Original article

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Lamotrigine is favourable for startle-induced seizures

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ABSTRACT – Falling due to startle-induced seizures (SISs) often leads to injury. The triggers of SIS are mostly unexpected auditory stimuli, which are too common to avoid in daily life. As SISs are often refractory to conventional medications, effective therapeutic options have to be established. We report a small series of six patients treated with lamotrigine (LTG) as add-on therapy. Seizure control was improved greatly in three of the six patients, resulting in less restricted daily life, but no effect was observed in two and a skin rash developed in one. Patient 1 was a 19-year-old man. His seizure comprised of a sudden tonic extension of the extremities induced by auditory or visual stimulus. He fell down due to SISs, five to ten times a day, with frequent injuries. After adding LTG to treatment with valproate (VPA) and clobazam (CLB), SISs were reduced to once a month. Patient 2 was a 51-year-old woman. Sudden tonic extension of all limbs induced by unexpected sounds frequently threw her down onto the floor. Addition of LTG to treatment with CLB, zonisamide and phenytoin reduced her SISs from several to less than once a day. Patient 3 was a seven-year-old girl with post-encephalitic epilepsy. After adjunctive treatment of LTG to VPA, the severity of SISs became milder thus avoiding injury, although seizure frequency did not decrease. LTG is potentially effective for the treatment of SISs and may prevent falling. The addition of LTG treatment dramatically improved the lives of the patients presented here and should be considered as an option for startle-induced seizures.

Key words: lamotrigine, startle-induced seizures, falling, effectiveness

Startle-induced seizures (SISs) are often very resistant to antiepileptic drugs and are disabling. The triggers of SISs are unexpected visual, somatosensory, or auditory stimuli, which are too common to avoid in daily life. Falling due to SISs often leads to injury and restricts the patients' daily activities. Nevertheless, there are few reports of successful treatments for SISs. A case report suggests that management with drugs for focal seizures may be effective in milder cases (Cokar *et al*., 2001). Effective therapeutic options have yet to be established.

Objective and methods

We reviewed the records of patients referred to the Shizuoka Epileptic Center, Japan, and identified

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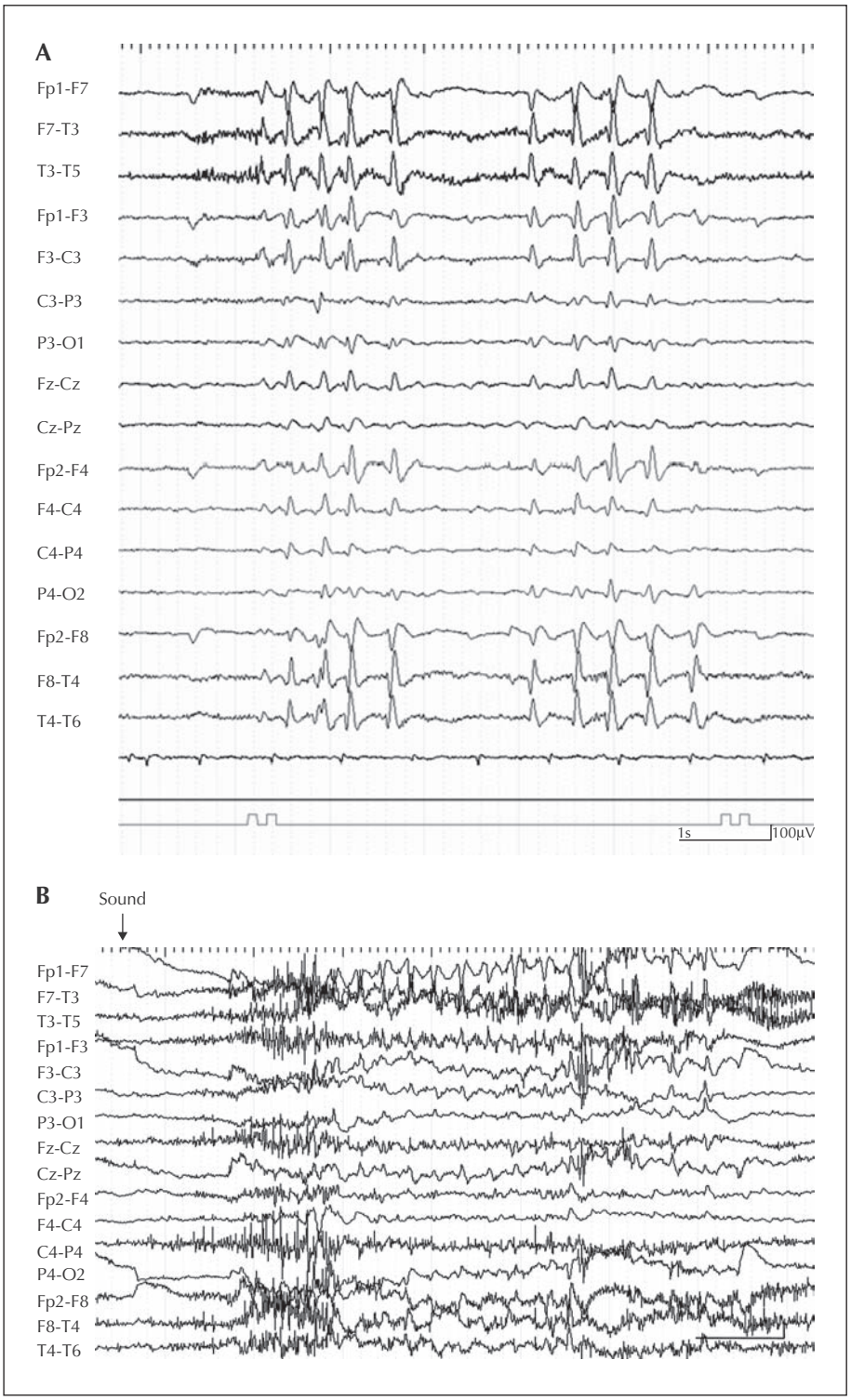

