESM	CPS	N	Mild	17:5
5	M	Unknown	8:10	2:0	–	2:4	2:5	B (DQ 71)	GTS	+	RT-T	Flexor type ES	10>/day	15	Generalized biphasic HVS	C	N	Rt-pT↓	P	KD	ES	GSW	Mo	6:5
6	F	Chiari 1 malformation	7::2	1:6	–	1:6	1:11	N (DQ 80)	GTCSCPS	+	–	Flexor type ES	5–6/day, 5–8c/day	12	Generalized biphasic HVS	C/S	Chiari 1 malformation	Bil. F↓	Ex	–	N	F	N	5:3
7	F	Unknown	20:9	0:4	+	1:1	4:1	Mild	AA	+	pTO	Flexor type ES	10</day	15	Generalized biphasic HVS	S	N	N	Ex	–	ES	GSW	S	16:8
8	M	Unknown	8:10	1:5	–	1::5	1:6	N	–	+	Lt-C	Flexor type ES	3c/day	11	Generalized biphasic HVS	C/S	Lt-FCD?	Lt-FT↓	Ex	–	CPS	Lt-FT	Mo	7:4
9	M	Unknown	4:8	0:7	+	3:10	4:3	Mo (DQ 30)	GTS AA	+	–	Flexor type ES	4–5/day	3	Generalized biphasic HVS	C/S	Cerebral atrophy	ND	Ex	–	ES	N	S	0:5
10	M	CFC syndrome	7:9	2:0	+	2:6	6:3	S	AA	+	RT-T	Flexor type ES	5–10/day	8	Generalized brief flattening of BGA	S	Cerebral atrophy	ND	ND	LTG	ES	O,pT	S	1:6
11	F	Unknown	12:10	3:2	–	3:2	3:7	Mo (DQ 54)	–	+	–	Flexor type ES	10C</day	22	Generalized brief flattening of BGA	C	N	ND	ND	VPA	N	N	B (DQ 70)	9:8
12	F	Unknown	11:6	2:2	+	3:6	5:3	Mo	–	+	–	Subtle ES followed by falling	8–12c/day	8	Generalized biphasic HVS	C/S	N	Bil. F↓	TE	CC	ES	GSW	S	6:3
13	M	FCD	7:0	2:10	–	2:10	3:3	Mo	GTCS AA	+	Rt-F	Subtle ES followed by falling	10–20c/day	11	Generalized biphasic HVS	C/S	Rt F FCD	Rt-O↓	TE	–	ES	Ft-F	Mo (IQ 48)	3:6
14	M	FCD	9:0	0:5	+	1::5	2:4	Mild	GTS	+	–	L > R Flexor type ES	10</day	3	Generalized biphasic HVS	S	FCD Lt-P	Lt-P	ND	Focal resection	N	N	N (IQ 80)	4:0
15	F	Unknown	7:1	2:0	–	2:5	2:11	B	–	+	Rt-FT	L > R Flexor type ES	10–20/day	10	Generalized biphasic HVS	S	Cerebral atrophy	Rt-F↓	Ex	–	N	Rt-F	B	4:2
16	M	NCL	5:5	3:4	+	3:4	3:8	S	GTCS	+	–	Myoclonic-atonic seizures	10</day	3	GSW	S	Cerebrocerebellar atrophy	ND	ND	–	N	N	S	2:0
17	M	Lipoma + AVM	2:9	0:11	–	1:0	1:2	N	–	+	Rt-CP	Myoclonic-atonic seizures	10</day	9	GSW	S	Lipoma + AVM	Rt-P↓	ND	VPA	N	Rt-C	B	1:7
18	M	GLUT-1 DS	15:2	0:4 (myoclonic attacks)	–	2:1	2:3	Mild (DQ 64)	Febrile seizures	+	–	Atonic seizures	2–7/ day	3	GSW	S	N	cerebellum↓, thalamus↓(FDG-PET)	ND	KD	AA	GSW	Mo(IQ 35)	13:1
19	F	Unknown	21:1	1:8	+	1:8	4:0	Mo	AA	+	–	Atonic (absence) seizures	10–20/day	2	GSW	S	N	ND	TE	VPA + ESM + LTG	N	GSW	Mo	17:1
20	F	Unknown	22:0	2:6	+	3:9	3:8	Mo	AA	+	–	Atonic (absence) seizures	10–20/day	3	GSW	S	N	ND	TE	VPA+ESM+LTG	N	GSW	Mo	18:4
21	F	Unknown	7:0	3:4	+	4:5	6:0	Mo	AA	+	–	Atonic (absence) seizures	5–15/day	14	GSW	S	N	ND	TE	VPA+ESM+LTG	N	GSW	Mo	1:0

