View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Seizure 21 (2012) 522–528

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Efficacy of topiramate for intractable childhood generalized epilepsy with epileptic spasms: With special reference to electroencephalographic changes

Fumika Endoh, Katsuhiro Kobayashi *, Yumiko Hayashi, Takashi Shibata, Harumi Yoshinaga, Yoko Ohtsuka

Department of Child Neurology, Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, 5-1 Shikatacho 2-chome, Kita-ku, Okayama 700-8558, Japan

ARTICLE INFO

Article history:
Received 14 January 2012
Received in revised form 9 May 2012
Accepted 11 May 2012

Keywords:
Epileptic spasms
Intractable epilepsy
Topiramate
Children
Electroencephalogram

ABSTRACT

Purpose: Epileptic spasms (ES) beyond infancy are a highly refractory type of seizures that require the development of an effective treatment. We therefore studied the efficacy and safety of topiramate (TPM), which is a drug that is indicated to be effective for intractable childhood epilepsy, for ES.
Methods: Out of 58 children with ES, we enrolled 33 patients treated with TPM at ≤12 years of age. The administration of TPM was limited to cases of epilepsies that were resistant to any other potent treatment. We retrospectively investigated the efficacy of TPM for seizures and changes in electroencephalogram (EEG) findings.
Results: The median age at the start of TPM treatment was 5 years, 8 months. All patients had ES and 28 also had tonic seizures. As for the efficacy of TPM for all seizures, five patients became seizure-free and two had a ≥50% reduction in seizures. Seizure aggravation was observed in six patients. Of 29 patients whose EEG findings were compared before and during TPM treatment, nine showed EEG improvement with reduced epileptic discharges. Adverse effects were observed in 13 patients and included somnolence, anorexia, and irritability. In general, TPM was well tolerated.
Conclusions: TPM can be effective at suppressing very intractable ES in a proportion of patients who do not respond to any other treatment. The efficacy of TPM may be predictable based on EEG changes observed early in the course of treatment. TPM is promising for the treatment of extremely intractable childhood epilepsy and it has largely tolerable adverse effects.
© 2012 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Topiramate (TPM) was initially approved as adjunctive therapy for partial-onset seizures in adults; this has been the case in Japan since July 2007. The use of TPM is currently extended to include childhood epilepsies in many other countries. TPM appears to be effective for a broad range of seizure types, including generalized seizures, particularly intractable seizures in severe epilepsies during infancy and childhood.

Epileptic spasms (ES) are typically observed in West syndrome (WS), a representative type of age-dependent epileptic encephalopathy, but ES are occasionally observed in patients who persistently exhibit clinical findings similar to WS beyond infancy, and in patients with generalized epilepsies during later childhood, including Lennox–Gastaut syndrome (LGS). ES, particularly those occurring beyond infancy, are generally resistant to treatment.[1–5]

There are several reports on the efficacy of TPM for intractable childhood epilepsy, including WS and LGS; the efficacy rate of ≥50% seizure reduction has ranged from 24 to 60%.[6–18] However, the efficacy of TPM for ES beyond infancy has not yet been intensively investigated. We therefore retrospectively analyzed the efficacy and adverse effects of TPM along with the concomitant EEG changes for children who had intractable generalized epilepsy with ES.

2. Subjects and methods

The study subjects were patients who (1) had been visiting Okayama University Hospital for treatment of epilepsy commencing as Ohtahara syndrome, WS, LGS, or a related disorder, (2) were found to have ES during the period from 2008 to 2010, and (3) were ≤12 years of age during this period. The administration of TPM was limited to cases of epilepsies that were resistant to any other potent treatment. Written informed consent was obtained from the parents of the patients, after stating that TPM was approved as adjunctive therapy for patients with partial-onset seizures at ≥16 years of age in Japan. This study included subjects who were

* Corresponding author. Tel.: +81 86 235 7372; fax: +81 86 235 7377.
E-mail address: k_koba@md.okayama-u.ac.jp (K. Kobayashi).

1059-1311/$ – see front matter © 2012 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.seizure.2012.05.009