Figure 1. Interictal (**A**) and ictal (**B**) EEG of Patient 1.
Interictal EEG during wakefulness shows the appearance of frequent spikes bilaterally but predominantly over left temporal and frontal regions. Ictal EEG initially shows muscle artefacts followed by repetitive spikes on the left anterior temporal-frontal region. The seizure was induced by the sounds of his mother's shoes, with sudden extension of both arms and legs with tonicity.

patients with video-documented startle-induced seizures. The definition of SIS was a clinical event clearly related to auditory or somatosensory stimulation, accompanied by a clear ictal EEG pattern. The EEG and video sequences of 19 patients fulfilled these criteria. Six patients were treated with lamotrigine (LTG). One of the six patients discontinued LTG due to LTG-induced skin rash, two showed no changes with LTG treatment, and three were significantly improved by LTG treatment and were able to lead a less restricted daily life. We reviewed these three patients with respect to the underlying aetiology, neurological comorbidities, additional non-SISs, age at onset of epilepsy and SISs, MRI, and treatment. The follow-up periods ranged from five to 14 months.

Case study

Patient 1 was a 19-year-old man with mild mental retardation. There was no relevant family and personal history. Epilepsy and SISs started at seven months. SISs consisted of sudden tonic extension of the arms and legs induced by unexpected auditory (such as ringing of the telephone, slamming of doors or windows [even in neighbouring residences], the sound of letters being dropped into the post box, or coughing of persons nearby), visual (such as a human figure or sudden showing of cards) or touch stimuli. He fell down due to SISs five to ten times a day, causing frequent injuries. To avoid making sounds, there were no doors or drawers in his home, and everything was covered with a buffer material. He moved by crawling and had meals lying down. He always stayed indoors at home, and was irritable and took his frustrations out on his family. He also had spontaneous epileptic spasms.

Interictal EEG showed frequent spikes predominantly over left temporal and frontal regions *(figure 1A)*. Ictal EEG of SISs initially showed muscle artefacts followed by repetitive spikes on the left anterior temporal-frontal region *(figure 1B)*. MRI showed diffuse mild cerebral atrophy *(figure 2)*. He had several seizures (SISs and epileptic spasms) daily even with carbamazepine (CBZ), clobazam (CLB), phenobarbital (PB) and lorazepam. Combination of valproate (VPA) and clonazepam (CZP), γ-globulin or adrenocorticotropic hormone therapy was effective to control SISs and epileptic spasms, but the effect was transient. After adding 225 mg/day LTG to 800 mg/day VPA and 8 mg/day CLB, SISs and spontaneous seizures decreased to once a month. Blood VPA level was 55.1 μg/mL and LTG level was 13.32 μg/mL four months after starting LTG. Blood VPA level remained unchanged before and after LTG addition. Because of seizure reduction, he no longer had to crawl all day. Moreover, after taking LTG, his parents found an improvement in his social behaviour including reduced irritability, excitability and autistic symptoms.

