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Forced normalisation precipitated by lamotrigine

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Summary

Purpose: To report two patients with lamotrigine-induced forced normalization (FN).
Methods: Evaluation of the patient files, EEG, and video-EEG records, with special reference to the parallel clinical and EEG changes before, during, and after FN.
Results: This is the first documented report of lamotrigine-induced FN. The two epileptic patients (one of them was a 10-year-old girl) were successfully treated with lamotrigine. Their seizures ceased and interictal epileptiform events disappeared from the EEG record. Simultaneously, the patients displayed de novo occurrence of psychopathologic manifestations and disturbed behaviour. Reduction of the daily dose of LTG led to disappearance of the psychopathological symptoms and reappearance of the spikes but not the seizures.
Conclusions: Lamotrigine may precipitate FN in adults and children. Analysis of the cases showed that lamotrigine-induced FN is a dose-dependent phenomenon and can be treated by reduction of the daily dose of the drug.

Introduction

The relationship between epilepsy and psychopathology is a highly complex matter. Antagonism between recurring epileptic seizures and episodes of disturbed behaviour is a characteristic alternating pattern of events, which was observed in a lot of treated and untreated epileptic patients.[1] The introduction of effective drugs for focal and generalized epilepsy considerably enhanced the number of patients who became seizure free but experienced diverse psychopathologic phenomena at the same time.[2–4] Landolt introduced EEG into the systematic investigation of this peculiar antagonism and created the term ''forced normalization'' (FN). In his original paper he wrote: ''Forced normalization is the phenomenon characterized by the fact that, with the occurrence of psychotic states, the EEG becomes more normal or entirely normal as compared with previous and subsequent EEG findings''.[3] Later investigations confirmed the existence of FN and the role of most anticonvulsive drugs in precipitating FN. All but two of the widely used antiepileptics were reported to precipitate episodes of FN.[4–10]

Abbreviations: FN, forced normalization; LTG, lamotrigine; CBZ, carbamazepine

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As far as is known (based on the thorough search of the Medline database 1990—2003) there are no full-length papers indicating that FN was precipitated by lamotrigine and gabapentine. Recently, a single abstract[11] was cited by a few authors as an example for lamotrigine-induced FN. However, even the authors wrote ''acute psychosis'', and no EEG changes were reported in this abstract. Another matter of interest is that FN has been very rarely reported in children or adolescents.[5,12] In this paper, we report on two patients who experienced episodes of disturbed behaviour and EEG normalization precipitated by lamotrigine treatment.

Methods

The original patient files, 19-channel EEG and video-EEG records, cranial CT and MRI images of the two patients were thoroughly revised by the author. Parallel clinical and EEG changes were extracted in the form of case reports.

Results

Patient 1

The girl was born in 1993. Developmental milestones were normal and there were no neuropsychiatric items in her medical history. She did very well at school. At the age of 7 years she experienced 5—10 brief episodes of numbness and a few clonic movements of the right arm and hand daily. Epilepsy had not been suspected until we investigated her at the age of 8. A lot of seizures were observed by the author and recorded by video-EEG. Investigating the patient, she did not show neurological abnormalities or behavioral disturbances. EEG showed frequent left centro-parietal spike activity (Fig. 1). MRI disclosed abnormal thickness of the gray matter of the