Abbreviations: DA, drop attacks; M, male; F, female; +, present; –, absent; N, normal; B, boderline; Mo, moderate; S, severe; CHD, congenital heart disease; CFC, cardio-facio-cutaneous; FCD, focal cortical dysplasia; NCL, neuronal ceroid lipofuscinoses; GLUT-1 DS, glucose transporter type 1 deficiency syndrome; ES, epileptic spasms; AA, atypical absence; GTS, generalized tonic seizures; GTCS, generalized tonic-clonic seizures; CPS, complex partial seizures; GSW, generalized spike-and-wave; SW, spike-and-wave; HVS, high voltage slow wave; BGA, background activity. DA occurrence: S, single; C, cluster; C/S, both clusters and single occurrence. AVM, arterio-venous malformation; VPA, valproic acid; ESM,ethosuximide; LTG, lamotrigine; KD, ketogenic diet; CC, corpus callosotomy. Effect of ACTH: Ex, excellent; ND, not done; TE, transient effect; DQ, developmental quotient; IQ, intelligence quotient.

Table 2
Comparisons of the clinical and video-polygraphic findings of epileptic drop attacks between symptomatic epilepsy and idiopathic MAE.

	Symptomatic epilepsy	Idiopathic myoclonic-astatic epilepsy	*P* values
Number of patients	21	20	
Number of EDA analyzed	188 (2–22; median: 8)	182 (2–51; median: 7)	0.9563
Ages at onsets of EDA (months)	8–53 (median: 25)	17–53 (median: 37)	0.0242
Age at EDA study (months)	8–75 (median: 39)	17–95 (median: 41.5)	0.2849
Follow-up period (months)	5–220 (median: 88)	6–155 (median: 92)	0.9989
Types of EDA seizure types			
1. Epileptic spasms	15	0	0.000*
2. Atonic seizures	4	0	
3. Myoclonic-atonic seizures	2	16	
4. Myoclonic-flexor seizures	0	4	
Mode of seizure occurrences			
Clusters in a periodic fashion	8	0	0.0034*
Ictal EEG pattern			
1. Generalized high-amplitude biphasic slow discharges	11	0	0.000*
2. Generalized flattening of background activity	2	0	
3. Generalized spike or polyspike-and-slow wave complexes	4	20	
4. Runs of rhythmic spike-and-wave complexes	4	0	
Associated seizure types			
1. Generalized tonic-clonic seizures	4	17	0.0093*
2. Generalized tonic seizures	4	0	
3. Atypical absence seizures	8	12	
4. Complex partial seizures	1	0	
Interictal EEG findings			
1. Frequency of generalized spike-and-wave complexes	1–2.5	1.5–3	
2. Independent focal or multifocal accentuations of generalized spike-and-wave complexes	9	0	0.0008*

* After the Bonferroni correction, a *P* value of less than 0.0055 was considered significant.

patients. Detailed examinations of the videos and polygraphs revealed the exact seizure types of EDA as epileptic spasms (ES) in 15 patients, followed by atonic seizures in 4, and myoclonic-atonic seizures in 2 (Tables 1 and 2). EDA caused by ES were characterized by sudden dropping of the body due to forward flexion of both the head and trunk (flexor type ES: Fig. 1A and B). In two patients, ES caused dropping as if the body was collapsing forwards or downward due to a combination of subtle spasms, followed by reduced EMG activity corresponding to falling of the trunk, which resembled atonic seizures (subtle spasms followed by falling). All patients had symmetric EDA, except for two who showed either asymmetric jerking of the arms or falling obliquely on the left side. Some concordant asymmetry was observed in the interictal epileptic EEG abnormalities in these two patients despite the lack of responsible brain MRI lesions.

ES occurred singly in seven patients, being both clustered in a periodic fashion and singly in six cases and always clustered in a periodic fashion in the remaining 2. Ictal EEG showed generalized high-amplitude biphasic slow discharges ($n = 11$), generalized slow sharp-and-slow wave complexes ($n = 2$), and generalized brief flattening of background activity ($n = 2$), which corresponded to ES.

EDA caused by myoclonic-atonic seizures ($n = 2$) manifested as subtle momentary jerks in both arms followed by dropping forward or directly downward depending on the posture before EDA. Ictal EEG showed generalized polyspike-and-wave complexes corresponding to small EMG discharges followed by the interruption of ongoing EMG activity (Fig. 2).

EDA caused by pure atonic seizures in three of the four patients showed "slow falling" with one or two stepwise dropping of the trunk downward onto the ground, corresponding to runs of 2 Hz generalized bilaterally synchronous spike-and-wave complexes (Fig. 3). The remaining one patient with glucose transporter type 1 deficiency syndrome (GLUT-1 DS) showed momentary dropping of the head and trunk, corresponding to the 2.5-Hz generalized spike-and-wave complex.