Patient 2 was a 51-year-old woman. Her cousin had episodes of epileptic seizures in his younger age. There was no relevant past history. She had onset of epilepsy and SISs at age eight years. Sudden tonic extension of all limbs induced by unexpected sounds (such as coughing, ringing of the telephone, or slamming of doors or windows) frequently threw her down to the floor. Almost all SISs were induced by sounds and rarely by visual or touch stimuli.

Interictal EEG showed bilateral spike- or polyspike-waves over fronto-centro-parietal areas. Ictal EEG showed diffuse attenuation and was covered by artefacts *(figure 3)*. She had also spontaneous seizures with tonic extension of the right extremities. MRI revealed no relevant abnormality *(figure 4)*. Nitrazepam (NZP), CZP, acetazolamide (AZA), and CBZ were not effective against spontaneous seizures and SISs, while CLB, zonisamide (ZNS), phenytoin (PHT), and VPA were partially effective. At the age of 57 years, addition of 150 mg/day LTG to 5 mg/day CLB, 300 mg/day ZNS and 187.5 mg/day PHT reduced her SIS frequency from 5-15 times per day to less than once a day, and attenuated the intensity of seizures. Spontaneous seizures also remained, but their frequency and intensity were reduced. Before taking LTG, she moved by crawling and had meals lying down because of the risk of injury. After SISs were reduced following addition of LTG, she was able to move in a wheelchair. Reduction of seizures dramatically improved her daily life.

Patient 3 was a seven-year-old girl. There was no family history. She had no perinatal problems, but had influenza-associated encephalitis at the age of 12 months, followed by quadriplegia. She had onset of epilepsy at 13 months and SISs at 14 months. Unexpected sounds (such as coughing or sneezing of persons nearby, slamming of doors or windows, or ringing of the telephone) caused massive myoclonus with vocalisation followed by tonic extension of upper limbs, which frequently led her to collapse. In the initial stage, SISs were also induced by sudden touch. Interictal EEG showed multifocal slow waves and spikes or sharp waves *(figure 5A)*. Ictal EEG showed bilateral diffuse spikes followed by attenuation *(figure 5B)*. She had also spontaneous seizures without falling. SISs occurred twice as often as spontaneous seizures. SISs occurred around 100 times a day and she was frequently injured. MRI revealed diffuse cerebral atrophy, predominantly in both frontal lobes *(figure 6)*. Carbamazepine, zonisamide and clonazepam were not effective. A ketogenic diet decreased the frequency of SISs to three to four a day and improved development. Nitrazepam, topiramate (TPM) and a combination of VPA and ESM were partially effective, however seizures still occurred frequently. After addition of 20 mg/day LTG to 300 mg/day

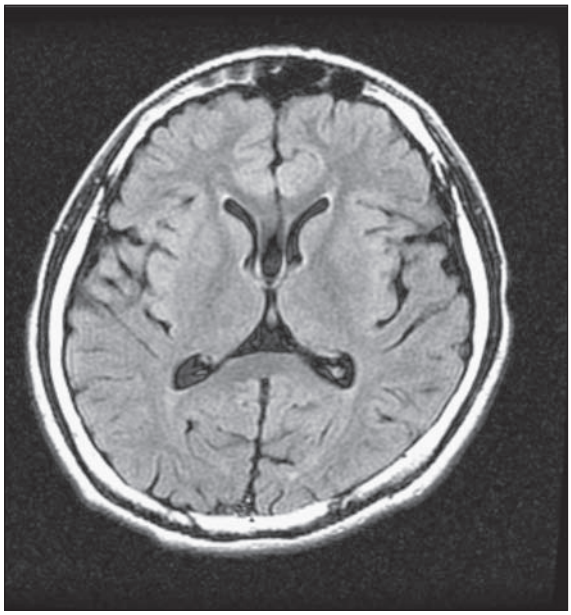

Figure 2. FLAIR MRI of Patient 1.
MRI shows diffuse mild cerebral atrophy.

