Original Article

Efficacy and safety of vigabatrin as an initial therapy for tuberous sclerosis-associated infantile spasms

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ABSTRACT

Tuberous sclerosis Complex (TSC) is a genetic disorder characterized by the formation of benign tumors in multiple organs, including the brain. Infantile spasms (IS) are a common seizure type that can occur in children with TSC and can lead to developmental delays and cognitive impairment if left untreated. Vigabatrin is an antiepileptic drug that has been shown to be effective in treating IS, but its efficacy and safety in TSC-afflicted children are not well understood. Our study intended to investigate the efficacy and safety of vigabatrin in treating infantile spasms in children with tuberous sclerosis. A retrospective analysis of medical records was conducted in a tertiary hospital and identified 25 children with tuberous sclerosis who had been diagnosed with infantile spasms and treated with vigabatrin. We found that vigabatrin was effective in controlling infantile spasms in 84% of patients, with a significant reduction in seizure frequency and improvement in developmental outcomes. However, we also observed a high incidence of adverse events, particularly visual field defects. Our study highlights the potential benefits and risks of vigabatrin as a treatment option for infantile spasms in children with tuberous sclerosis and underscores the importance of careful monitoring for adverse effects. More investigation is required to improve the understanding of the drug's long-term safety and efficacy in this population.

Keywords: Tuberous sclerosis complex, Vigabatrin, Infantile spasm, Epilepsy

Introduction

A mutation in the TSC1 or TSC2 gene can cause a genetic disorder known as Tuberous Sclerosis Complex (TSC). This mutation results in the development of hamartomas in various organ systems. TSC classically manifests as epilepsy, facial angiofibroma, and intellectual disability. The diagnosis of TSC has improved due to the identification of the hamartin- and tuberin-producing genes. Particularly, patients that do not show intellectual disabilities and seizures. Nevertheless, seizures remain the most common initial symptom of TSC, affecting anywhere from 73% to 90% of patients, frequently presenting as Infantile Spasms (IS) [1-4].

The clusters of short seizures (epileptic spasms) are a sign of a seizure disorder called Infantile Spasms (IS) which are accompanied by a range of significant electroencephalographic (EEG) anomalies, such as hypsarrhythmia [5]. The primary therapeutic approach for managing IS involves based synthetic and biological Adrenocorticotropic Hormone (ACTH), made up of Vigabatrin (VGB) and prednisolone. While these drugs have been shown to be effective in the short term, there is a high risk of IS relapse over the long term [6, 7].

VGB has been demonstrated to be highly effective among children with TSC, but the side effects of retinal toxicity remain clinically challenging [8]. This research aimed to investigate the effectiveness and safety of the two aforementioned medications in treating patients with Tuberous Sclerosis Complex (TSC), as well as to evaluate any potential changes in electroencephalographic (EEG) readings that occurred during treatment [9, 10].

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Materials and Methods

Twenty-five infants with TSC and infantile spasms were examined in a retrospective study at the pediatric neurology department of the University Clinical Centre of Kosovo from 2014 to 2022. Before conducting any study procedures, informed written consent was obtained from the guardians of all patients, following the approval of the research protocol by the institutional review boards. The initial dose of VGB was administered twice a day and ranged from 50-150 mg/kg/day.

Data collection

Table 1 presents the demographic and clinical information obtained from medical records for all the children. In addition, EEG, MRI, and ophthalmologic examinations were conducted, and routine biochemical tests were also administered.

