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CASE REPORT

Thyroxine-induced hypermotor seizure

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Thyroxine-induced epilepsy is a very rare condition occurring in epileptic patients. Here we report a boy with thyroxine-induced hypermotor seizure (HMS) following thyroxine administration for his central hypothyroidism secondary to surgery and cranial radiation for his brain tumor. After 3 years seizure-free period, he had repeated HMS, seven to eight attacks per day, after initiation L-thyroxine treatment. Following reduction of the daily thyroxine dose, his seizures decreased in frequency. To our knowledge, this is the first reported case of HMS associated with L-thyroxine administration.

Key words: hypermotor seizure; L-thyroxine treatment.

INTRODUCTION

Thyroxine lowers the seizure threshold of experimental animal models[1,2], produces high amplitude photic response in healthy volunteers[3] and caused seizures in patients with Graves' disease[4]. Previously, L-thyroxine-induced petit mal status epilepticus and, absence seizures in juvenile myoclonic epilepsy (JMCE) were reported in two different studies[5,6]. But, seizure due to thyrotoxicosis and, thyroid storm presenting with seizures was notified different study in pediatric patients[7–9].

In the semiologic seizure classification hypermotor seizures (HMSs) are defined as seizures consisting of complex, organised movements which affect mainly the proximal portion of the limbs and lead to a marked increase in motor activity and most frequently associated with frontal lobe[10].

We describe a patient with partial secondary generalised tonic–clonic seizures (GTCS), well controlled by carbamazepine and phenobarbital treatment in whom HMS were provoked by L-thyroxine administration without affecting the frequency or severity of his GTCS.

CASE REPORT

An 11-year-old boy with operated anaplastic oligodendrogliotic tumor was brought to Department of Pediatrics, Dokuz Eylül University Faculty of Medicine with the complaint of seizures for the last 1 month. He had been diagnosed with anaplastic oligodendrogliotic tumor (left frontal lobe) 5 years ago when he first presented with acute confusional state and headache. Post-operatively he had no neurological deficits or seizures. He began phenytoin treatment 10 mg kg^{-1} per day for seizure prophylaxis for 6 months after the operation. During the first 4 months following surgery, he had no seizures or pathological electroencephelography (EEG) findings. Approximately 4 months after the surgery while he was being treated with cranial radiotherapy, he was readmitted to our hospital with GTCS lasting 15 minutes. On admission, physical examination was unremarkable and neurological examination revealed that he was mildly confused and had retrograde amnesia but cranial nerves, motor and sensory examinations were unremarkable in postictal state. Interictal state whole neurological examination was normal. His interictal EEG showed almost

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continuous epileptic activity originating in the left temporal lobe. A diagnosis of partial seizure with secondary generalised tonic–clonic convulsions was made and carbamazepine (15 mg kg^{-1} per day) was added to the current regimen. After this first seizure, GTCS and complex partial seizures recurred, and therefore carbamazepine dose was increased and phenobarbital (5 mg kg^{-1} per day) was added while phenytoin was decreased gradually and stopped. After 3 years of epilepsy-free period, the patient was referred to the Pediatric Endocrinology Unit for evaluation of his obesity and pituitary functions. His physical examination revealed an obese boy with a weight of 58.5 kg (>95th percentile) and a height of 135.1 cm (10th percentile). On laboratory tests, T3: 1.01 ng ml^{-1} (normal range (NR): 0.60–1.81), T4: 8.7 μg dl^{-1} (NR: 4.5–12.6), free T3 (fT3): 2.32 pg ml^{-1} (NR: 2.3–4.20), free T4 (fT4): 0.9 ng ml^{-1} (NR: 0.9–2.0) and thyrotropin stimulating hormone (TSH): 3.69 mIU l^{-1} (NR: 0.35–5.5) which indicated a mild central hypothyroidism. Growth hormone (GH) provocative test with insulin hypoglycemia revealed that he had inadequate GH but sufficient cortisol response to hypoglycemia. Therefore, he was diagnosed with central hypothyroidism and hyposomatotropism and was started on L-thyroxine medication of 25 μg per day and the dose was increased gradually to 100 μg per day.