3.1.2. EDA in idiopathic MAE

The exact seizure types of EDA were identified as myoclonic-atonic seizures in 16 patients and

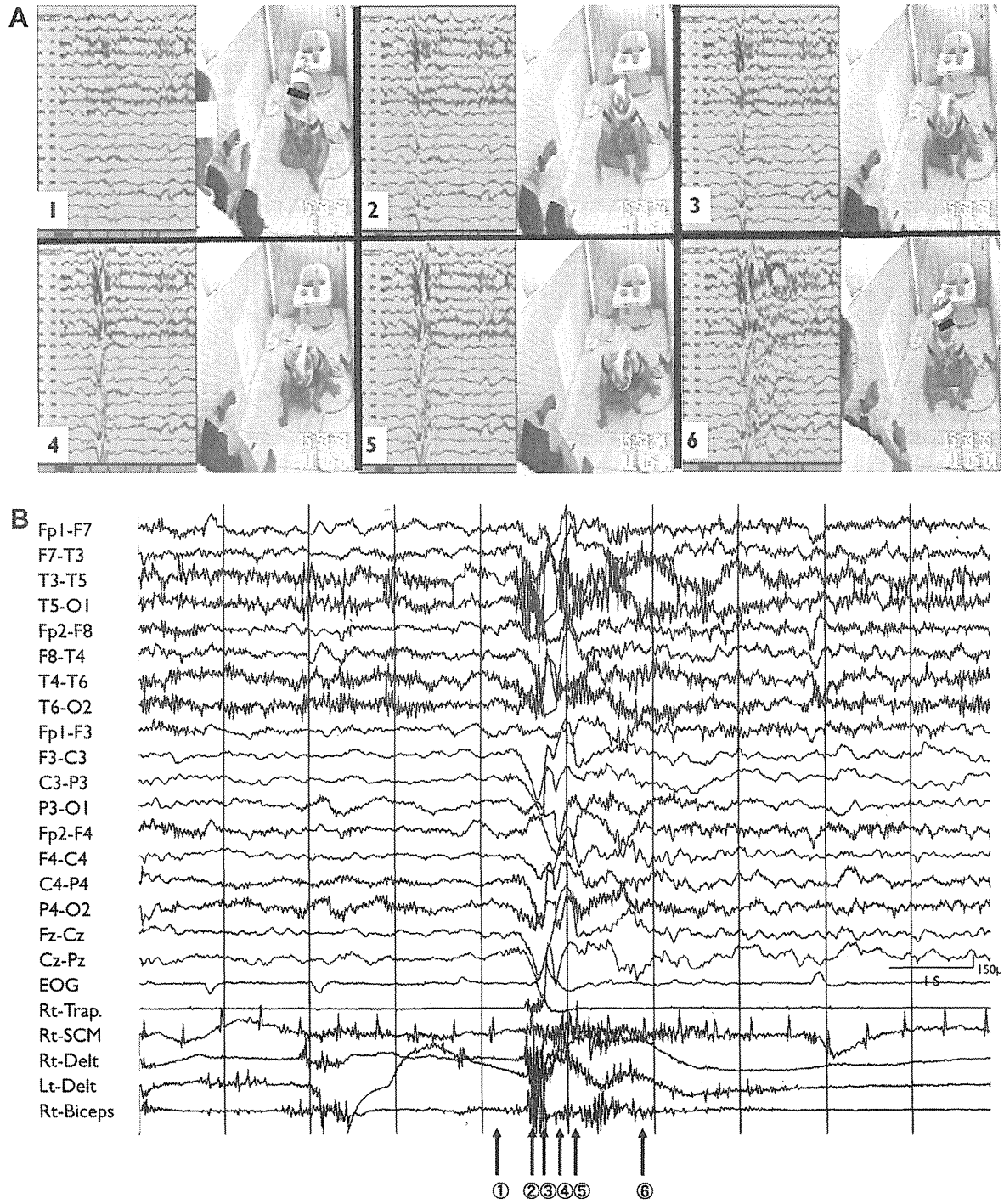

Fig. 1. Ictal video-polygraph of epileptic drop attacks due to Flexor type epileptic spasms (Case No. 3). The patient started to have EDA at 1 year and 5 months of age when his psychomotor development was grossly normal. The seizures gradually increased in frequency despite the antiepileptic drug treatment at the local hospital under the tentative diagnosis of MAE, and he was subsequently referred to our hospital at 3 years of age. He was moderately retarded and had daily EDA, as shown in the figure. (A) Ictal video: Before the attack, he was playing with his mother (1). He suddenly dropped his head simultaneously while abducting both his arms (2–3), bent his trunk further at the waist, and touched both his hands on the bed (4–5). He quickly recovered his previous position (6). Numbers indicate the sequence of events. (B) Ictal polygraph: Ictal EEG showing paroxysmal high amplitude biphasic slow discharges, corresponding to EMG discharges involving the right trapezius, sternocleidomastoid, deltoid, and biceps muscles. There were no atonia following the spasms on EMG discharges. Trap, trapezius muscle; Delt, deltoid muscle; SCM, sternocleidomastoid muscle; Biceps; biceps muscle.