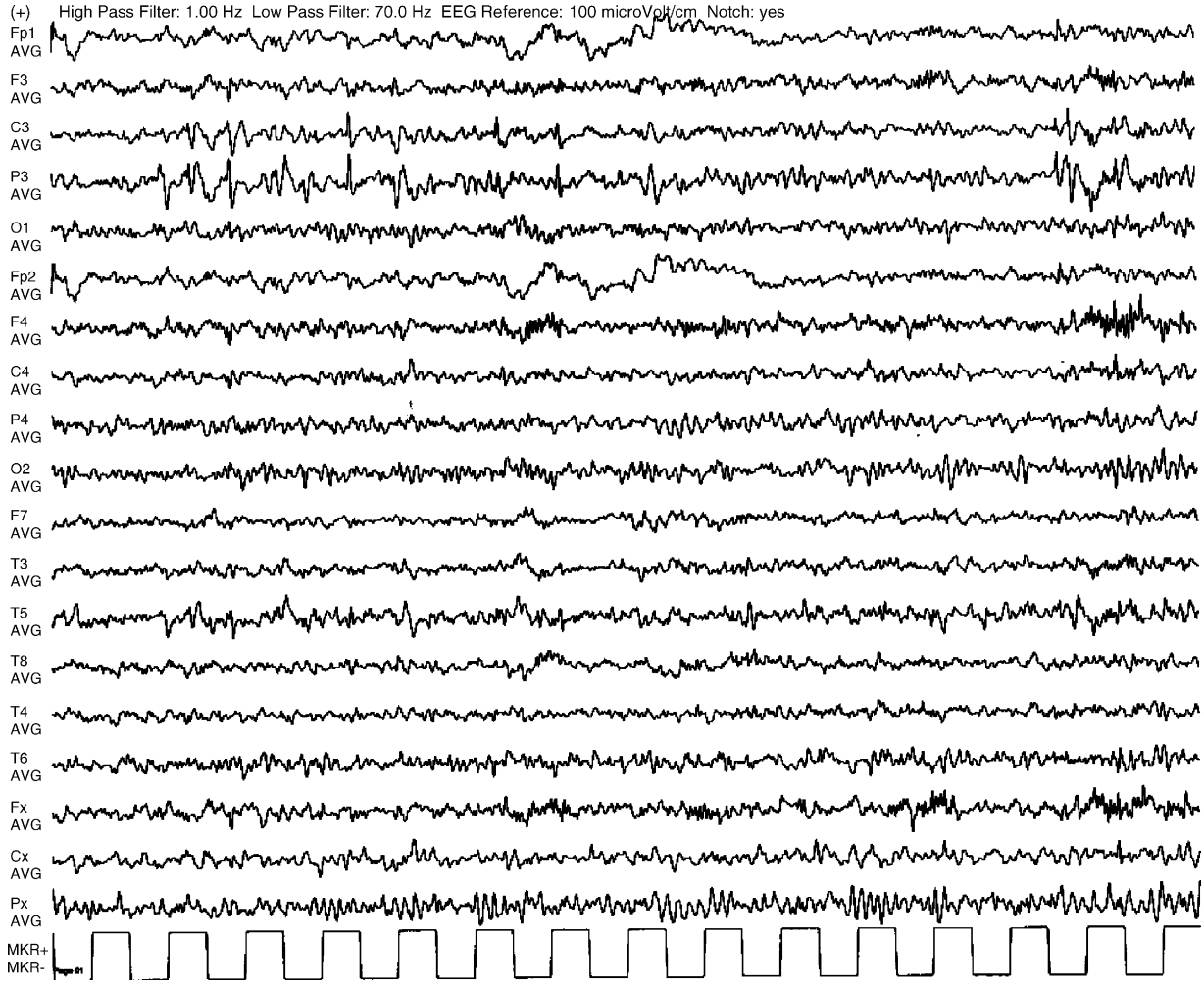

Figure 1 Patient 1: before FN. Waking EEG, focal slowing in C3, P3, T5 leads, frequent spikes in the left centro-parietal area. AVG: common average reference, MRK: marker. Filters were set at 1.0 and 70 Hz.

left postcentral gyrus. Carbamazepine (CBZ) and clobazam did not influence the seizure frequency. Hence, clobazam was discontinued and lamotrigine (LTG) was introduced. The starting dose of 25 mg/day was gradually increased by steps of 25 mg/week. Parallel with the increasing LTG dose, CBZ was reduced and discontinued. Increase of the daily dose of LTG was associated with decreasing seizure frequency. In the next 5 months the patient took 175 mg LTG daily, and the seizure frequency was 1—2/month. Her neurological condition and behaviour did not change, repeated EEG recordings invariably showed significant left centro-parietal spike activity. Thereafter, a moderate increase of the seizure frequency was reported, for which reason the daily dose of LTG was increased to 225 mg. Two days later the parents reported that the attacks became very frequent (daily 20—30), and were ''stronger'' than before. At the same time the girl seemed to be frightened and agitated. Again, neurological examination revealed no alterations, no symptoms of neurotoxicity, but the girl who had been uncomplaining and good cooperating previously was irritable, restless and frequently cried during the session. The next day, three attacks were recorded by video-EEG. The attacks were composed of alternating rhythmic movements of the right arm and kicking with both legs. EEG showed no abnormal EEG patterns during these attacks. Spike potentials completely disappeared from the 6-h long EEG record. Thus, we diagnosed ''occurrence of mood changes, pseudoseizures and forced normalization''. Reducing the daily dose of LTG to 150 mg led to rapid disappearance of the conversion phenomena, irritability, and restlessness. In the next months the seizure frequency was relatively low (1—5/month). Finally, all the seizures disappeared. From that time she has been completely free of seizures and behavioural problems. Spike potentials reappeared in the following EEG records and showed an increasing frequency during the next months. Now she is 11 years old and she has been seizure-free for 1.5

