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Case Report

Extremely low-dose vigabatrin for West syndrome with tuberous sclerosis

Naomi Hino-Fukuyo[a,*], Yuko Sato[a], Yosuke Kakisaka[a], Wakaba Endo[a], Yuki Kubota[a], Atsuo Kikuchi[a], Tomoko Kobayashi[a], Kazuhiro Haginoya[a,b], Mitsugu Uematsu[a], Yurika Numata[a], Hiroshi Doi[c], Masato Mori[d], Hitoshi Osaka[d] and Shigeo Kure[a]

[a]*Department of Pediatrics, Tohoku University, School of Medicine, Sendai, Japan*
[b]*Department of Pediatric Neurology, Takuto Rehabilitation Center for Children, Sendai, Japan*
[c]*Department of Ophthalmology, Tohoku University, School of Medicine, Sendai, Japan*
[d]*Department of Pediatrics, Jichi Medical University, School of Medicine, Tochigi, Japan*

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Abstract. Treatment of west syndrome in patients with tuberous sclerosis, the relevant effective period and doses of vigabatrin (VGB) to avoid serious side effects still needs further investigation. We report on a Japanese girl who showed good results with a very low dose of VGB. Tonic spasms appeared at 5 mo of age. Adrenocorticotropic hormone therapy resulted in incomplete seizure control. VGB at the lowest practical dose (30 mg/kg/d) showed complete control after 3 d. With reduction of the dose to 10 mg/kg/d, side effects such as hyperactivity, irritability, and sleep disturbances improved. She was seizure-free for the next 6 mo with an improved developmental quotient. Ophthalmological evaluation revealed no abnormality. The present case illustrates that low-dose VGB therapy (10 mg/kg/d) has fewer side effects and may bring prompt seizure control in west syndrome with tuberous sclerosis.

Keywords: West syndrome, infantile spasms, tuberous scrlerosis complex, vigabatrin

1. Introduction

In 1990, vigabatrin (VGB), an irreversible and highly selective inhibitor of gama-aminobutyric acid transaminase, was found to be effective in treating infantile spasms, particularly in those affected by tuberous sclerosis complex (TSC). The overwhelming majority of responders (86%) were reported to be those who used VGB as a first-line drug for infantile spasms due to tuberous sclerosis [1]. VGB has been reported to be effective in European studies of infantile spasms, where most studies used doses of 100–200 mg/kg/d [2].

Currently, the relevant effective period and doses of VGB to avoid serious side effects still need further investigation [3]. Here, we describe a clinical case of west syndrome with tuberous sclerosis, where VGB was efficacious at a markedly lower dose than previously reported.

2. Case report

A 20-month-old girl had been delivered at 38 wk gestation by cesarean section. Her birth weight was 2662 g, and Apgar scores at 1 and 5 min were 8 and 9,

*Corresponding author: Dr. Naomi Hino-Fukuyo, Department of Pediatrics, Tohoku University School of Medicine, Seiryo-Machi 1-1, Aoba-ku, Sendai 980-8574, Japan. Tel.: +81 22 717 7287; Fax: +81 22 717 7290; E-mail: naomi-h@zc4.so-net.ne.jp.

respectively. She was the second offspring of healthy unrelated parents, and her older sister was healthy. No family history of neurological disease was evident. She was suspected of having TSC because of cardiac rhabdomyomas noted during pregnancy. She was diagnosed with TSC based on leucoderma shaped like a leaf of the skin and multiple tubers in subcortical white matter on magnetic resonance imaging at birth; a hamartoma of the left retina was also observed.

The first episode of spasms in a cluster occurred when she was 5-month-old. Thereafter, her smile and head control disappeared. The electroencephalogram (EEG) showed hypsarrhythmia. She was diagnosed with symptomatic west syndrome due to TSC. Vitamin B6 was not effective. Adrenocorticotropic hormone (ACTH) therapy at a dose of 0.0125 mg/kg (0.5 IU/kg) synthetic ACTH was given daily for 2 wk, then on alternate days for 1 wk and two times for 1 wk, failed to bring a complete cessation of spasms. Spasms in clusters were resistant to several antiepileptic drugs and combinations of sodium valproate (VPA) and nitrazepam. She was referred to our hospital for further treatment at 8 mo of age, taking VPA. She had no head control or sitting without assistance. Visual fixation and pursuit were observed, but no social smile.

Her developmental quotient (Enjoji scale of infant development) was 36. EEG showed hypsarrhythmia interictally. Electroretinography (ERG) revealed no abnormality. At 8-month-old, she was started on VGB (30 mg/kg/d) with VPA (12 mg/kg/d). Because it was available neither commercially nor for investigational use in Japan at that time, we obtained VGB from abroad after receiving approval from the ethics committee of Tohoku University Hospital to use VGB for a fixed period of time (6 mo). Spasms disappeared 3 d after the first administration of VGB. We reduced and then stopped VPA because of the appearance of hyperactivity, irritability, and sleep disturbances. However, these symptoms showed no improvement. We then reduced the dose of VGB slowly to 6 mg/kg/d at 12 d after starting VGB therapy, when her EEG showed no epileptic discharge. The hyperactivity, irritability, and sleep disturbances improved slowly after reducing the VGB dose. We increased the dose of VGB to 10 mg/kg/d 15 d after starting VGB therapy because episodes of eye deviation to the right side after blinking became apparent. However, after video-EEG monitoring confirmed that there was no epileptic discharge associated with the episodes of eye deviation. VGB was continued at the same dose (10 mg/kg/d). No recurrence of spasms occurred in 6 mo, and no seizure of any other type was ever seen.

