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Efficacy of Vigabatrin for Treatment of a Case of Infantile Spasms with Tuberous Sclerosis Complex in Taiwan

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Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome affecting multiple organ systems and featuring highly variable clinical manifestations. Epilepsy occurs in more than two-thirds of TSC victims, and up to one-third of TSC sufferers will develop infantile spasms (IS), a condition that is often medically intractable. Vigabatrin (VGB) has proved to be an effective antiepileptic drug for the treatment of IS resulting from TSC. A number of previous studies have indicated that earlier control of epilepsy contributes to a better prognosis for TSC-related mental retardation. To our knowledge, however, reports of treatment with VGB for IS for TSC victims are limited in Taiwan. Herein, we report on a case of IS associated with TSC that was effectively treated with VGB; successful treatment was defined as the patient achieving a complete recovery of electroencephalogram (EEG) recordings and being seizure free for at least six months. Moreover, we followed up this case for a period of more than one year from diagnosis, during which time the patient was seizure free and their psychomotor development remained within normal milestones.

Key words: Vigabatrin, tuberous sclerosis complex, infantile spasms, hypopigmented macule

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder featuring highly variable clinical manifestations. The impact of TSC on bodily organs has been comprehensively described in previous investigations, with the typical organs affected including the brain (cortical and subcortical tubers, subependymal nodules, and giant cell astrocytoma), heart (rhabdomyoma), skin (shagreen patches, facial angiofibromas, and periungual fibromas), and eye (retinal haematomas)[1]. Epilepsy is one of the major neurological complications of TSC, affecting around 85% of TSC-afflicted patients at some stage in their lives, and is a condition that often begins in the first year of life for TSC sufferers[2]. Up to one-third of children afflicted with TSC will develop infantile spasms (IS)[3]. To the best of our knowledge, only a very small number of cases of vigabatrin (VGB) treatment for IS amongst TSC sufferers have been reported in Taiwan. Herein, we report on a case of IS in a TSC-afflicted victim who was successfully treated with VGB. Further, we review the current related literature[4].

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CASE REPORT

A five-month-old boy suffered from a number of seizure attacks commencing five days prior to his hospital admission. The patient's symptoms commenced, initially, with an involuntary "bobbing" of the head, an upward gaze immediately followed by repeated rapid limb extensor-muscle spasms alternately over time intervals of a few seconds. Such spasms were repeated 10-20 times, occasionally more, during each spasm cluster. This individual's parents were nonconsanguinous, and each featured a positive family history of TCS. The patient's physical examination revealed a relatively large cutaneous hypopigmented macule over his buttocks, as illustrated in Fig. 1. Upon neurological examination, the patient demonstrated a normal deep-tendon reflex without any evidence of the presence of any pathological reflex. Abdominal sonography revealed the presence of two renal cysts within the capsule of the right kidney. No significant retinal lesions were detected via funduscopy. Electroencephalograms (EEGs) revealed hypsarrhythmia with multiple focal spikes and waves. Magnetic resonance imaging (MRI) of his brain in T1-weighted mode displayed multiple small subependymal nodules, which appeared hyperintense compared with nor-

Fig. 1 An unusual and huge hypopigmented macula over the patient's buttocks appeared at the age of five months.

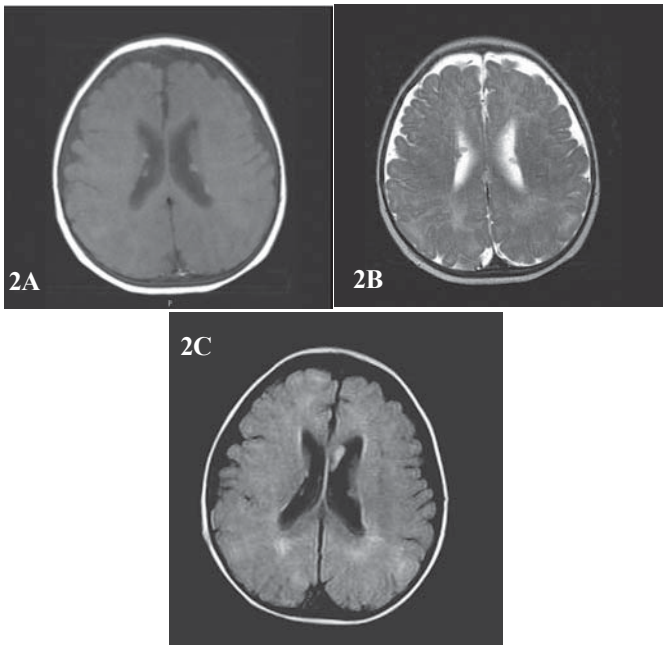

Fig. 2 Multiple small subependymal nodules around the lateral ventricles that appear hyperintense to brain parenchymal tissue, as revealed upon a (A) T1-weighted (TE/TR:14/630 ms) image, (B) T2-weighted image (TE/TR:120/5816 ms), and (C) FLAIR (TE/TR:120/6000 ms) image of the patient's brain.