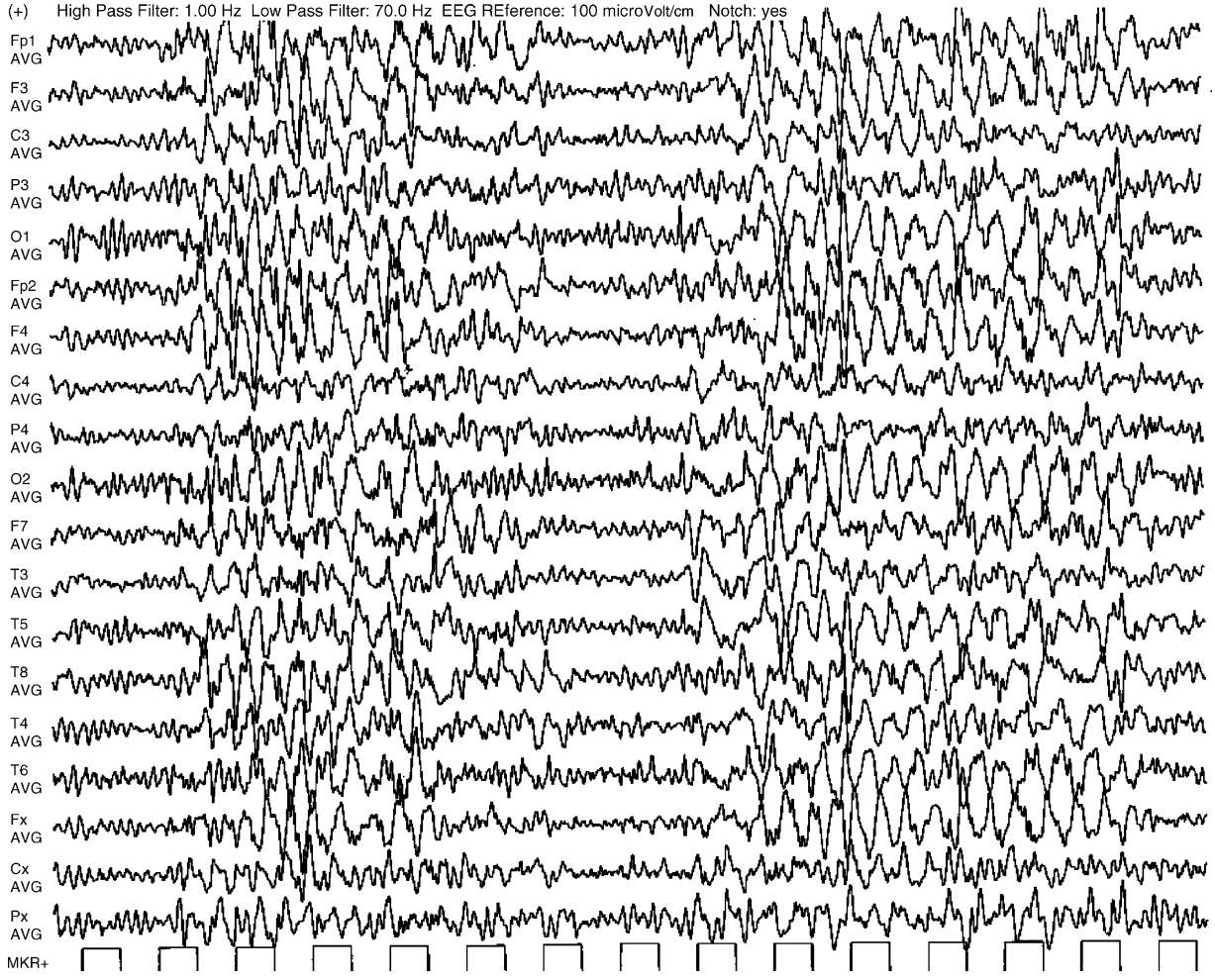

Figure 2 Patient 2: before FN. Waking EEG, 8—9 Hz alpha background activity, frequent bilateral-synchronous high voltage paroxysms of sharp waves. AVG: common average reference, MRK: marker. Filters were set at 1.0 and 70 Hz.

years. However, EEG follow-up invariably shows frequent spikes with the habitual localisation and morphology.