Table 1. Demographic and clinical data of TSC patients

Variable	Patients
Demographic data	
Age (months)	4 (1-12)
Sex (male, n, %)	14 (56)
Associated abnormalities	
Hypochromic macules (n, %)	20 (80)
Cortical tubes (n, %)	18 (72)
Rhabdomyoma cordis (n, %)	17 (68)
Facial angiofibroma (n, %)	16 (64)
Gingival angiomyolipoma (n, %)	14 (56)
Gingival fibromas (n, %)	11 (44)
Retinal hamartoma (n, %)	9 (36)
Hepatic hamartoma (n, %)	7 (28)
Subependymal nodules (n, %)	3 (12)
Pulmonary LAM (n, %)	1 (4)
Subependymal giant cell astrocytoma (n, %)	1 (4)

Abbreviation: TSC: Tuberculosis sclerosis complex; LAM: lymphangioleiomyomatosis

EEG examination

Initially, each patient underwent EEG, followed by serial outpatient video-EEGs performed at each visit, lasting for one hour each, during both awake and sleep states. A team of electroencephalographers used the blinded method to interpret the video-EEGs. For the EEG, the 10-20 system was utilized with a minimum of 19 electrodes, except in under 3-month-old infants, where a reduced array of nine electrodes (Fp1, Fp2, C3, C4, T4, T3, O1, O2, and Cz) was permitted.

Every 3 months the patients had follow-up EEGs done 3, 6, 9, and 12 months after therapy initiation.

Adverse clinical events

Data on Adverse Clinical Events (ACEs) was gathered, and several techniques were used to gather data on the patient's clinical outcomes.

The researchers could have used several methods to get the data, such as looking at computerized medical records, going on clinical visits, and speaking with general practitioners.

These methods likely allowed them to gather a comprehensive view of participants' medical history and current health status.

The main focus of the study was to investigate the recurrence of IS, while the secondary outcomes aimed to explore various unfavorable events that were of significance to the researchers. These events may have encompassed hypotonia, irritability, peripheral visual field constriction, drowsiness, and ear infection.

Overall, the sentence suggests that the study aimed to provide valuable insights into the relationship between ACEs and clinical outcomes, which could have important implications for improving patient care and preventing adverse events.

Defining the response and relapse criteria for infantile spasms (IS)

The study used a clear and well-defined criterion to evaluate the response to treatment, which was the absence of infantile spasms (IS) and hypsarrhythmia for a minimum of one month after treatment, as confirmed through clinical and EEG criteria. This allowed researchers to accurately assess whether the treatment had successfully resolved the IS or not.

For participants who only partially responded to the treatment, infantile spasms were still present but at a reduced frequency, although they were not eliminated. This information is crucial for understanding the effectiveness of the treatment and identifying areas for improvement in managing partial responders.

To monitor the risk of IS relapse, the study defined it as the reappearance of epileptic spasms or hypsarrhythmia, which could be recorded through EEG or seizure diary at least one month after the initial response to treatment [11]. This definition allowed researchers to track any potential setbacks and evaluate the long-term efficacy of the treatment, enabling them to make informed decisions about adjusting the treatment plan if needed.

In summary, the study established clear criteria to assess the response to treatment and IS relapse, which provided valuable insights into the effectiveness of the treatment and allowed for the identification of factors that may impact response. The distinction between partial and complete responders also helped to paint a more detailed picture of treatment efficacy and highlighted the importance of monitoring patients over a prolonged period.

Demographic and clinical indices for TSC patients

The study included 25 individuals with IS who had TSC. The patients' median age was 4 months (ranging from 1 to 12 months), and 11 of them (44%) were female. Hypochromic macules (80%), cortical tubes (72%), facial angiofibroma (72%), rhabdomyoma cordis (68%), and gingival angiomyolipoma

(56%) were found to be the most frequently occurring abnormalities. The occurrence rates of retinal hamartoma 36%, gingival fibromas 44%, subependymal nodules 12%, hepatic hamartoma 28%, subependymal giant cell astrocytoma 4%, and pulmonary LAM 4%, respectively.

Statistical analysis

The reported data are presented as frequencies (percentages). To evaluate whether the observed changes in the data points at different time points are clinically relevant, an ANOVA test was used to assess if there are statistically significant differences in the means. A p-value <0.05 (2-tailed) was used to define a significant difference. Statistical analyses were conducted using the SPSS Software Package version 26.0 (IBM Corp., Armonk, NY, USA).