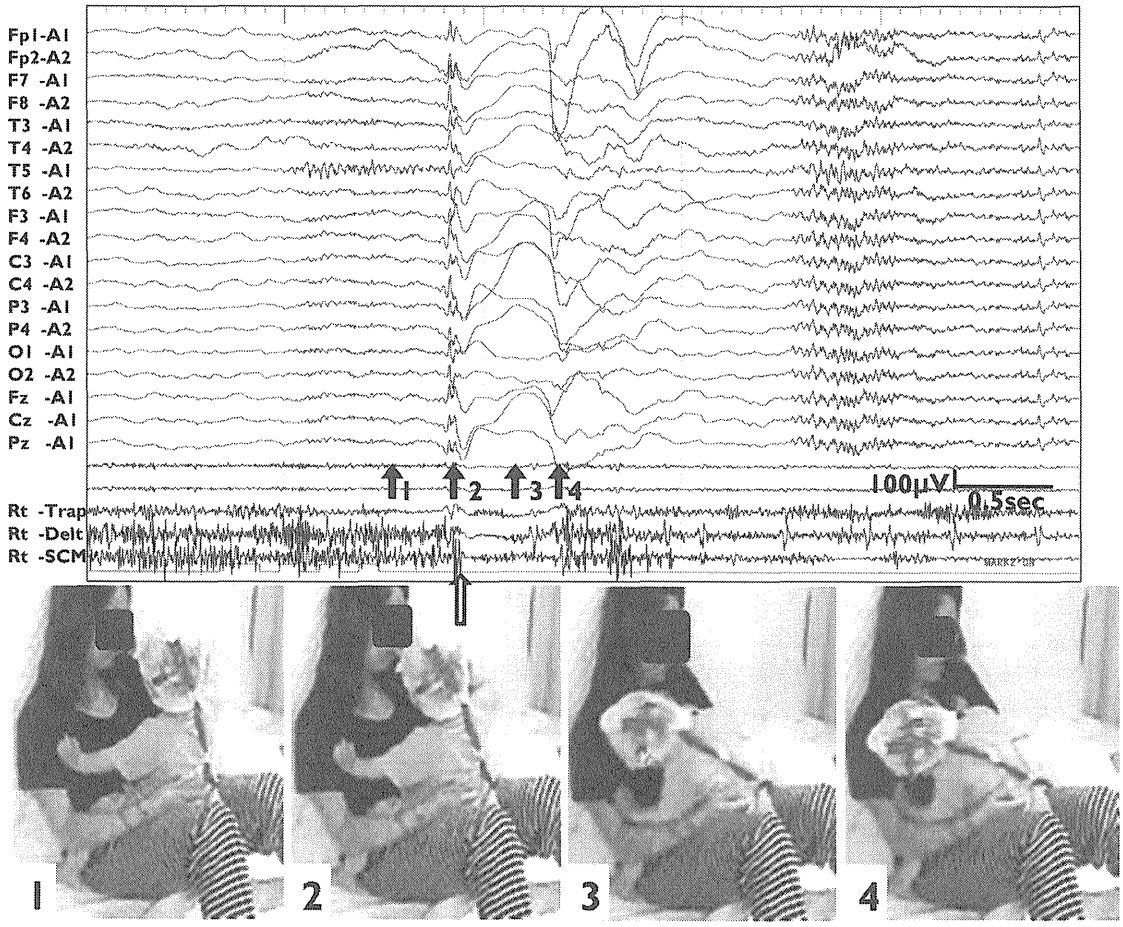

Fig. 2. Ictal video-polygraph of epileptic drop attacks caused by myoclonic-atonic seizures (Case No. 17). The patient developed EDA at 1 year of age and was referred to our hospital 2 months later. Brain MRI showed lipoma and arterio-venous malformation in the midline structure. Ictal polygraph: Ictal EEG showed paroxysmal high amplitude spike-and-slow discharges, corresponding to the interruption of ongoing EMG discharges (approximately 500 ms) involving the right trapezius, sternocleidomastoid, and deltoid muscles. There was a brief EMG discharge immediately before the silencing of EMG discharges (white arrow). Ictal video: Before the attack, he was sitting on his mother's knee (1). He suddenly froze his movements (2) and collapsed his body onto his mother's chest (3–4). Numbers indicate the sequence of events.

myoclonic-flexor seizures in the remaining four. The former seizure type was video-polygraphically identical to those observed in the two patients with symptomatic epilepsy. The latter showed initial flexion of the upper trunk at the waist followed by dropping of the body, with the intensity depending on the strength of the myoclonic seizures. They occurred singly in all patients and corresponded to generalized high amplitude spike or polyspike-and-wave complexes (Table 2, Fig. 4).