Two weeks after initiation of L-thyroxine treatment, the patient began to experience pre-symptoms such as epigastric discomfort and dizziness and panic reaction like episodes. Following these symptoms usually in the morning hours, he experiences an urge to run forward without any rotation and then contractions of his left extremity. According to his parents' observation, if he was erect during the episode, he ran for 20–45 seconds, then took a deep breath and the seizure stopped. This new type of seizure started a few weeks after the initiation of L-thyroxine treatment. The frequency of seizures increased with increasing dosage of L-thyroxine and reached up to seven to eight seizures per day. The parents have noticed that when the L-thyroxine dose was decreased to 75 μg per day by the parents, the daily number of seizures decreased as well. Re-evaluation of his new onset seizure activity has shown that his blood chemistry results, EKG, cranial and pituitary MRI were all normal, except operation and maybe cranial radiotherapy marks on MRI. Phenobarbital and carbamazepine serum concentrations were in effective doses. A routine eight-channel EEG showed no epileptic focus, but during the EEG tracing, the patient had a seizure lasting for about 40 seconds. A long-term video-EEG monitoring with long-term awake and sleeping period were performed also. These EEG tracings demonstrated infrequent discharges of sharp and slow wave complexes, especially FP_2–F_8 channels during awaken period and 2–2.5 Hz focal discharges at the end of rapid eyes movement (REM)-I and non-REM changing period, respectively (Figs 1 and 2). Valproic acid was added at a dose of 10 mg kg^{-1} per day to the antiepileptic regimen of carbamazepine while phenobarbital was discontinued gradually. The parents discontinued L-thyroxine medication completely for 3 weeks and a repeat thyroid function tests showed fT4: 0.70 ng ml^{-1} (NR: 0.9–2.0), TT3: 0.78 ng ml^{-1} (NR: 0.60–1.81), TT4: 3.6 μg dl^{-1} (NR: 4.5–12.6) and TSH: 5.85 mIU l^{-1} (NR: 0.35–5.5) which indicated that he has central hypothyroidism. While he was seizure free when L-thyroxine medication was discontinued, he still would need L-thyroxine treatment for his central hypothyroidism. Therefore, he was started on 25 μg per day of L-thyroxine and the dose will be adjusted more gradually and meticulously to avoid provocation of his seizures.

DISCUSSION

The corner stone of the definition of HMS are motor manifestations, which consist of organised movements affecting especially the proximal muscles of the limbs[10]. HSM are involuntary contractions lasting for about 14–44 seconds with associated repetitive movements, simple automatism, complex automatism and contractions of motor muscles of tongue. In about 80% of patients, an aura with somatosensory findings are experienced. According to the clinical findings and presenting symptoms, HMS are classified as tonic, hypermotor, tonic + hypermotor, pure hypertonic seizures[10]. In our case, EEG and video EEG monitorisation findings as well as description of the episodes by the parents were consistent with hypermotor tonic seizures with aura originating from frontal cortex.

There are numerous factors that predispose patients with brain tumours for having seizures. Some of these factors are intrinsic to the disease while others are due to primary or secondary effects of treatment such as radiation therapy. In our patient, we investigated the factors that may provoke or cause seizures such as primary recurrence of cranial tumor, presence of cranial lesions secondary to radiotherapy or metabolic disturbances but no precipitating factor was demonstrated. However, clinically there was a strong association between initiation or dosage of L-thyroxine treatment and seizure activity.

There have been few reports in the literature demonstrating the association between the rapid attainment of L-thyroxine dosage and occurrence of seizures in predisposed patients[5]. Although the cause of this association has not been well understood, there are some proposed mechanisms.