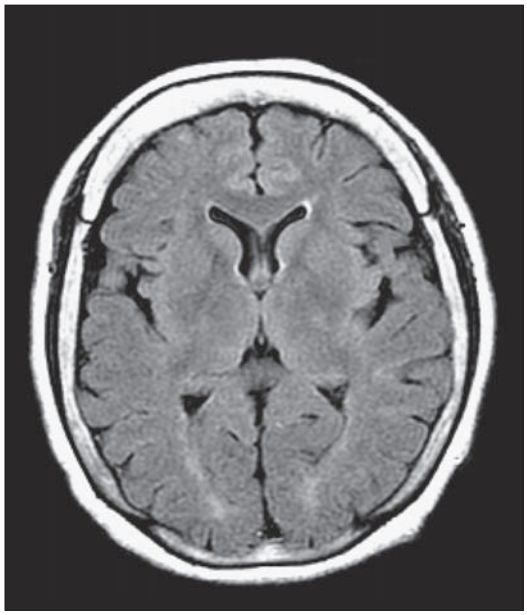

Figure 4. FLAIR MRI of Patient 2.
MRI revealed no relevant abnormality.

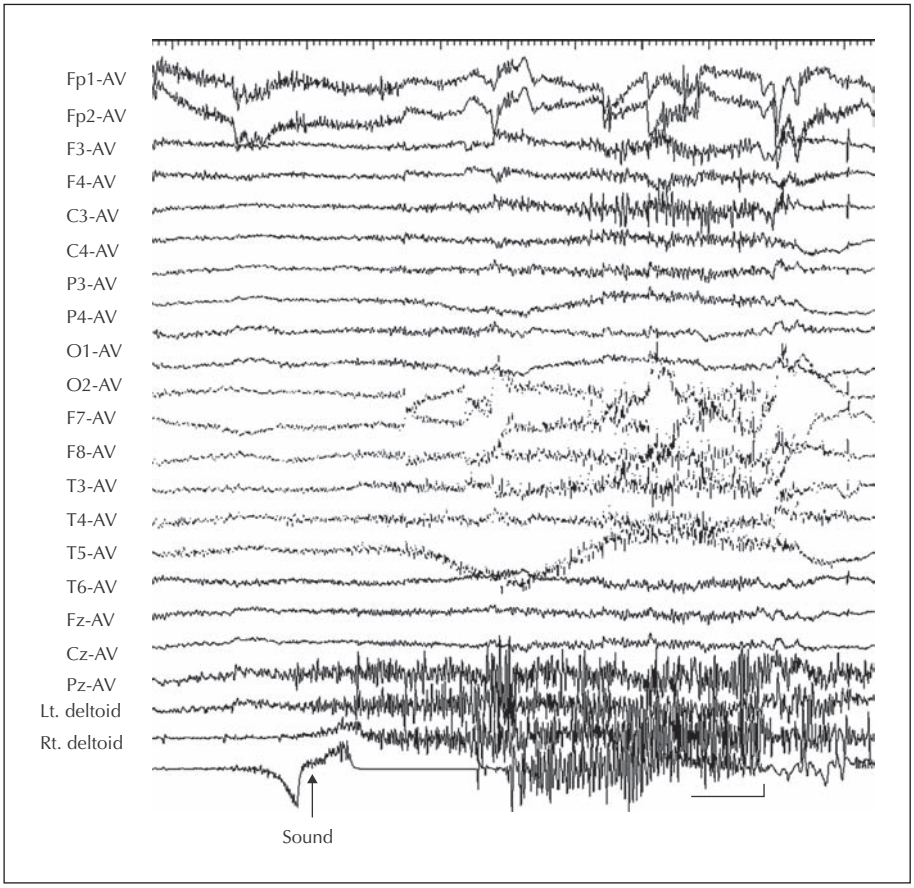

Figure 3. Ictal EEG of Patient 2. Ictal EEG shows diffuse attenuation and is hidden by artefacts. The seizure was induced by the sounds of the television, with sudden extension of both arms and legs with tonicity.