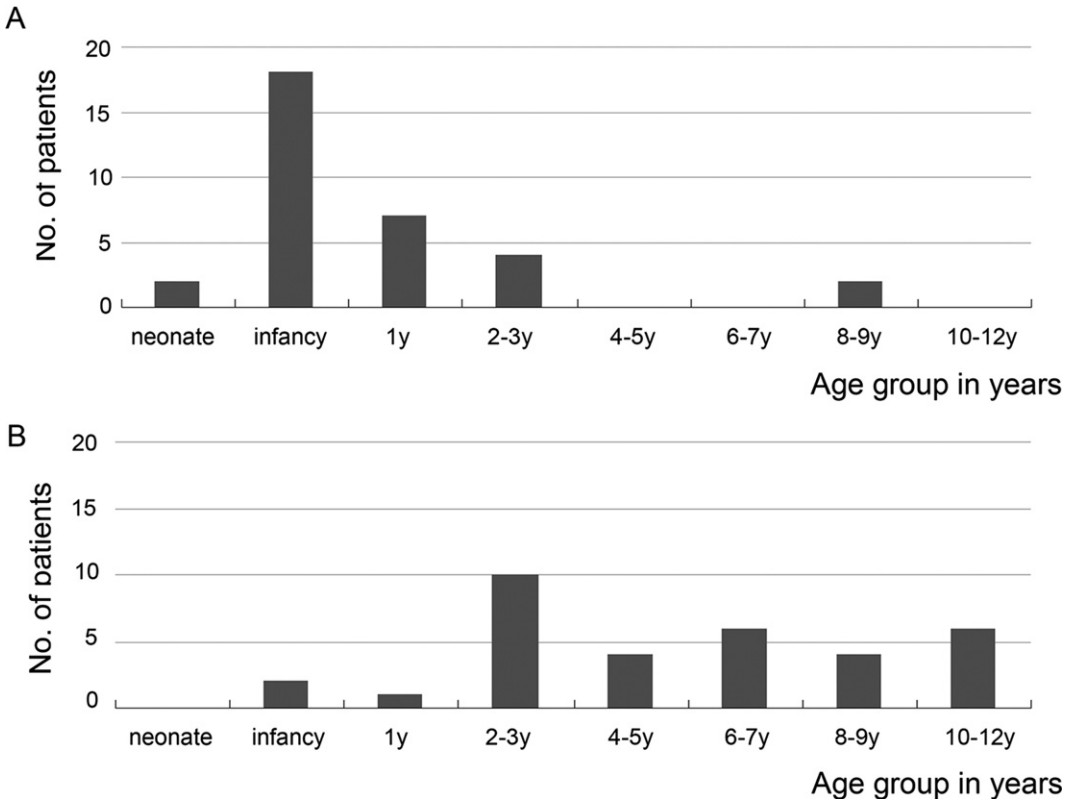

Fig. 1. Age distribution of patients treated with topiramate (TPM): age at epilepsy onset (A) and age at start of TPM treatment (B).

treated with TPM at ≤12 years of age, and excluded patients who were undergoing trials for other drugs without usage of TPM during the study period and patients whose parents were reluctant about using an unapproved drug.

As for the TPM prescription, the initial dosage was 0.5–1 mg/kg. TPM dosage was increased by 1–2 mg/kg increments every 2–4 weeks, up to a maximum of 10 mg/kg, in accordance with a previous study on childhood refractory epilepsy.[12]

The efficacy of TPM was categorized as (1) excellent, when seizures were suppressed for a period of ≥2 months; (2) good, when seizure frequency was reduced by ≥50%; (3) minimal, when seizures were reduced by 25–50%; (4) unchanged, when seizures were reduced by <25% or not at all; and (5) worsened, when seizure frequency increased. The responder rate was defined as the percentage of patients that achieved seizure freedom or ≥50% seizure reduction.

We retrospectively investigated the efficacy of TPM on seizures, changes in EEG findings, and retention of TPM, as of the last evaluation day, September 30, 2011, in children with intractable generalized epilepsy.

Statistical analysis of the responder rate was performed with Fisher's exact test using SPSS (Japanese ver. 17; SPSS, Tokyo, Japan) for age of seizure onset, diagnosis that was linked to the types of EEG findings, and usage of representative concomitant drugs. Values of $p < 0.05$ were considered significant.

3. Results

3.1. Clinical findings of the subjects (Table 1)

There were a total of 58 candidate patients for this study (36 boys and 22 girls); 33 subjects (21 boys and 12 girls) were treated with TPM. As for patients treated with TPM, age at the onset of epilepsy ranged from 2 days to 8 years, 10 months, and was <2 years in 27 patients (82%) (Fig. 1A). Age at the start of TPM treatment ranged from 6 months to 12 years, 3 months (mode: 2–3 years) (Fig. 1B). The latency from the onset of epilepsy to the start of TPM treatment ranged from 5 months to 12 years (median: 3 years). Seizure frequency was daily in most patients. All patients had ES and 28 also had tonic seizures. Mental retardation was observed in all patients, and was particularly severe in 28 (85%).

As for the epilepsy diagnosis and EEG findings in children treated with TPM and children not treated with TPM, LGS, which is characterized by the presence of multiple seizure types and/or tonic seizures and an EEG pattern of diffuse slow spike-waves with or without concomitant multifocal spikes, was diagnosed in 18 and 13 patients, respectively. Severe epilepsy with multifocal independent spike foci (SE-MISF),[19,20] which is characterized by the presence of generalized seizures, including tonic seizures, and EEG findings of dominant multifocal spikes reminiscent of hypsarrhythmia with or without sporadic diffuse discharges, was observed in 9 and 10 patients in each treatment group, respectively. WS with ES and hypsarrhythmia in EEG was diagnosed in one patient in each treatment group; early myoclonic encephalopathy (EME) with ES and myoclonus was diagnosed in three patients treated with TPM; and other unspecific types of symptomatic generalized epilepsy were diagnosed in two patients and one patient in each treatment group, respectively.

