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Vigabatrin and mental retardation in tuberous sclerosis: infantile spasms vs focal seizures

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Abstract

Tuberous sclerosis complex is a genetic disorder resulting in epilepsy and mental retardation. Vigabatrin has shown efficacy in the treatment of infantile spasms caused by tuberous sclerosis complex, but its effects on focal seizures caused by tuberous sclerosis complex have not been determined. We compared the efficacy of vigabatrin in patients with tuberous sclerosis complex-induced focal seizures and infantile spasms and assessed the mental outcomes in both groups.

We retrospectively evaluated 31 children with tuberous sclerosis complex and epilepsy, who were treated with vigabatrin in single tertiary center in Seoul, Korea. Vigabatrin treatment resulted in spasms cessation in 16 of 18 (88.9%) patients with infantile spasms, whereas 6 of 13 (46.2%) patients with focal seizures became seizure-free. Initial response to vigabatrin had no effect on intellectual disability. Vigabatrin was highly effective in eliminating infantile spasms caused by tuberous sclerosis complex, but was less effective in patients with focal seizures.

Keywords

Tuberous sclerosis complex; vigabatrin; infantile spasms; focal seizures

Introduction

Tuberous sclerosis complex is an autosomal dominant genetic disorder that occurs in about 1 in 5,800 individuals.¹ Of these, 95% show brain involvement, and 70–80% suffer from epilepsy, which is often refractory to treatment.² Most patients with tuberous sclerosis complex experience their first seizures during the first year of life, some experience infantile

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Author contribution

Mi-Sun Yum, MD, PhD; First author, who proposed the hypothesis, performed data analysis and wrote this whole manuscript

Eun Hye Lee, MD; Second author who contributed to data collection and correction of the manuscript

Tae-Sung Ko, MD, PhD; Corresponding author who directed this study, gave guidance of the paperwork, and corrected this manuscript

Conflict of Interest

None of the authors has any conflict of interest to disclose.

Ethical Approval

We confirm that this retrospective study was approved by the Asan Medical Center institutional review board.

spasms, a catastrophic epileptic syndrome characterized by age-specific seizures, hypsarrhythmia on electroencephalography and profound mental retardation. During the natural history of tuberous sclerosis complex with epilepsy, focal seizures sometimes precede, coexist with or evolve from infantile spasms,³ with the latter being a major factor associated with mental retardation in patients with tuberous sclerosis complex⁴.

Vigabatrin is a structural analog of gamma-aminobutyric acid that greatly increases whole-brain concentrations of gamma-aminobutyric acid⁵ and has shown efficacy in the treatment of patients with infantile spasms or focal seizures.^{6,7} Although vigabatrin is particularly effective in the treatment of infantile spasms caused by tuberous sclerosis complex,^{8–11} its efficacy in patients with focal seizures caused by tuberous sclerosis complex has not been determined^{12,13}. We therefore assessed and compared the efficacy of vigabatrin in patients with infantile spasms and focal seizures caused by tuberous sclerosis complex. We also assessed mental outcomes and sought to identify the clinical risk factors associated with intellectual disability in these groups of patients.

Methods

A retrospective review of the computerized database of the Pediatric Neurology Department of the Asan Medical Center, Seoul, Korea, identified 39 patients diagnosed with tuberous sclerosis complex¹⁴ and epilepsy and treated with vigabatrin between 1991 and 2010. The diagnosis of infantile spasms was based on age-specific spasms, a sudden flexion, extension or mixed extension-flexion of predominantly proximal and truncal muscles that is usually occur in clusters (<12 months) and/or hypsarrhythmia on electroencephalography. Seizure types and the usage of anti-epileptic drugs were identified. To avoid selection bias and to exclude the impact of drug interactions, we selected the 31 patients who had received first-line vigabatrin monotherapy (23 patients) or with second-line vigabatrin add-on therapy (8 patients) initiated within the first month after seizure onset. Vigabatrin was started from a small dosage (50mg/kg/day) and titrated to a higher dosage (maximum 150–200mg/kg/day) according to the clinical responses. If seizure stops before the usual recommended dose of 100mg/kg/day, the lowest effective dosage was maintained to minimize the dose-responsive side effects of vigabatrin. Vigabatrin efficacy in patients with focal seizures was defined as no seizures for 1 year after initiation of treatment, whereas vigabatrin efficacy in patients with infantile spasms was defined as the cessation of spasms according to the guidelines of the West Delphi Group.¹⁵ Age at onset of seizures or spasms (in 1-month intervals), brain magnetic resonance imaging findings, genetic testing, intellectual status (intellectual quotient or developmental quotient), and seizure evolution were also reviewed.