Four mo after starting VGB, when the patient was 1-year-old, her developmental quotient was 65 (Enjoji scale of infant development). EEG showed some spikes in the bilateral occipital areas, although hypsarrhythmia was not seen. The developmental quotient of Enjoji scale of infant development improved to 78 at 6 mo after starting VGB therapy when she was 14-month-old. EEG at 16 mo of age revealed no epileptic discharge. ERG revealed no abnormality at 4 or 6 mo after starting VGB therapy. After 6 mo of VGB therapy in our hospital, she continued to take VGB (10 mg/kg/d) at home, obtained by her parents from abroad. She has continued to have no further seizures to her current age of 20 mo.

3. Discussion

We report on a Japanese patient with west syndrome, who was well controlled with very low-dose VGB therapy. A survey of the literature found that daily doses of VGB range from 18 to 400 mg/kg/d (Table 1). Elterman et al. [4] compared the efficacy of two different doses (low-dose, 18–36 mg/kg/d vs. high-dose, 100–148 mg/kg/d). The response rate of subjects in the high-dose treatment group was greater than that of subjects in the low-dose treatment group (spasm cessation rates for the high-dose and low-dose treatment groups were 11% and 26%, respectively). On the other hand, Mitchell et al. [5] reported their experience on the use of VGB in the treatment of infantile spasms with or without TSC. Parents were instructed to begin VGB at the lowest practical dose. If response occurred at the lower dose, they were instructed to continue it. Twelve of 20 patients responded with complete cessation of spasms and resolution of hypsarrhythmia at doses ranging from 25 to 135 mg/kg/d. Clinical response was often observed after 1–2 wk. They concluded that the response to VGB in infantile spasms was dose independent [5].

As seen in the reports of Aicardi et al. [2] and Chiron et al. [6], where the elimination of spasms was achieved at an average of 4 d in those patients who responded to VGB, the effect of VGB was observed within 1 wk in the vast majority of patients [7,8]. This is a very prompt response compared with

Table 1
Efficacy of vigabatrin in 117 patients with tuberous sclerosis complex

Authors [Ref.] (year)	Type of study	Dose of vigabatrin (mg/kg/d)	Number of tuberous sclerosis complex patients	Number of responders*
Chiron et al. [6] (1990)	Open, add on	50–200	8	7
Chiron et al. [6] (1991)	Open, add on	50–200	14	12
Vles et al. [11] (1993)	Open	50–100	1	1
Schmitt et al. [12] (1994)	Open, monotherapy, add-on	Up to 150	2	2
Appleton [7] (1995)	Retrospective	80–120	3	3
Aicardi et al. [2] (1996)	Retrospective	20–400 (average 99)	28	27
Vigevano et al. [8] (1997)	Open randomized	100–150	3	3
Chiron et al. [6] (1997)	Open randomized	150	18	18
Mitchell et al. [5] (2002)	Open	25–135	1	1
Elterman et al. [4] (2010)	Randomized	18–148	38	22
Present case	Case report	10	1	1

*A responder is defined as a patents in whom there was total cessation of spasms.

that observed with steroids, benzodiazepines, or VPA. However, those reports used relatively high doses, ranging from 80 to 150 mg/kg/d.

In contrast, Parisi et al. [9] have suggested that VGB can be rapidly effective at low doses in TSC infants if the treatment is started very soon after the onset of spasms. In the present patient, cessation of spasms was observed within 3 days after starting low-dose VGB therapy, and the development and seizure prognosis were excellent at the age of 16 mo. Thus, if an early diagnosis of TSC is made and spasms are controlled at an early stage using low-dose VGB, learning and behavioral outcomes in TSC infants may be further improved. Mitchell et al. [5] recommended that VGB be initiated at the lowest practical dose (generally approximately 20–30 mg/kg/d) and gradually increased until both clinical and EEG response are observed, rather than beginning at a higher dose, such as 100 mg/kg/d, as recommended previously.

Currently the minimum duration and doses of VGB treatment that can produce side effects are unknown. Although a marked decrease in ERG responses from scotopic threshold response has been suggested as early marker of retinal toxicity, there is still no definite measure for monitoring retinal toxicity induced by VGB. It is suggested that children on VGB should be followed by ERG every 6 mo to 1 yr throughout the treatment course [10]. Unfortunately, we could not examine ERG after 6 mo of treatment because the patient moved to another hospital close to her home. Careful follow up is needed to see if long-term use of low-dose VGB contributes to visual difficulties.

As a reason why low-dose VGB had an efficacy on this patient, other medicine tried before low-dose VGB, such as ACTH, VPA or vitamin B6, might be related to the favorable result. We need further observations to evaluate the long-term prognosis in this patient. However, we believe that low-dose VGB therapy (10 mg/kg/d) has fewer side effects and may bring prompt seizure control in TSC, although more cases are needed before reaching any conclusion.

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