Magnetic resonance imaging (MRI) was performed on all patients: various degrees of brain atrophy were observed in 11 children treated with TPM and 13 not treated with TPM. Lissencephaly was observed in one and three patients in each treatment group, respectively; other types of cortical development malformation in three patients in each treatment group, brain infarction in one patient in each treatment group, tuberous sclerosis was observed in two patients treated with TPM, and a small unidentified white matter lesion was observed in one patient

Table 1
Demographic data of patients.

	No. of patients treated with TPM	No. of patients not treated with TPM
Total	33	25
Gender		
Male	21	15
Female	12	10
Etiology		
Cryptogenic	2	0
Symptomatic	31	25
Perinatal complications	5	6
Cortical dysplasia	4	5
Tuberous sclerosis	2	0
Encephalitis/encephalopathy	3	4
Infarction	1	1
Multiple anomalies	2	0
Unknown	14	9
Diagnosis		
EME	3	0
West syndrome	1	1
Lennox–Gastaut syndrome	18	13
SE-MISF	9	10
Symptomatic generalized epilepsy	2	1
Seizure frequency		
Daily	30	21
Weekly	3	4
Seizure type		
Epileptic spasms	33	25
Tonic seizures	28	22
Mental retardation		
Mild	2	0
Moderate	3	1
Severe	28	24
Age at the onset of epilepsy	0–106 mo (median: 6)	0–90 mo (median: 5)
Age at the start of TPM treatment	6–147 mo (median: 68)	–
Latency from epilepsy onset to TPM treatment	5–144 mo (median: 38)	–
Number of previous AEDs	4–12 (mean: 6)	3–12 (mean: 5)
Number of concomitant AEDs	1–5 (mean: 3)	–

AEDs, antiepileptic drugs; EME, early myoclonic encephalopathy; SE-MISF, severe epilepsy with multifocal independent spike foci.

not treated with TPM. No abnormalities were detected in the remaining 15 and 4 patients, respectively.

The number of antiepileptic drugs (AEDs) used before TMP administration ranged from four to 12 (mean: 6). The number of concomitant drugs at the start of TPM administration ranged from one to five (mean: 3). Concomitant drugs included sodium valproate (VPA) (used in 26 patients), zonisamide (ZNS) (20 patients), lamotrigine (LTG) (13 patients), and clobazam (CLB) (17 patients). Before TPM, synthetic adrenocorticotropic hormone (ACTH) therapy was performed in 21 patients, oral steroid therapy in four, thyrotropin-releasing hormone (TRH) therapy in two, and ketogenic diet therapy in two.

3.2. Efficacy of TPM

The efficacy of TPM for all seizures was excellent in five patients (15%), good in two (6%), minimal in three (9%), unchanged in 17 (52%), and worsened in the remaining six (18%) (overall responder rate: 21%, 7 of 33 patients). Of the five patients with excellent responses, two experienced relapse of ES after 2 or 3 months of seizure freedom, but seizures continued to be completely suppressed in the remaining three patients as of the last follow-up (i.e., seizure freedom for 10 months, 1 year and 1 month, and 1 year, 6 months). In terms of the efficacy of TPM according to seizure type, the responder rate was 21% (7 of 33 patients) for ES, and 29% (8 of 28) for tonic seizures (Table 2), with no apparent difference between seizure types.

The seizure aggravation observed in six patients was related to ES in one patient and tonic seizures in the other five.

3.3. EEG findings during TPM treatment

EEG findings before and during the TPM treatment were compared in 29 patients, excluding four who had to stop TPM early without EEG recording because of adverse effects. We observed EEG improvement with reduced epileptic discharges in 9 patients (31%), no improvement in 17 (59%), and worsening in the remaining 3 (10%).

Of the nine patients with EEG improvement, TPM efficacy was excellent in five, good in one, minimal in one, and unchanged in the remaining two. In the EEGs of the three patients with persistent seizure freedom, the epileptic discharges disappeared. The two patients with seizure relapse after temporary freedom had transient EEG improvement with reduction of spikes and slow waves during the period of seizure suppression.

Of the three patients with EEG worsening, the TPM treatment caused aggravation of seizures in two and had no effect in the other.

The relationships between TPM effects on seizures and EEG findings are presented in Table 3.