Of the 31 patients, 11 showed evolution of seizure types. To evaluate response to vigabatrin, patients were classified by seizure types at the start of vigabatrin treatment. Patients with concurrent infantile spasms and focal seizures were classified as infantile spasms. One patient developed infantile spasms after treatment of focal seizures with zonisamide and one patient developed focal seizures after adrenocorticotrophic hormone-induced cessation of infantile spasms (Fig. 1).

Intellectual outcomes were regarded as the final outcomes. Patients aged over 6 years underwent psychometric evaluation using the Korean Educational Development Institute-Wechsler Intelligence Scale for children, and patients aged less than 5 years underwent developmental evaluation using the Korean Infant and Children Developmental Tests. The developmental quotient of the Korean Infant and Children Developmental Test was defined as the mean developmental quotient of the five areas (gross motor, fine motor, social-personal, language, and cognitive-adaptive). The Korean Infant and Children Developmental Test was not administered to one patient with tuberous sclerosis complex,

hemimegalencephaly and concurrent focal seizures and infantile spasms. Patients with an intellectual quotient or developmental quotient <70 were considered mentally retarded. In the three patients who underwent epilepsy surgery, we evaluated the intellectual quotient or developmental quotient before the surgery.

Demographic variables in the infantile spasms and focal seizures groups were compared using the chi-square test or Fisher's exact test for categorical variables and the t-test for continuous variables. Multiple logistic regression analysis with backward elimination was used to determine clinical variables affecting response to vigabatrin.

Logistic regression analysis was also used to evaluate the risk factors for intellectual disability. Variables statistically significant ($p < 0.05$) on univariate logistic regression analysis were tested in multiple logistic regression analysis with backward elimination.

Results

The clinical characteristics of the two groups of patients are shown in Table 1. The mean age of onset was earlier in the infantile spasms (5.4 months, range 1–12 months) than in the focal seizures (11 months, range 0–48 months) and the maximum dose of vigabatrin was higher in the infantile spasms (89 mg/kg/day) than in the focal seizures (81 mg/kg/day) group. After cessation of infantile spasms, seven patients developed focal seizures and two developed Lennox-Gastaut syndrome. Only one infantile spasms patient had focal seizures before the development of infantile spasms but none of the vigabatrin-treated patients with focal seizures developed infantile spasms (Fig 1). Vigabatrin treatment was significantly more effective in the infantile spasms than in the focal seizures group.

For the 23 patients with vigabatrin as a first-line monotherapy, 13 (92.9%) of the 14 patients with infantile spasms became seizure free, whereas 3 (33.3%) of 9 patients with focal seizures became seizure free. Taking together with first-line monotherapy and second add-on therapy with vigabatrin, 16 (88.9%) of the 18 infantile spasms patients became seizure-free, compared with 6 of 13 (46.2%) patients with focal seizures (odds ratio, 9.3; 95% confidence interval, 1.5–58.2; $p = 0.017$). The adjusted odds ratio for infantile spasms was 17.6 ($p = 0.012$) by multiple logistic regression analysis with backward elimination (Table 2). We also performed a case-control analysis for intellectual disability, using the risk factors, sex, magnetic resonance imaging abnormality, history of infantile spasms, early seizure onset (<6 months), response to vigabatrin, and evolution of seizure types. The crude odds ratios and their 95% confidence intervals are shown in Table 3. Four factors were significantly associated with intellectual disability: male sex (odds ratio, 0.2; $p = 0.029$), history of infantile spasms (odds ratio, 5.2, $p = 0.041$), early seizure onset (<6 month) (odds ratio, 6.2, $p = 0.045$), and evolution of seizure types (odds ratio, 13.5; $p = 0.023$). Multiple logistic regression analysis with backward elimination showed that the adjusted odds ratios for early seizure onset (<6 month) and evolution were 9.1 (95% confidence interval 1.2–69.3; $p = 0.033$) and 19.0 (95% confidence interval 1.7–214.9; $p = 0.017$), respectively (Table 3).

Of the 12 patients with focal seizures only, 4 (33%) had intellectual disability during follow-up. Of the 10 patients with seizure evolution, 9 (90%) had intellectual disability.