mal brain parenchymal tissue, the nodules being located around the lateral wall of both lateral ventricles (Fig. 2A). Upon T2-weighted imaging (Fig. 2B) and fluid-attenuated inversion-recovery (FLAIR) investigation (Fig. 2C), several misshapen broadened gyri, featuring central hyperintense cortical and subcortical lesions, as well as mass-like cortical tubers were detected. These were located bilaterally over both parietal lobes and also over the left temporal lobe. Therefore, under the diagnosis of TCS with IS, VGB (25 mg/kg qd) was prescribed initially for this patient. Subsequently, the dosage was increased to 75 mg/kg qd as a "target" dosage. During this time, the patient's EEG was monitored regularly, initial results revealing hypsarrythmia (Fig. 3A), although this EEG progressively converted to a near normal EEG recording at around three months after commencement of this patient's management (Fig. 3B). The patient remained seizure free during the follow-up period, and the development evaluated by the Denver Developmental Screening Test was normal at the one-year follow-up examination.

DISCUSSION

The presence of "white spots" on the skin of individuals afflicted with TSC is usually an important sign, because the detection of such spots is often the first firm evidence of the presence of this disease[5]. The most common dermatological characteristics of TSC are, initially, the presence of a hypomelanotic macule and/or ash-leaf spots on the affected individual's skin. Such lesions are typically 1-3 cm in diameter, are located on the patient's trunk and/or buttocks, and can be rather easily identified using ultraviolet light. On rare occasions, as for the case we present herein, a large-to-huge hypopigmented macula may be detected, extending over a substantial proportion of the buttocks, which for our patient were the entire buttocks. In our case, we noted a number of skin lesions that appeared to be atypical for TSC sufferers. According to the relevant literature, such a huge hypopigmented macula arising for individuals of a similar age to our patient is quite rare[6].

Cortical tubers are the hallmark of TSC and are associated with epileptogenicity[7]. TSC patients typically develop epilepsy within the first year of life and often display the presence of epilepsy as IS, which to our knowledge, are always intractable[8]. Epilepsy of TSC afflicted individuals may be related to the downregulation of glutamate and γ-aminobutyrate (GABA) receptor mRNA expression, leading to decreasing levels of GABA receptors[9]. VGB, a structural analogue of the inhibitory neurotransmitter GABA, acts by irreversibly inhibiting the degradative enzyme GABA-aminotransferase, thus elevating GABA levels and eventually causing antiepileptic effects. This seizure-benefit effect of VGB is dose-related, and when administered at an appropriate dose results in a significant elevation of the concentration of GABA in the brain and cerebrospinal fluid[10]. VGB has often been demonstrated to reveal a rather high efficacy as a first-line monotherapy for