The clinical and EEG findings of three patients (Patients 1–3) with seizure freedom and marked EEG improvement are presented below. As for Patient 2, who had symptomatic LGS, EEG recorded at 3 years of age before the start of TPM showed multifocal epileptic discharges over a slow background comprising theta and delta waves during wakefulness, and a persistent mixture of diffuse slow spike-waves and multifocal discharges during sleep (Fig. 2A). On the fifth day of TPM administration, when seizure reduction was not yet apparent, some improvement in the EEG pattern was observed, with a decrease in slow waves and epileptic discharges during wakefulness (Fig. 2B). On the 13th day of TPM treatment, when tonic seizures were suppressed but ES remained, EEG showed occipital rhythmic activity with a further reduction in slow waves during wakefulness and a reduction in diffuse epileptic discharges during sleep as well (Fig. 2C). On the 19th day of TPM treatment, when seizures were finally suppressed with a dose of 7.5 mg/kg, EEG no longer showed epileptic discharges (Fig. 2D).

With respect to Patient 3 with symptomatic SE-MISF, EEG recorded at 5 years, 8 months of age before the start of TPM showed numerous epileptic discharges over a slow background without occipital rhythms during wakefulness, and even more multifocal epileptic discharges during sleep. EEG showed a reduction in epileptic discharges during both wakefulness and sleep on the fourth day of TPM treatment, and seizures began to decrease 3 days later. On the 15th day of TPM treatment, when seizures were finally suppressed with a dosage of 2 mg/kg, EEG showed occipital 7 Hz theta rhythms and no epileptic discharges during wakefulness, and a considerable reduction in epileptic discharges during sleep. Later examination revealed that epileptic discharges in sleep EEGs finally disappeared after 6 months of TPM administration.

As for Patient 1, who had symptomatic LGS, EEG recorded at 3 years, 3 months of age before the start of TPM treatment showed multifocal spikes over a slow background without occipital rhythms during wakefulness, and intense generalized epileptic discharges including slow spike-waves during sleep. The frequency of tonic seizures began to decrease after about 3 months of TPM administration, and both tonic seizures and ES disappeared 1 month later at a dosage of 6 mg/kg. EEG then showed occipital 8 Hz alpha rhythms during wakefulness and rare central spike-waves during sleep.

Table 2
TPM efficacy.

	No. of patients	Excellent	Good	Minimal	Unchanged	Worsened
Seizure type						
All seizures	33	5	2	3	17	6
Epileptic spasms	33	5	2	2	23	1
Tonic seizures	28	5	3	2	13	5
Age of seizure onset[a]						
Neonatal period	2	0	0	0	1	1
Infancy	18	3	1	0	13	1
1–2 yr	7	1	0	2	1	3
2–4 yr	4	1	1	0	1	1
8–10 yr	2	0	0	1	1	0
Diagnosis[b]						
EME	3	0	0	0	2	1
West syndrome	1	1	0	0	0	0
LGS	18	3	1	3	8	3
SE-MISF	9	1	1	0	6	1
Symptomatic GE	2	0	0	0	1	1
Seizure frequency						
Daily	30	4	2	4	15	6
Weekly	3	1	0	0	2	0
EEG findings						
Hypsarrhythmia	6	1	0	0	4	1
Multifocal SWs[c]	9	1	1	0	5	2
Diffuse slow SWs	18	3	1	3	8	3
Drugs[d]						
VPA	26	3	2	2	13	6
ZNS	20	3	2	1	11	3
CLB	17	2	2	0	9	4
LTG	13	3	1	1	6	2
Miscellaneous[e]	32	4	0	2	20	6

EME, early myoclonic encephalopathy; LGS, Lennox–Gastaut syndrome; symptomatic GE, symptomatic generalized epilepsy; SE-MISF, severe epilepsy with multifocal independent spike foci; SWs, spike-waves; VPA, sodium valproate; ZNS zonisamide; CLB, clobazam; LTG, lamotrigine. Responders are defined as patients who had excellent or good responses with ≥50% seizure reduction, and its relation with each of the following items is indicated below.

[a] Age of seizure onset was categorized as whether neonate/infancy (<12 months) or later childhood (≥1 year) ($p = 1.000$). There were no patients who had an onset of epilepsy between 4 and 8 years of age.

[b] Diagnosis was categorized as whether LGS with slow spike-waves or otherwise ($p = 1.000$).

[c] Multifocal SWs with or without concomitant diffuse discharges.

[d] With respect to the usage of concomitant drugs, $p = 0.623$ (VPA), $p = 0.676$ (ZNS), $p = 1.000$ (CLB), and $p = 0.393$ (LTG).

[e] Miscellaneous drugs include clonazepam (used in a total of 7 patients), phenobarbital (6), vitamin B6 (5), phenytoin (4), carbamazepine (3), ethosuximide (3), sulthiame (2), potassium bromide (1), and nitrazepam (1).