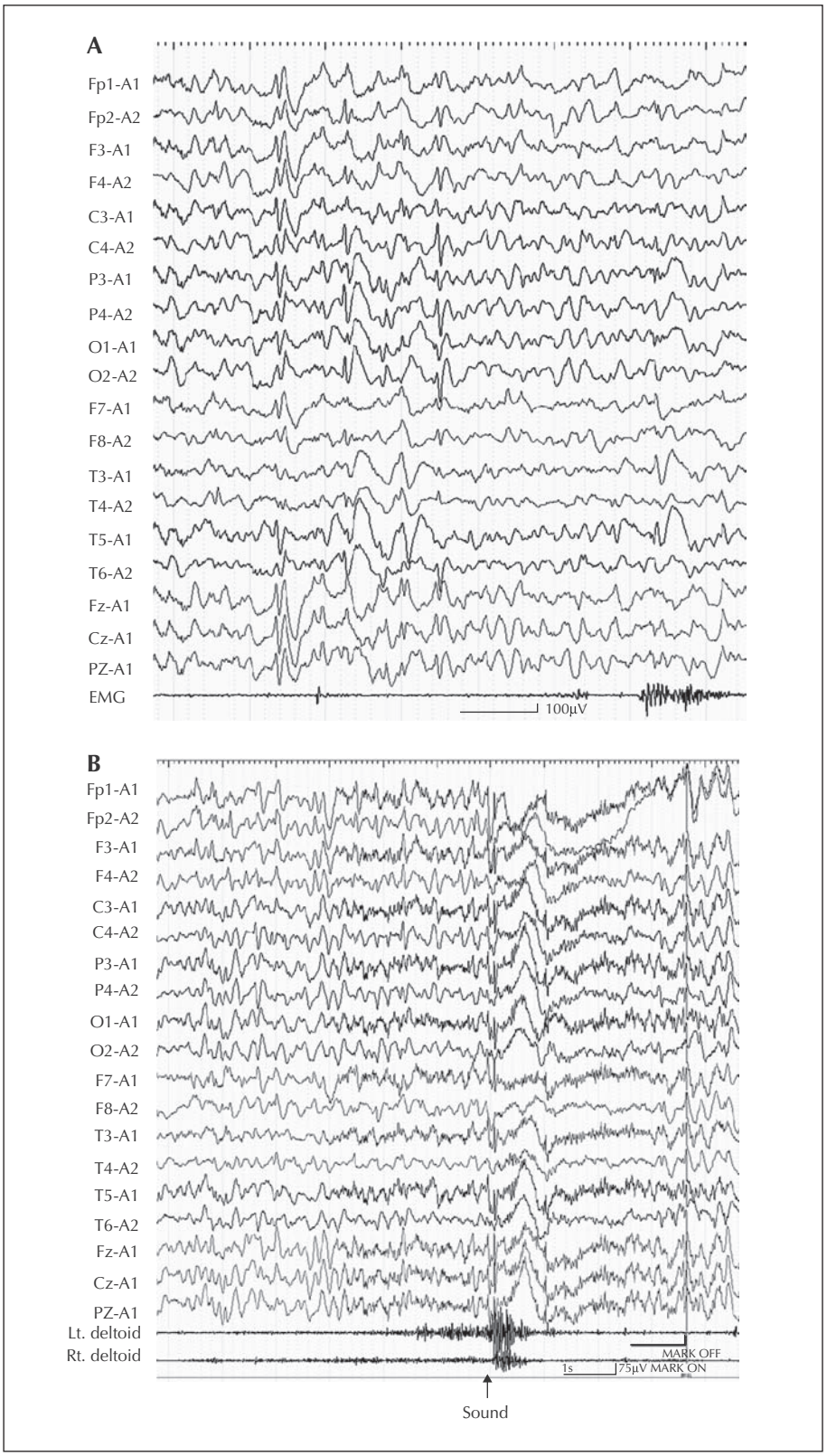

Figure 5. Interictal (**A**) and ictal (**B**) EEG of Patient 3.
On interictal EEG, multifocal slow waves and spikes or sharp waves are seen. Ictal EEG shows bilateral diffuse spikes followed by attenuation. While she was sitting in her buggy, a cough of the mother induced a seizure with sudden extension of all limbs with increased tonicity.

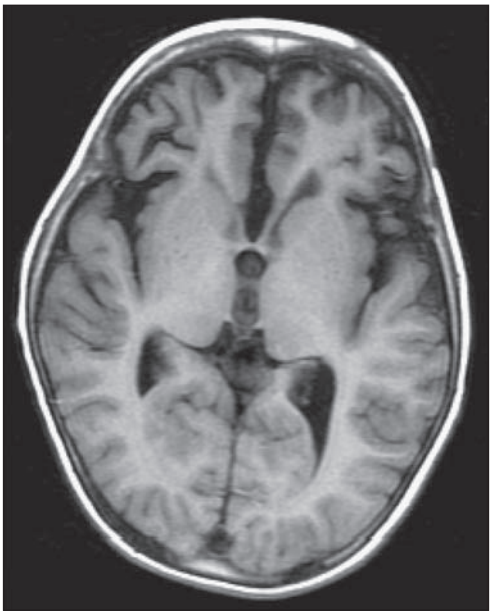

Figure 6. MRI (T1) of Patient 3. MRI revealed diffuse cerebral atrophy, predominantly in both frontal lobes.