In conclusion, EDA in symptomatic epilepsy were more often caused by ES and occurred in clusters than those in idiopathic MAE ($P < 0.05$).

3.2. Other demographic data

Associated seizure types and interictal as well as ictal EEG findings were described in Tables 1 and 2. The associated seizure types as well as interictal EEG patterns were different; generalized tonic-clonic seizures (GTCS) were more frequent in idiopathic MAE, and the independent focal or multifocal accentuations of generalized spike-and-wave complexes were more frequent in the symptomatic group ($P < 0.05$).

3.3. Development and intelligence at the investigation

No subjects had an abnormal perinatal history. In the symptomatic group, development before the onset of epilepsy was normal in 10 patients and significantly retarded in the remaining 11. At the first visit to our hospital, development was normal in four patients, borderline to mildly retarded in 6, moderately retarded in 9, and severely retarded in 2. The four patients with normal development demonstrated both brain MRI and SPECT abnormalities at the first examination in our hospital and their EDA was caused by ES. Three of the four patients who showed normal development at the first visit were given an erroneous diagnosis of idiopathic MAE at the local hospital.

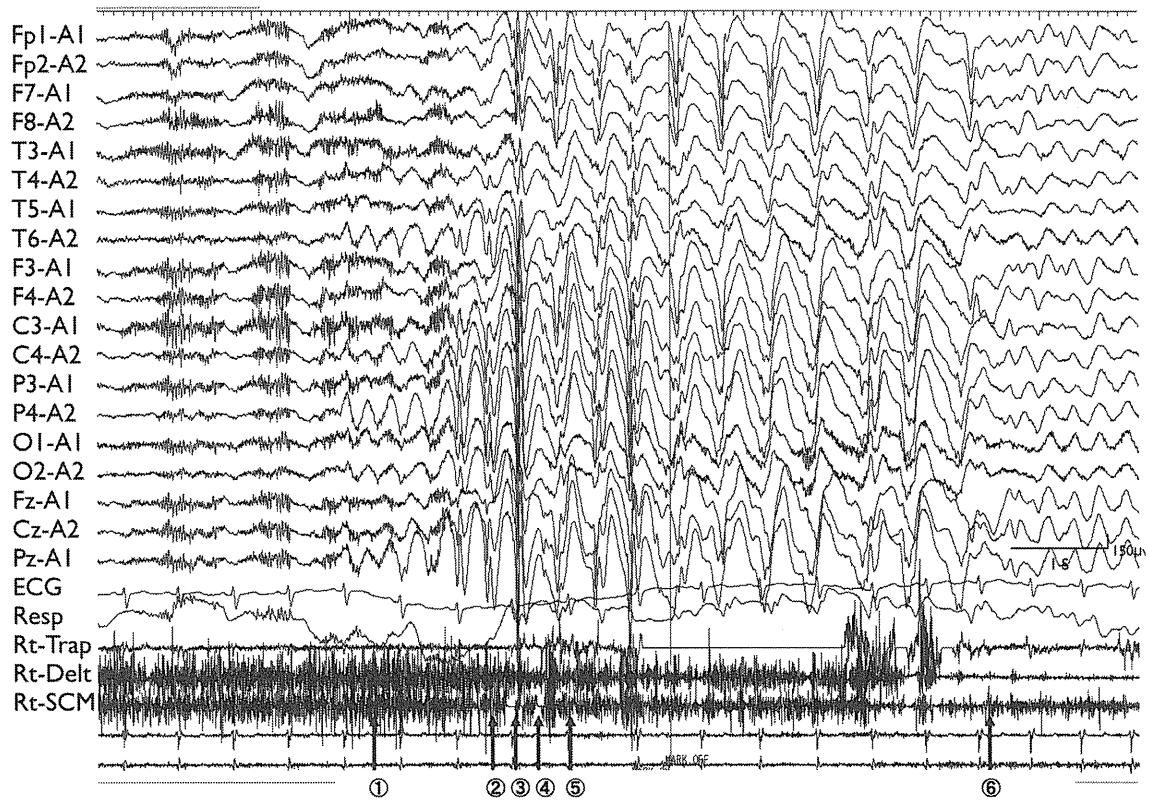

Fig. 3. Ictal polygraph of atonic seizures caused by rhythmic runs of generalized spike-and-wave complexes (Case No. 21). The patient started to have atypical absence seizures at 3 years and 4 months of age and combined daily EDA one year later. She exhibited moderate mental retardation before the onset of epilepsy despite the lack of a brain MRI abnormality. Ictal polygraph: Ictal EEG showing a rhythmic burst of generalized spike-and-wave complexes lasting 5 s. A brief interruption in ongoing EMGs was observed twice (arrow) at the SCM muscles, which corresponded to her dropping her head on the video.