3.4. Details of TPM responders

The detailed findings of seven patients who responded to TPM are summarized in Table 4. All patients had both ES and tonic seizures and at least four AEDs were tried in all patients before TPM. Synthetic ACTH therapy was also performed in five patients. TPM dosage at the time of seizure suppression varied and ranged from 3 to 9 mg/kg; it was ≤4 mg/kg in three patients. The three patients with long-lasting seizure freedom (Patients 1–3) also exhibited mental improvement following seizure termination, manifested as an ability to smile and to provide better responses to various stimuli. Patient 5, who had a seizure relapse, also exhibited some developmental improvement during the temporary seizure freedom.

3.5. TPM retention

TPM was discontinued at the time of follow-up in 17 patients, including six with seizure aggravation whose TPM dosage at the time of seizure aggravation was relatively low: 1 mg/kg in two patients, 2–3 mg/kg in two patients, 4 mg/kg in one patient, and 8 mg/kg in the remaining patient. The reasons for TPM discontinuation were the adverse effects (mentioned below) in seven patients and ineffectiveness in four patients.

Sixteen patients continued taking TPM, with the maximum dosage ranging from 1.7 to 10 mg/kg (mean: 7.3 mg/kg). Duration of TPM administration ranged from 3.4 to 36.2 months (mean: 17.6 months).

Table 3
Relationships between TPM effects on seizures and EEG findings.

Seizures	EEG findings			
	Improved	Unchanged	Worsened	Not recorded
Excellent	5			
Good	1	1		
Minimal	1	2		
Unchanged	2	11	1	3
Worsened		3	2	1

3.6. Adverse effects

Adverse effects caused by TPM were observed in 13 of 33 patients (39%), namely, anorexia in eight, somnolence in five, irritability in five, and hypotonia/inactiveness in three, with overlaps. No patient showed abnormalities in liver or renal function. The maximum TPM dosage in the 13 patients with adverse effects ranged from 1 to 9.3 mg/kg (mean: 5.1 mg/kg). In the seven patients who stopped TPM because of adverse effects, the mean dosage was 3.2 mg/kg, which was not high. Adverse effects were relatively severe in three patients: two with anorexia resulting in weight loss and the other with somnolence and hypotonia causing glossoptosis and dyspnea. The TPM dosage of these patients ranged from 1 to 3 mg/kg. Three of the remaining four patients experienced adverse effects at a small TPM dosage ranging from 2 to 3 mg/kg. In patients who had adverse effects at a small TPM dosage and showed little or no amelioration of seizures, increasing the dosage was problematic and TPM treatment was inevitably discontinued.