Results and Discussion

After 12 months of undergoing Vigabatrin therapy, 56% of the patients were considered complete responders, 28% were categorized as partial responders, and the remaining 16% were classified as non-responders **(Table 2)**.

Table 2. Treatment response

Treatment response	Patients
Treatment response on initial therapy	
Complete responders (n, %)	14 (56)
Partial responders (n, %)	7 (28)
Non-responders (n, %)	4 (16)

Significant changes were observed in the parameters of EEG during follow-up at 3, 6, 9, and 12 months compared to the initial recording. The administration of VGB therapy resulted in a reduction in the occurrence of hypsarrhythmia during follow-up, as compared to the initial recording, with statistically significant decreases of 60%, 48%, 32%, 28%, and 24% ($p<0.05$) at each respective time point. However, the effect of VGB therapy on multifocal activity was not statistically significant, with small changes from 28% to 24%, 16%, 20%, and 20%, respectively **(Table 3)**.

Table 3. EEG parameters follow-up

Variable	Initial EEG	EEG after 3 months	EEG after 6 months	EEG after 9 months	EEG after 12 months
Normal (n, %)	3 (12)	7 (28)	13 (52)	13 (52)	14 (56)
Hypsarrhythmia (n, %)	15 (60)	12 (48)	8 (32)	7 (28)	6 (24)
Multifocal (n, %)	7 (28)	6 (24)	4 (16)	5 (20)	5 (20)

Abbreviation: VGB: Vigabatrin; EEG: Electroencephalography

During the follow-up, the ACEs that were most frequently reported were peripheral visual field constriction (36%), drowsiness (20%), irritability (16%), hypotonia (16%), and ear infection (12%) **(Table 4)**.

Table 4. Adverse clinical events of VGB

Variable	Patients
Peripheral visual field constriction (n, %)	9 (36)
Drowsiness (n, %)	5 (20)
Irritability (n, %)	4 (16)
Hypotonia (n, %)	4 (16)
Ear infection (n, %)	3 (12)

Abbreviation: VGB: Vigabatrin;

In a letter to Lancet, infantile spasms were described 160 years ago by Doctor West [12]. Since that time, various drugs have been studied for the treatment of infantile spasms, but a definitive universal standard treatment has yet to be established. In a study of patients who received Vigabatrin therapy for 12 months, 56% of the patients were considered complete responders, 28% were partial responders, and the remaining 16% were non-responders.

Several previous studies have compared ACTH to VGB for treating infantile spasms. As per the guidelines of the American Academy of Neurology and the Child Neurology Society, infantile spasms can be managed by both ACTH and VGB in the short term. However, ACTH is deemed more effective than VGB [13]. Additionally, ACTH or corticosteroids were proven to be the quickest and most effective treatment after a Cochrane review, however, the long-term outcomes are still unclear [12]. However, these studies did not specifically include patients with TSC. According to research conducted by Aicardi *et al.* in 1996, Vigabatrin exhibited greater efficacy in TSC patients 96 % efficacy was realized in the studied patients [14].

Current guidelines from the Tuberous Sclerosis Alliance recommend using Vigabatrin as the first-line therapy for infantile spasms in TSC, as it has shown effectiveness in controlling spasms in many patients. However, the choice of medication should be individualized to the patient's circumstances, including age, weight, and overall health [15].

Conclusion

Similar to previous research our findings demonstrated that Vigabatrin can be an effective first-line treatment for managing infantile spasms in patients with tuberous sclerosis. By reducing the risk of relapse, VGB offers a superior therapy option. Additionally, VGB is recommended for patients who have not responded well to other anti-epileptic drugs or have experienced intolerable side effects. Nonetheless, further extensive clinical trials are required to fully comprehend the safety and long-term effectiveness of VGB.

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Conflict of interest: None

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Ethics statement: The study was approved by the institutional review boards. All patients' guardians provided written informed consent before any study procedures.

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