Patient 2

The 43-year-old female has temporal epilepsy with complex partial seizures from the age of 6 years. She was admitted to the Epilepsy Centre in Feburary 2000. Medical documentation concerning the results of the previous investigations and the course of the illness was very sparse. In the last few years her seizures consisted of staring, cessation of ongoing activities, and sometimes meaningless speech. Apart from memory problems, the patient and her husband did not report psychiatric symptoms or disturbed behaviour interictally. At investigation there were no neurological abnormalities. CT scan showed no abnormalities. EEG showed very frequent bilateral-frontotemporal trains of sharp waves and spike-and slow complexes (Fig. 2). The admixture of some slow activity and lateralized sharp waves indicated a right-sided focus. Video-EEG recordings disclosed that the EEG abnormalities are interictal and are not accompanied by clinically detectable transient cognitive impairment. Because of the persisting complex partial seizures the daily dose of CBZ was increased to the maximal tolerable dose. Repeated neurological investigations did not indicate neurotoxicity. In the next weeks repeated EEG records invariably showed a great amount of paroxysmal activity and even the seizures became more frequent. In October 2002, the daily dose of CBZ was reduced to 1050 mg and lamotrigine was introduced. Increasing the dose of the latter drug to 100 mg b.i.d. abolished the seizures in a few days. In this period the patient became more and more irritable, severely distracted and insomnic. Finally, paranoid ideation and, presumably, hallucinations appeared. At the same time EEG showed complete disappearance of all paroxysmal activities. Forced normalization was diagnosed, LTG was tapered off to 50 mg b.i.d. and haloperidol was given. Her psychotic symptoms disappeared during the next 2 weeks and did not recur even when she refused further intake of haloperidol. Since then she has been seizure free and no episodes of psychotic or disturbed behaviour occurred. A month later the EEG record showed a moderate amount of spike-wave activity.

Discussion

The described episodes of our patients fulfilled all the so-called essential diagnostic criteria for FN,[13] and also one supportive criterion.[13] The symptoms we observed are on the list of FN-related behavioral disturbances in adults,[4,7,13] and in children.[5,12] The fact that decreasing the daily dose of LTG led to rapid disappearance of the disturbed behaviour is a further argument for LTG-induced FN.[13,14] The antagonism between psychopathology and interictal epileptiform activity was further supported by the fact that mental normalization was accompanied by the recurrence of interictal epileptiform potentials. In all the patients, EEG abnormalities were invariably found in at least four EEG records, and disappearance of these abnormalities was based on EEG and video-EEG records that lasted a few hours. The number and length of the EEG records were sufficiently great to assess the presence or absence of interictal paroxysms.[15] Thus, we do not think that electroencephalographic sampling problems confounded our results.

The mechanisms of FN are far from understanding. A few authors thoroughly discussed the theoretically possible ways of FN but the results do no allow a synthesis at present.[7,16] Our case reports suggest the antagonism between EEG-spikes and psychopathology as originally suggested by Landolt,[3] rather than between the seizures and psychopathology. Going into yet unsolvable issues concerning the relationship between LTG (or any other drug) and FN was not the aim of these case reports. Nevertheless, it is not very surprising that LTG, a drug, which mitigates depolarizing sodium and calcium currents in neurons, suppresses spike activity[17] and alters thalamocortical electromagnetic oscillations[18] causes clinically significant changes in the mental state and in the EEG.

Conclusions

(1) Lamotrigine can precipitate FN in adults and children and (2) lamotrigine-induced forced normalization is a dose-dependent phenomenon and can be easily reversed by reducing the daily dose. The optimal daily dose of LTG can result into a seizure-free state without psychopathology.

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