Discussion

Vigabatrin has been consistently shown effective in the treatment of focal seizures and infantile spasms,^{12,16} as well as more effective than adrenocorticotrophic hormone in the treatment of infantile spasms caused by tuberous sclerosis complex.^{17,18} We also found that vigabatrin was highly effective for patients with infantile spasms caused by tuberous

sclerosis, with 16 of 18 patients becoming seizure-free after treatment. Vigabatrin, however, was less effective in patients with focal seizures caused by tuberous sclerosis complex, with only 6 of 13 (46.2%) becoming seizure free, making the adjusted odds ratio for infantile spasms relative to focal seizures 17.6. Previously, Chu-Shore et al.¹⁹ reported that most patients with epilepsy and tuberous sclerosis developed multiple seizure types with typical onset in the first year of life. Although most patients with infantile spasms later evolved to other seizure types, either focal seizures or Lennox-Gastaut syndrome, no patient with focal seizures developed infantile spasms during vigabatrin treatment irrespective of their response to vigabatrin. This suggests the specific efficacy of the vigabatrin for infantile spasms caused by tuberous sclerosis.

At present, the mechanisms of development of epilepsy in tuberous sclerosis complex patients and the pathophysiologic mechanisms of infantile spasms are still unknown. Tubers are widely believed to serve as epileptogenic foci, and tuber resection is often performed to treat intractable epilepsy in patients with tuberous sclerosis complex.^{20,21} Nevertheless, the relative importance of abnormal glioneuronal development of the brain, tubers and normal neighboring neurons irritated by dysgenetic areas of the brain has not yet been determined.²² The mechanisms by which infantile spasms and focal seizures develop may differ, resulting in different response to vigabatrin.

Vigabatrin is a selective and irreversible inhibitor of gamma-aminobutyric acid-transaminase that greatly increases whole-brain concentrations of gamma-aminobutyric acid.⁵ Vigabatrin has been shown to increase gamma-aminobutyric acid concentrations in human cerebrospinal fluid,²³ and vigabatrin-induced increases in gamma-aminobutyric acid concentrations in the brain have been found to correlate with seizure control.²⁴ During the development of infantile spasms, dysfunctional gamma-aminobutyric acid may be involved in generalization of the epileptogenic activity of tuberous sclerosis complex, and vigabatrin may act during this step to ameliorate the infantile spasms. Namely, the vigabatrin-induced increase in gamma-aminobutyric acid concentration may attenuate the development of infantile spasms by disturbing the generalization of epileptiform activity due to its dysfunction in cortical-subcortical circuits,²⁵ but not the focal seizures caused by the region itself. Peri-lesional and lesional molecular analyses in patients with tuberous sclerosis complex have shown decreased expression of gamma-aminobutyric acid_A receptors and gamma-aminobutyric acidergic neurons at the circuit level,^{26–28} a finding that may explain, at least in part, why vigabatrin was less effective in focal seizures than in infantile spasms associated with tuberous sclerosis complex.

There was only one case with initial focal seizures followed by infantile spasms in present study and none of the vigabatrin-treated patients with focal seizures developed infantile spasms irrespective of their response to vigabatrin. It is plausible that some subtle focal seizures preceding infantile spasms can be underdetected and vigabatrin could be effective in stopping focal seizures at the very early onset and preventing the evolution toward an epileptic encephalopathy. If so, early intervention with vigabatrin in infants is recommended in patients with tuberous sclerosis complex to prevent this evolution of epileptic encephalopathy.

In agreement with previous results, we found that evolution of seizure types and early seizure onset were the main risk factors for intellectual disability.^{19,29} We also found that response to vigabatrin did not affect the mental outcomes of our patients with tuberous sclerosis complex and epilepsy, suggesting that vigabatrin does not affect the natural history of epilepsy in tuberous sclerosis complex patients. However, of the seven patients with infantile spasms who responded to vigabatrin and did not experience further seizures, four (57%) had normal intellectual quotient or developmental quotient, in agreement with results

showing that early control of seizures improved long-term outcomes in children with tuberous sclerosis.^{4,13,30} Additional studies with longer term follow-up are required to assess the ability of vigabatrin treatment to induce the cessation of infantile spasms in patients with tuberous sclerosis complex.

It is currently unclear whether cognitive deficits in tuberous sclerosis complex patients arise from the effects of early seizures or by a distinct mechanism, such as an association with infantile spasms.²⁹ We found that the risks and degree of intellectual impairment were associated with the evolution of seizures and early seizure onset, indicating that the seizures themselves have some role in the severity of subsequent neurologic deficits.^{31,32} Seizure evolution or early onset may reflect the strong epileptogenic tendency, consistent with neuronal disorganization and hyperexcitability, and may in turn, cause severe intellectual disability.