No developmental delays were observed in the idiopathic group, except for one with a borderline delay at the first visit.

3.4. Etiology

Two patients had a genetically confirmed congenital anomaly syndrome including 21 trisomy syndrome and cardio-facio-cutaneous (CFC) syndrome in one patient each. The former exhibited dysmyelination and the latter hypoplasia of the cerebrum and corpus callosum on brain MRI. Four patients had cerebral dysgenesis including focal cortical dysplasia in two, brain lipoma combined with arteriovenous malformation in one, and Chiari type 1 malformation in the remaining one. Two patients were found to have the initial manifestations of late infantile neuronal ceroid lipofuscinoses (NCL) and glucose transporter type 1 deficiency syndrome (GLUT-1 DS), respectively. The patient with GLUT-1 DS exhibited transient myoclonic attacks during early infancy and had already exhibited psychomotor retardation and ataxia before the onset of EDA. As for postnatal etiology, cerebral infarction was detected in the right occipital lobe of one patient after surgery for Tetralogy of Fallot. The etiologies of the remaining 12 patients were unknown. The cerebrospinal fluid (CSF) was examined in these patients and no abnormal findings were revealed, including hypoglycorrhachia. Four patients had a family history of febrile seizures.

In idiopathic MAE, a family history of febrile seizures and epilepsy was found in six and three patients, respectively.

3.5. Treatment and outcome

The short-term outcome of EDA was relatively good, responding very well to adrenocorticotropic hormone (ACTH) therapy in eight cases, antiepileptic drugs in 7, ketogenic diet in 2, and epilepsy surgery in 1. The combination of valproic acid (VPA), ethosuximide (ESM), and lamotrigine (LTG) was effective in three patients with atonic seizures associated with runs of 2-Hz generalized bilaterally synchronous spike-and-wave complexes. VPA ($n = 2$), LTG ($n = 1$), and the combination of VPA and ESM ($n = 1$) were also