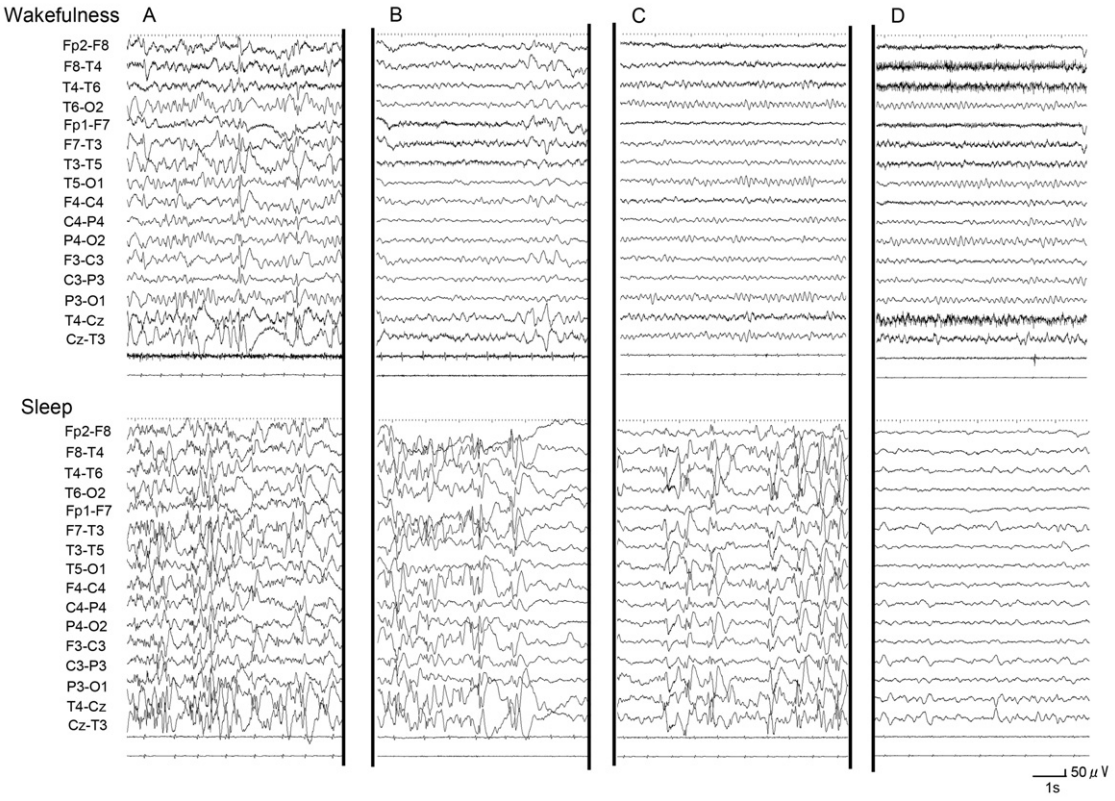

Fig. 2. Evolutional changes of EEGs in Patient 2 with TPM response. EEGs recorded during wakefulness are arranged at the top, with EEGs during sleep at the bottom. The EEG recorded at 3 years of age before the start of TPM shows a mixture of diffuse and multifocal discharges over a slow background during wakefulness and intensification of discharges during sleep (A). The EEG recorded on the fifth day of TPM administration with a dose of 3.8 mg/kg shows a reduction in slow waves in the background as well as a reduction in discharges during wakefulness (B). The EEG recorded on the 13th day of TPM treatment with a dose of 7.5 mg/kg shows further improvement with the appearance of 8 Hz occipital rhythmical activity during wakefulness (C). The EEG recorded on the 19th day of TPM treatment with a dose of 9 mg/kg showed no epileptic discharges during either wakefulness or sleep, when seizures were finally suppressed (D).

Table 4
Profiles of seven TPM responders.

Patient	Diagnosis	Mental retardation	Age at onset of epilepsy	Age at start of TPM	Number of AEDs before TPM	Special treatment before TPM	Efficacy of TPM	TPM dosage at suppression of Sz (mg/kg)	Maximum TPM dosage (mg/kg)	EEG effect	Adverse effect
1	Symptomatic LGS	Severe	5 mo	3 yr, 3 mo	6	ACTH, γ-globulin, ketogenic diet	Sz-free	6	6	Improved	Anorexia
2	Symptomatic LGS	Moderate	1 yr, 4 mo	3 yr, 1 mo	6	ACTH	Sz-free	9	9	Improved	Anorexia
3	Symptomatic SE-MISF	Severe	3 yr, 11 mo	5 yr, 8 mo	5	None	Sz-free	3	3	Improved	None
4	Symptomatic WS	Severe	3 mo	9 mo	4	ACTH	Sz-free for 2 mo, subsequent relapse	3	9	Temporarily improved	None
5	Symptomatic LGS	Severe	6 mo	5 yr, 5 mo	7	ACTH	Sz-free for 3 mo, subsequent relapse	4	9	Temporarily improved	Anorexia
6	Symptomatic SE-MISF	Severe	1 mo	6 yr, 6 mo	6	ACTH, oral steroid	≥50% reduction		2	Improved	None
7	Cryptogenic LGS	Moderate	2 yr, 4 mo	6 yr, 10 mo	5	None	≥50% reduction		10	No changes	None

Sz, seizure; LGS, Lennox–Gastaut syndrome; SE-MISF, severe epilepsy with multifocal independent spike foci; WS, West syndrome; ACTH, synthetic adrenocorticotropic hormone.

3.7. Statistical analysis

None of the statistical analysis results regarding the relationship between the responder rate and the various items were significant (Table 2). The age of seizure onset was categorized as either neonate/infancy (<12 months in 20 patients) or later childhood (≥1 year in 13 patients) $p = 1.000$. Diagnosis was categorized as either LGS with slow spike-waves (18 patients) or otherwise (15 patients) $p = 1.000$. Seizure frequency was daily in 30 patients and weekly in the remaining 3, $p = 1.000$. With respect

to the effects of representative concomitant drugs, $p = 0.623$ for VPA, $p = 0.676$ for ZNS, $p = 1.000$ for CLB, and $p = 0.393$ for LTG.

Significant relationships could not be found through logistic regression analysis either (see Supplementary Table 1).