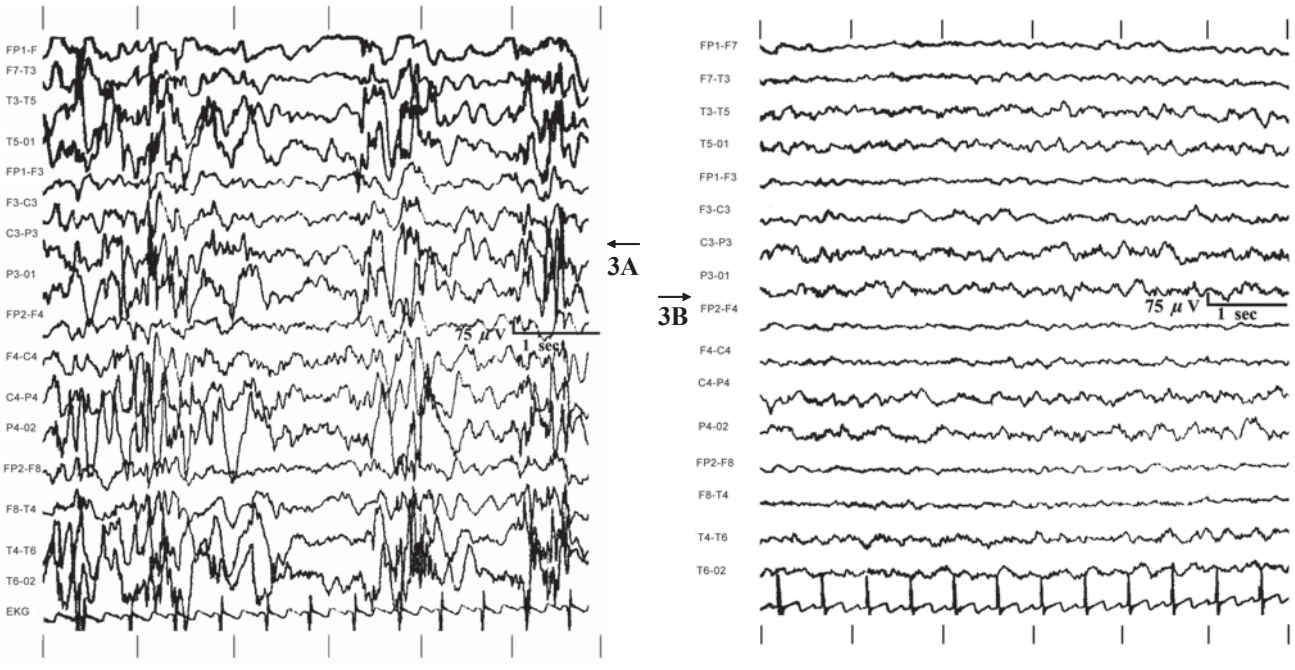

Fig. 3 (A) Polyspikes, polyspikes and waves, and burst suppression was revealed in the sleep EEG pattern for this patient prior to his treatment.(B) No significant epileptic discharge with relatively slow background activity was shown in the sleep EEG of the patient subsequent to the commencement of VGB treatment.

IS due to TSC when administered at a dosage ranging from 25 to 135 mg/kg qd[11]. In our case, VGB (50 mg/kg qd) was prescribed initially for the control of our patient's IS. Surprisingly, our patient's response to VGB was significant, since three days after VGB therapy we observed a marked improvement in electronic seizure activity. This was in terms of the almost complete absence of hypsarrhythmia appearing on follow-up of the EEG recording.

VGB is generally well tolerated in patients with epilepsy, but some adverse effects of VGB have been reported, including the occurrence of certain psychiatric problems, drowsiness, behavioral disorders, hypotonia, insomnia, and weight gain[12]. However, most of these side effects are transient[13]. Noticeably, the most significant side effect of VGB is the development of concentric visual field defects, typically occurring for 40%-50% of cases of epilepsy, which is possibly caused by a higher level of VGB in the retina than in other central nerve systems[14]. The problem of visual field defects is severe and occasionally irreversible, and continuation of the drug regime, especially in such cases, can be associated with progressive, and permanent, visual field loss[15]. Nevertheless, appropriate ophthalmological testing of visual fields for infants and young children is limited[16]. Thus, evoked visual potential and electroretinography should be indicated for such young patients in order to attempt to detect, as early as is practicable, impairment of an individual's visual field, particularly visual field constriction related to VGB therapy. However, the minimum dose and duration of VGB treatment that leads to the side effects have still not been established[17]. Nevertheless, even after low dosages and short-term treatment regimens with VGB, appropriate ophthalmological tests should be evaluated for individuals who use this drug.

The number, size, and location of cortical tubers in TSC may be associated with the subsequent development of cognitive issues, behavioral problems, the severity of epilepsy, and neurologic outcomes. Moreover, the presence of cortical tubers for TSC-affected individuals that are related to mental retardation has been reported[18]. Certainly, the earlier diagnosis of TSC has a relatively better outcome in terms of the potential control of seizures and the degree of mental retardation that eventuates. In view of dermatological characteristics, the presence of hypopigmented macules may be highly associated with the occurrence of seizures for individuals of a younger age, and may contribute to an early diagnosis of TSC[19].

In conclusion, detailed dermatological examinations, electroencephalography, and appropriate radiological in-

vestigations are essential to make an early definitive diagnosis of TSC with IS. Furthermore, an early diagnosis combined with early intervention with VGB therapy may provide a better outcome for patients with TSC than having a delayed diagnosis of TSC and treatment of IS with VGB. Simultaneously, appropriate and ongoing ophthalmological evaluation of the visual field for a TSC-afflicted child receiving VGB treatment is necessary for the early detection of possible progressive visual field loss.

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