There are several limitations in this study. The retrospective nature of this study and relatively small number of patients are major weaknesses. And we could not perform the prolonged ambulatory electroencephalography recordings for the patients with infantile spasms. Subclinical focal seizures proved to be very frequent in tuberous sclerosis patients with infantile spasms before, so that pure clinical approach may be not enough to define the patients as purely infantile spasms.³³ Thus, the patients classified as infantile spasms in this study might have simultaneous focal seizures at the time of vigabatrin trial and we considered the patients with concurrent infantile spasms and focal seizures as infantile spasms group.

But this is the first Korean study in this field and we have shown that vigabatrin has rather specific effects in patients with infantile spasms, but not focal seizures, caused by tuberous sclerosis complex as shown previously.^{6,34} This distinct efficacy of vigabatrin, coupled with the possibility of vigabatrin-induced visual field defects suggest that vigabatrin can be carefully used as a first choice for treatment of infantile spasms but not for focal seizures in patients with tuberous sclerosis complex. Additionally, initial response to vigabatrin was not associated with the mental outcome or epilepsy outcome of tuberous sclerosis complex patients in this study, suggesting the need for further research of epilepsy and intellectual outcome in tuberous sclerosis complex and more discreet use of vigabatrin in tuberous sclerosis complex patients.

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Figure 1.

Study design. Of the 39 patients with tuberous sclerosis complex and epilepsy, 31 patients had been treated with vigabatrin as first- or second-line therapy within 1 month of seizure onset. Patients were divided into those with infantile spasms and focal seizures at initiation of vigabatrin, except for one patient with concurrent infantile spasms and focal seizures, who was regarded as having infantile spasms. Thus, 18 patients had infantile spasms (underlined) and 13 had focal seizures (*italics*). Of the 17 patients who initially presented with infantile spasms, 9 evolved to other types of epilepsy, whereas, of the 13 patients who initially presented with focal seizures, only one evolved to infantile spasms. Abbreviations: TSC, tuberous sclerosis complex; VGB, vigabatrin; IS, infantile spasms; focal seizures, focal seizures; LGS, Lennox-Gastaut syndrome; ACTH, adrenocorticotrophic hormone; VPA, valproic acid

Table 1

Clinical characteristics of patients with infantile spasms and focal seizures treated with vigabatrin.

	Infantile spasms (N=18)	Focal seizures (N=13)	P value
Age of onset (months)	5.4 (1–12)	11 (0–48)	0.046 [*]
Sex (M : F)	8 : 10	8 : 5	1.000 [†]
vigabatrin as first vs second choice	11 : 7	9 : 4	0.011 [†]
Genetic testing	tuberous sclerosis complex 1: 1, tuberous sclerosis complex 2: 5, No mutation identified: 1	tuberous sclerosis complex 2: 1	-
Max. Dose (mg/kg/day)	89 (46–145)	81 (45–125)	0.362 [*]
Response rate ^{**}	16/ 18	6/13	0.029 [†]
Presence vs absence of intellectual disability	13 : 5	5 : 8	0.585 [†]

* Student's *t*-test[†] Chi-square test

^{**} "Response" was defined as the cessation of clinical spasms in patients with infantile spasms and being seizure-free for 1 year in patients with focal seizures

Table 2

Associations between clinical variables and response to vigabatrin

Variable	Association with the response to vigabatrin			Adjusted		
	OR	95% CI	p	OR	95% CI	p
Early onset (<6 months)	0.3	0.1–1.8	0.225			
Max. dosage	1.0	0.9–1.0	0.296	1.0	0.9–1.0	0.093
Duration	1.0	0.9–1.0	0.175			
Presence of infantile spasms	9.3	1.5–58.2	0.017	17.6	1.6–164.8	0.012

Table 3

Associations between clinical variables and intellectual outcomes.

Variable	Association with the intellectual outcome			Adjusted		
	OR	95% CI	P	OR	95% CI	P
Male	0.2	0.0–0.8	0.029			
MRI	1.3	0.1–23.5	0.844			
Response to vigabatrin	0.72	0.1–3.8	0.698			
Early onset	6.2	1.0–36.8	0.045	9.1	1.2–69.3	0.033
History of infantile spasms	5.2	1.1–25.3	0.041			
Evolution	13.5	1.4–128.3	0.023	19	1.7–214.9	0.017

Abbreviations: MRI, magnetic resonance imaging