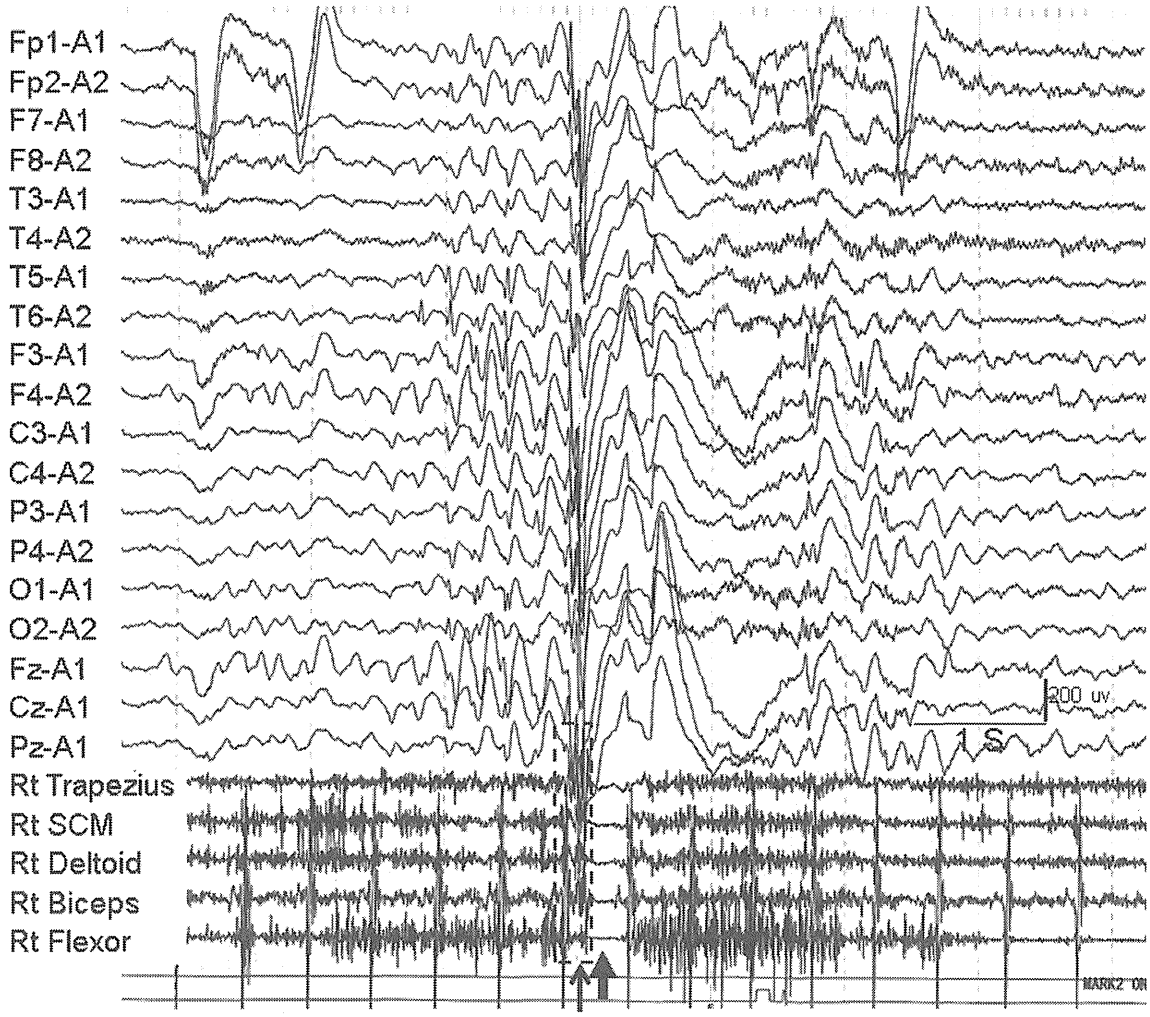

Fig. 4. Ictal polygraph of myoclonic-atonic seizures in a 3-year and 10-month-old boy with idiopathic MAE. He developed normally until 3 years and 6 months of age when he first had GTCS. A few weeks later, he started to have EDA refractory to antiepileptic drug treatment. He was referred to our hospital at 3 years and 10 months of age when he had daily EDA characterized by initial vocalization followed by collapsing forward or downward. Brain MRI was normal and interictal EEG showed frequent generalized spike-and-wave complexes at 2–3 Hz. Ictal EEG showed a high-amplitude polyspike-and-wave complex corresponding to initial brief EMG discharges (myoclonic component: small arrow) followed by an interruption in ongoing EMG activity (atonic component: big arrow).

effective. One patient underwent focal resection for left parietal focal cortical dysplasia, resulting in the cessation of EDA for 7 years. Total corpus callosotomy was performed in the other patient following the failure of ACTH and ketogenic diet therapy, and this resulted in only a partial improvement in EDA. At the last follow-up, EDA continued in six patients with ES, while EDA evolved to complex partial seizures in two patients and atypical absence in one patient.

In idiopathic MAE, EDA were controlled by ACTH therapy in four patients, VPA in 2, clonazepam (CZP) in one, and a combination of VPA and ESM in 6. In the other six patients, EDA gradually disappeared or were replaced by GTCS and GTS. In the remaining patient, EDA continued without responding to ACTH or ketogenic diet therapy at the final follow-up period.

4. Discussion

The aim of this study was to clarify what seizure types were responsible for causing EDA in infants and young children with symptomatic epilepsy, and also to identify differences in the seizure types causing EDA between those with symptomatic epilepsy and those with MAE [2,8,14]. Since the treatment strategy for EDA depends mostly on the exact seizure type responsible for falling of the body, it is important to make a correct diagnosis of the seizure types causing EDA, i.e. the response to ketogenic diet therapy has been reported to be favorable in idiopathic MAE [9].

In this study, EDA in symptomatic epilepsy were attributed to flexor type ES, myoclonic-atonic seizures, and atonic seizures in this order; therefore, ES were

the most frequent cause, accounting for EDA in 71% of all patients, which was consistent with earlier findings [11,12]. Previous studies reported that flexor or axial spasms were the most frequent cause of EDA in older children and adults with LGS or related syndromes. In our study, no patients fulfilled the strict LGS criteria in part due to the inclusion criteria of younger ages [8]. Some were not able to satisfy the EEG criteria of LGS and others had only ES in clusters closer to the concept of late-onset infantile spasms [15–17]. The epilepsy syndrome classification is not always accurate, i.e. LGS and idiopathic MAE, when patients are too young and also early in the clinical course because the epileptic process is still evolving. It also takes time for the presence of typical clinico-electrical pictures to develop.