VPA at age six years, the severity of SISs was attenuated to a degree that injury was avoided, although decrease in seizure frequency was not significant. Spontaneous seizures faded away. She could be trained to walk more safely than before. The blood level of VPA was 81.2 μg/mL and LTG 6.53 μg/mL.

Discussion

Alajouanine and Gastaut (Alajouanine and Gastaut, 1955) first defined startle epilepsy and distinguished this entity from abnormally prolonged, exaggerated startle response. The seizures of our three patients were characteristically induced by sudden and unexpected stimuli, usually sudden sounds and occasionally visual or touch stimuli. The seizures were frequent and consisted of a startle response, a myoclonus, followed by a brief tonic phase with slight asymmetry. All our patients fell down due to SISs, causing frequent injuries, and their families therefore took every care to prevent injury. Patient 1 and 2 lived on the floor, crawling and doing most activities lying down.

Some reports indicated that patients with startle-induced seizures had an epileptogenic focus in the frontal lobe (Aguglia *et al*., 1984; Saenz-Lope *et al*., 1984; Chauvel *et al*., 1992; Manford *et al*., 1996; Oguni *et al*., 1998; Nolan *et al*., 2005). Bancaud *et al*. (1967) evaluated startle-induced seizures using depth electrodes, and recorded ictal epileptiform discharges from the supplementary sensorimotor area (SSMA). Surgical ablation of the SSMA controlled the seizures. In another case, surgical resection of a region in the frontal lobe, including the SMA and adjacent sensorimotor areas, rendered the patients seizure-free (Oguni *et al*., 1998). In one report, an epileptogenic lesion was identified in the dorsolateral frontal lobe with involvement of the SMA in the generation of startle-induced seizures (Nolan *et al*., 2005). However, the pathophysiology of SISs remains unclear. Several mechanisms have been suggested to explain the triggering of SISs. One hypothesis postulates a direct projection of sensory afferents to the motor or premotor cortex (SMA) which triggers the paroxysmal evoked response and seizure. The supplementary motor area is considered a multimodality convergence zone for somesthetic and auditory stimuli (Wiesendanger *et al*., 1973; Tanji and Kurata, 1983; Vignal *et al*., 1998). A related hypothesis proposes the existence of a relay in the primary auditory cortex with secondary projection through a corticocortical loop towards the motor or premotor cortex in the case of an auditory startle trigger. Another hypothesis is that the startle response is a necessary intermediate step in triggering the seizure, because physiological startle depends on a subcortical loop. The stimulus provokes a startle, which activates the lemniscal pathway that projects to the sensorimotor cortex (Vignal *et al*., 1998).

Most antiepileptic drugs are ineffective for the treatment of SISs, as evidenced in our cases and previous reports (Aguglia *et al*., 1984; Saenz-Lope *et al*., 1984; Manford *et al*., 1996). CBZ, VPA and TPM have been reported to be useful in rare cases (Saenz-Lope *et al*., 1984; Mayer and Specht, 1995), but CBZ (all patients) and TPM (Patients 2 and 3) were not effective in our patients. Moreover, benzodiazepines, CZP and CLB were described to be effective for SISs (Aguglia *et al*., 1984; Tinuper *et al*., 1986; Manford *et al*., 1996), although CLB (Patient 1) and CZP (Patients 2 and 3) failed to control SISs in our patients. Chlordiazepoxide (Cohen *et al*., 1961) and levetiracetam (Gürses *et al*., 2008) were reported to be effective.

On the other hand, LTG controlled or reduced SISs associated with falling and dramatically improved the quality of life in three of the six patients in our series who took this drug. Faught (1999) also previously reported four patients with startle-induced seizures who were refractory and responded dramatically to LTG with elimination of falls from seizures. It is difficult to explain why LTG was effective in these patients. This may reflect simply a wide spectrum of LTG efficacy, or there may be a unique pharmacological mechanism for LTG in seizures like SISs. Because LTG improves mood (Uvebrant and Bauziene, 1994; Brodie, 1992; Cramer *et al*., 2004; Yagi, 2009), there may be a positive effect of LTG on SISs in this regard.

We conclude that LTG may be effective in some patients with SISs, although our experience was limited to only six patients with short follow-up period because LTG has only been available in Japan since 2009. Further trials of LTG for SISs are needed to confirm its effectiveness. □

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

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