4. Discussion

In the current study, generalized epilepsy with ES appeared to be essentially intractable. The TPM responder rate was 21% (21% for ES, 29% for tonic seizures) and therefore lower than that in previous reports, including LGS and WS. As for LGS, Sachdeo et al.[6] reported rates of ≥50% seizure reduction as 28 and 33% for drop attacks and major seizures, respectively, in a double-blind placebo-controlled study. There are other reports of open-label studies, and the rate of ≥50% seizure reduction was 40–50% in most studies, though it was as low as 13 and 25% in some studies.[7,9,10,12,14] The TPM responder rate for WS was 70–88% in some studies[8,15,16] and tended to be better than that for LGS. The contrast in the responder rate between WS and generalized epilepsy with ES in the current study illustrates the considerable difference between these two disorders even though they share similar clinical findings of ES. ES beyond infancy are observed in patients with generalized epilepsies, including LGS, SE-MISF, and unsuppressed WS with a protracted clinical course. ES persisting beyond infancy are a unique type of seizures and may not be the same as ES in most infants with WS. It has been suggested that a subset of older children with ES actually have focal cortical-onset seizures[21]; such mechanisms may complicate the pathophysiology and make the treatment in ES beyond infancy difficult. The majority of the patients in our study underwent ACTH therapy to no avail, and an average of six drugs had already been tried before the TPM treatment, with limited usefulness. Therefore, the low efficacy of TPM in these patients was to be expected. The neurological and mental prognosis of children with ES is grim.[1–4] Of the current 33 patients, 31 had symptomatic epilepsy and all were mentally retarded (severely in 85%).

In this so-far unreported research on TPM treatment for children with generalized epilepsy with ES beyond infancy who did not respond to any prior conventional AEDs or ACTH therapy, it is noteworthy that TPM was effective in 21% of all patients. It is of particular note that it provided seizure suppression for ≥2 months in 15% of all patients. Three children have been enjoying seizure freedom for approximately 1 year, with some developmental improvement in responsiveness to various stimuli. It is expected that the suppression of seizures and the amelioration of EEG abnormalities that TPM treatment provides may contribute to enhanced neurocognitive development.

Reports that include EEG findings related to TPM treatment remain rare[8,16,17]; they mainly provide observations concerning the disappearance or persistence of epileptic discharges in responders but offer no detailed information regarding EEG changes during the treatment. In the present EEG study involving 29 patients (88%) of a 33-patient cohort, with comparison before and during TPM treatment, EEG improvement was observed in nine patients, including six responders in seizures. In two dramatic responders, EEG improvement preceded the clinical improvement of seizure reduction; EEG improvement was first observed during wakefulness with a decrease in not only epileptic discharges but also slow waves in the background. We previously investigated the efficacy of LTG in childhood epilepsy and found that EEG scarcely improved even in LTG responders, and that the disappearance of epileptic discharges in EEGs was not observed in any of the patients.[22] Thus, the close relation between changes in seizure frequency and EEG findings was remarkable in TPM treatment but lacking in LTG treatment. EEG may therefore serve as a prognostic indicator in TPM treatment.

Seizure aggravation is occasionally observed in patients undergoing TPM treatment despite its generally positive effect on intractable epilepsy. This was the case in six patients (18%) in the current study—a rate similar to the 10–21% observed in other reports.[9,10,12,14,18] Types of seizures aggravated by TPM were not described in detail in other reports, but five out of six cases of aggravation in the current study related to tonic seizures, suggesting that they may be more easily aggravated by TPM than ES.

Of the 13 patients that suffered adverse effects, such as anorexia, the effects were severe in 3 patients and mild in the remaining 10. This distribution was comparable to that indicated in previous reports. However, the emergence of adverse effects as a consequence of low-dose TPM (1–3 mg/kg) was problematic because such situations impeded subsequent titration to achieve sufficient beneficial effect and resulted in early discontinuation of TPM treatment.

Our findings lead us to conclude that TPM is effective and well tolerated in children with intractable generalized epilepsy with ES, and that some patients can even expect to achieve seizure freedom. Although ES beyond infancy are extremely resistant to treatment, TPM may be a useful treatment option for children who continue to suffer from ES. TPM may exert its effect on intractable epilepsy through multiple mechanisms of action.[23] We were unable to identify any particular group of patients who may benefit more from TPM with statistical significance, but the effectiveness of TPM may be gauged by monitoring early EEG changes during TPM administration. The current study has inherent limitations due to the small number of subjects and a lack of control groups. In the future, we intend to extend the usage of TPM to more children with intractable epilepsy, particularly ES, in order to confirm its efficacy.

Conflict of interest statement

The authors have no conflict of interest to disclose.

Funding sources

This study is supported in part by the Health and Labour Sciences Research Grant: Research on catastrophic epilepsy in infancy and early childhood – epidemiology, diagnosis and treatment guide, in part by a Research Grant (21B-5) for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare, Japan, and in part by a Research Grant (19A-6) for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare, Japan.

Acknowledgement

We thank Professor Toshihide Tsuda of the Department of Environmental Medicine, Epidemiology, Okayama University, Okayama, Japan, for his important suggestions for statistical analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2012.05.009

References

1. Talwar D, Baldwin MA, Hutzler R, Griesemer DA. Epileptic spasms in older children: persistence beyond infancy. *Epilepsia* 1995;**36**:151–5.
2. Ohtsuka Y, Kobayashi K, Ogino T, Oka E. Spasms in clusters in epilepsies other than typical West syndrome. *Brain and Development* 2001;**23**:473–81.
3. de Menezes MA, Rho JM. Clinical and electrographic features of epileptic spasms persisting beyond the second year of life. *Epilepsia* 2002;**43**:623–30.