In this study, symptomatic epilepsy with EDA was caused by various heterogeneous etiologies, ranging from focal cortical dysplasia to neurodegenerative or neurometabolic disorders causing the common seizure and EEG manifestations; EDA and generalized spike- or polyspike-and-wave EEG abnormalities. Sturge–Weber syndrome and glucose transporter 1 deficiency syndrome were recently identified as the underlying disorders of idiopathic MAE [18,19]. This study included one patient with GLUT-1 DS having EDA, who had recurrent atonic drop seizures and mild neurological abnormalities. During this age period, EDA were also detected in children with symptomatic focal and generalized epilepsy and, at times, should be differentiated from idiopathic MAE in cases of apparently normal development prior to the onset of EDA. We have to search extensively for the underlying metabolic or structural cause in such cases and consider a different treatment strategy. Four patients showed normal development at the first visit to our hospital, 3 of which were also given an erroneous diagnosis of idiopathic MAE in the referral hospital. They all had neuroimaging abnormalities indicating symptomatic etiologies as well as EDA caused by ES in spite of the absence of neurological abnormalities or developmental delays.

Although the exact prevalence of EDA has yet to be determined in children with symptomatic epilepsy, the absolute number of patients having EDA appears to be more frequent in symptomatic epilepsy than MAE because of the rare prevalence of the latter. Comparisons of EDA between symptomatic epilepsy and idiopathic MAE by means of detailed video-polygraphic examinations demonstrated clear differences in the exact seizure types between the two epilepsy types; ES were the most frequent seizure types causing EDA in the former, whereas myoclonic-atonic seizures were the most frequent in the latter. The mode of occurrence of EDA was also different because ES were more likely to occur in periodic clustering, while myoclonic-atonic seizures or myoclonic-flexor seizures occurred singly and did not cluster in a periodic fashion. A difference was also noted in the ictal EEG pattern; high amplitude biphasic slow discharges typical for the ictal EEG pattern of infantile spasms [9,20,21] were the most frequent in the former, whereas it was limited to generalized high-amplitude spike or polyspike-and wave discharges in the latter. In addition, the mode of EDA occurrence was also different between these two seizure types because ES were more likely to occur in periodic clustering while myoclonic-atonic or myoclonic-flexor seizures occurred singly and did not cluster in a periodic fashion.

Thus, the important point in history taking to differentiate EDA caused by ES in symptomatic epilepsy from those by myoclonic-atonic or myoclonic-flexor seizures in idiopathic MAE is the presence of periodic clustering in spite of ES in clusters being able to evolve to a single ES event with age. The independent focal or multifocal accentuations of generalized spike-and-wave complexes also suggest the presence of focal structural abnormalities causing ES, indicating a detailed brain MRI examination.

In conclusion, there is some overlapping in the age distributions of EDA onsets between patients with MAE and those with symptomatic epilepsy whose main seizure type is ES.

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Original article

Nationwide survey of glucose transporter-1 deficiency syndrome (GLUT-1DS) in Japan

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Abstract

Objectives: We conducted a nationwide survey of glucose transporter type-1 deficiency syndrome (GLUT-1DS) in Japan in order to clarify its incidence as well as clinical and laboratory information.

Subjects and methods: A questionnaire to survey the number of genetically and clinically confirmed cases of GLUT-1DS was sent to 1018 board-certified pediatric neurologists, which resulted in 57 patients being reported. We obtained the clinical and laboratory data of 33 patients through a secondary questionnaire.

Results: The age of the 33 patients (male: 15, female: 18) at the time of the study ranged between 3 and 35 years (mean: 13.5 years). The age of these patients at the onset of initial neurological symptoms ranged between the neonatal period and 48 months (mean: 9.4 months). GLUT-1DS was diagnosed at a mean age of 8.4 years (range: 1 year to 33 years). The initial symptom was convulsive seizures, which occurred in 15 cases, and was followed by abnormal eye movements in 7 cases and apneic or cyanotic attacks in 4 cases. The latter two symptoms most frequently occurred early in infancy. Thirty-two patients (97%) exhibited some type of epileptic seizure. Neurological findings revealed that most patients had muscle hypotonia, cerebellar ataxia, dystonia, and spastic paralysis. Mild to severe mental retardation was detected in all 33 cases. Furthermore, paroxysmal episodes of ataxia, dystonia/dyskinesia, and motor paralysis were described in approximately 1/3 of all patients. The factors that frequently aggravated these events were hunger, exercise, fever, and fatigue, in that order. The mean CSF/blood glucose ratio was 0.36 (0.28–0.48). Pathological mutations in the *SLC2A1* gene were identified in 28 out of 32 cases (87.5%).

Conclusion: The results described herein provided an insight into the early diagnosis of GLUT1-DS, including unexplained paroxysmal abnormal eye movements, apneic/cyanotic attacks, and convulsive seizures in infancy, as well as uncommon paroxysmal events (ataxia, atonia, and motor paralysis) in childhood.

Keywords: Glucose transporter type-1; Hypoglycorrhachia; Epilepsy; Movement disorders; Ketogenic diet

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