4. Goldstein J, Slomski J. Epileptic spasms: a variety of etiologies and associated syndromes. *Journal of Child Neurology* 2008;**23**:407–14.
5. Auvin S, Lamblin MD, Pandit F, Vallée L, Bouvet-Mourcia A. Infantile epileptic encephalopathy with late-onset spasms: report of 19 patients. *Epilepsia* 2010;**51**:1290–6.
6. Sachdeo RC, Glauser TA, Ritter F, Reife R, Lim P, Pledger G. A double-blind, randomized trial of topiramate in Lennox–Gastaut syndrome. Topiramate YL Study Group. *Neurology* 1999;**52**:1882–7.
7. Glauser TA, Levisohn PM, Ritter F, Sachdeo RC. Topiramate in Lennox–Gastaut syndrome: open-label treatment of patients completing a randomized controlled trial. Topiramate YL Study Group. *Epilepsia* 2000;**41**:S81–90.
8. Glauser TA, Clark PO, McGee K. Long-term response to topiramate in patients with West syndrome. *Epilepsia* 2000;**41**:S91–4.
9. Coppola G, Caliendo G, Veggiotti P, Romeo A, Tortorella G, De Marco P, et al. Topiramate as add-on drug in children, adolescents and young adults with Lennox–Gastaut syndrome: an Italian multicentric study. *Epilepsy Research* 2002;**51**:147–53.
10. Mikaeloff Y, de Saint-Martin A, Mancini J, Peudenier S, Pedespan JM, Vallée L, et al. Topiramate: efficacy and tolerability in children according to epilepsy syndromes. *Epilepsy Research* 2003;**53**:225–32.
11. Watemberg N, Goldberg-Stern H, Ben-Zeev B, Berger I, Straussberg R, Kivity S, et al. Clinical experience with open-label topiramate use in infants younger than 2 years of age. *Journal of Child Neurology* 2003;**18**:258–62.
12. Al Ajlouni S, Shorman A, Daund AS. The efficacy and side effects of topiramate on refractory epilepsy in infants and young children: a multi-center clinical trial. *Seizure* 2005;**14**:459–63.
13. Grosso S, Galimberti D, Farnetani MA, Cioni M, Mostardini R, Vivarelli R, et al. Efficacy and safety of topiramate in infants according to epilepsy syndromes. *Seizure* 2005;**14**:183–9.
14. Grosso S, Franzoni E, Iannetti P, Incorpora G, Cardinali C, Toldo I, et al. Efficacy and safety of topiramate in refractory epilepsy of childhood: long-term follow-up study. *Journal of Child Neurology* 2005;**20**:893–7.
15. Valencia I, Fons C, Kothare SV, Khurana DS, Yum S, Hardison HH, et al. Efficacy and tolerability of topiramate in children younger than 2 years old. *Journal of Child Neurology* 2005;**20**:667–9.
16. Kwon YS, Jun YH, Hong YJ, Son BK. Topiramate monotherapy in infantile spasm. *Yonsei Medical Journal* 2006;**47**:498–504.
17. Korinthenberg R, Schreiner A. Topiramate in children with west syndrome: a retrospective multicenter evaluation of 100 patients. *Journal of Child Neurology* 2007;**22**:302–6.
18. Kluger G, Schäuble B, Rettig K, Schreiner A, Holthausen H. Effectiveness of low dose of topiramate following rapid titration in multiply handicapped children and difficult-to-treat epilepsy. *Neuropediatrics* 2009;**40**:61–5.
19. Ohtahara S, Ohtsuka Y, Kobayashi K. Lennox–Gastaut syndrome: a new vista. *Psychiatry and Clinical Neurosciences* 1995;**49**:S179–83.
20. Yamatogi Y, Ohtahara S. Multiple independent spike foci and epilepsy, with special reference to a new epileptic syndrome of "severe epilepsy with multiple independent spike foci". *Epilepsy Research* 2006;**70**:S96–104.
21. Ramachandrannair R, Ochi A, Imai K, Benifla M, Akiyama T, Holowka S, et al. Epileptic spasms in older pediatric patients: MEG and ictal high-frequency oscillations suggest focal-onset seizures in a subset of epileptic spasms. *Epilepsy Research* 2008;**78**:216–24.
22. Watanabe K, Kobayashi K, Endoh F, Yoshinaga H, Ohtsuka Y. Lamotrigine add-on therapy for childhood-onset refractory epilepsy: comparison of efficacy between 3 months and 6 months after initiation. *No to Hattatsu* 2011;**43**:453–8 [in Japanese].
23. Bourgeois B. Pharmacokinetics and pharmacodynamics of topiramate. *Journal of Child Neurology* 2000;**15**:S27–30.