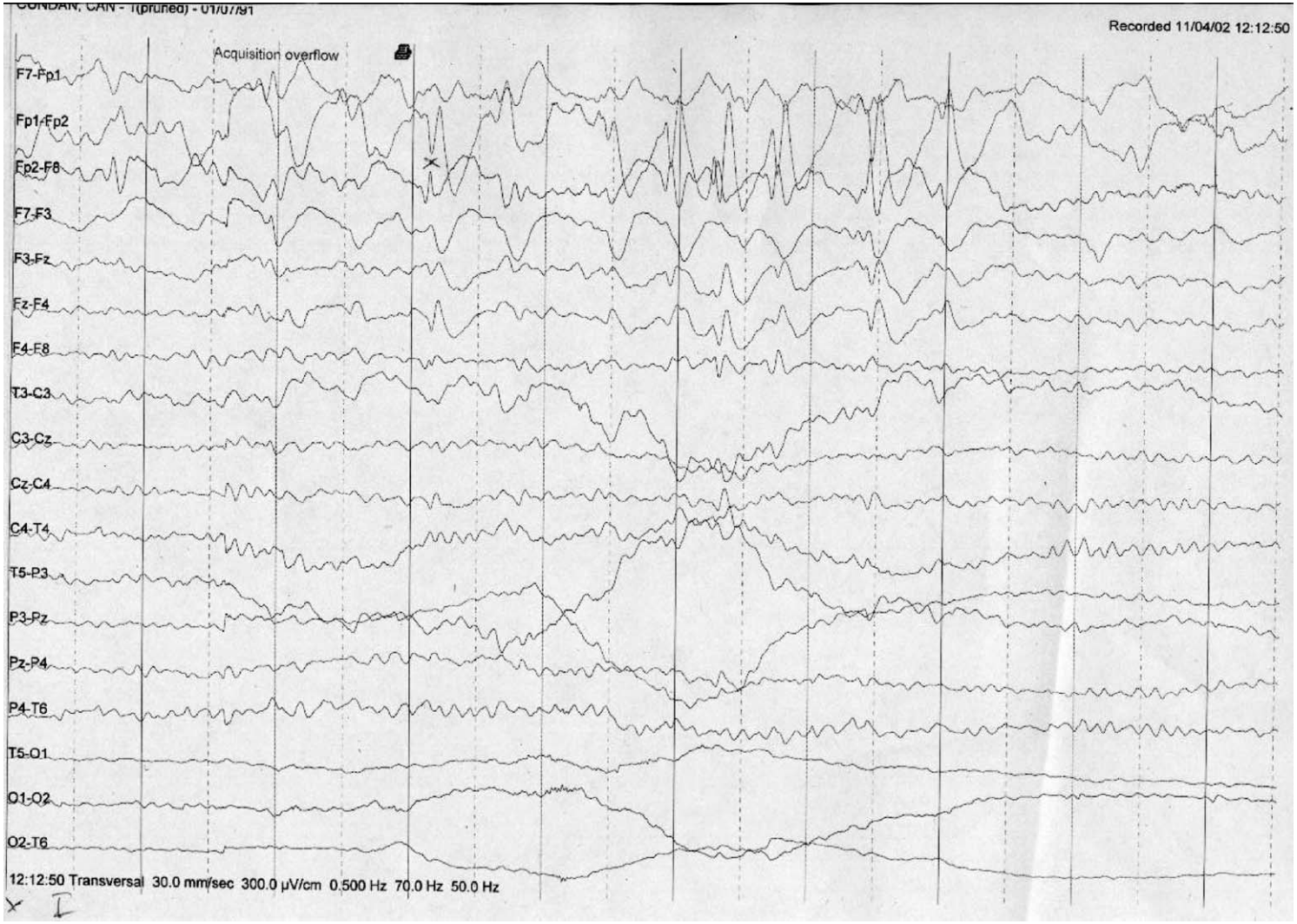

Fig. 1: EEG showing the right frontal hemisphere epileptic focus especially FP_2 (bipolar derivation) with spike and slow wave complexes of 2–2.5 Hz (transversal 30.0 mm second^{-1}, 300.0 μV cm^{-1}, 70 Hz).

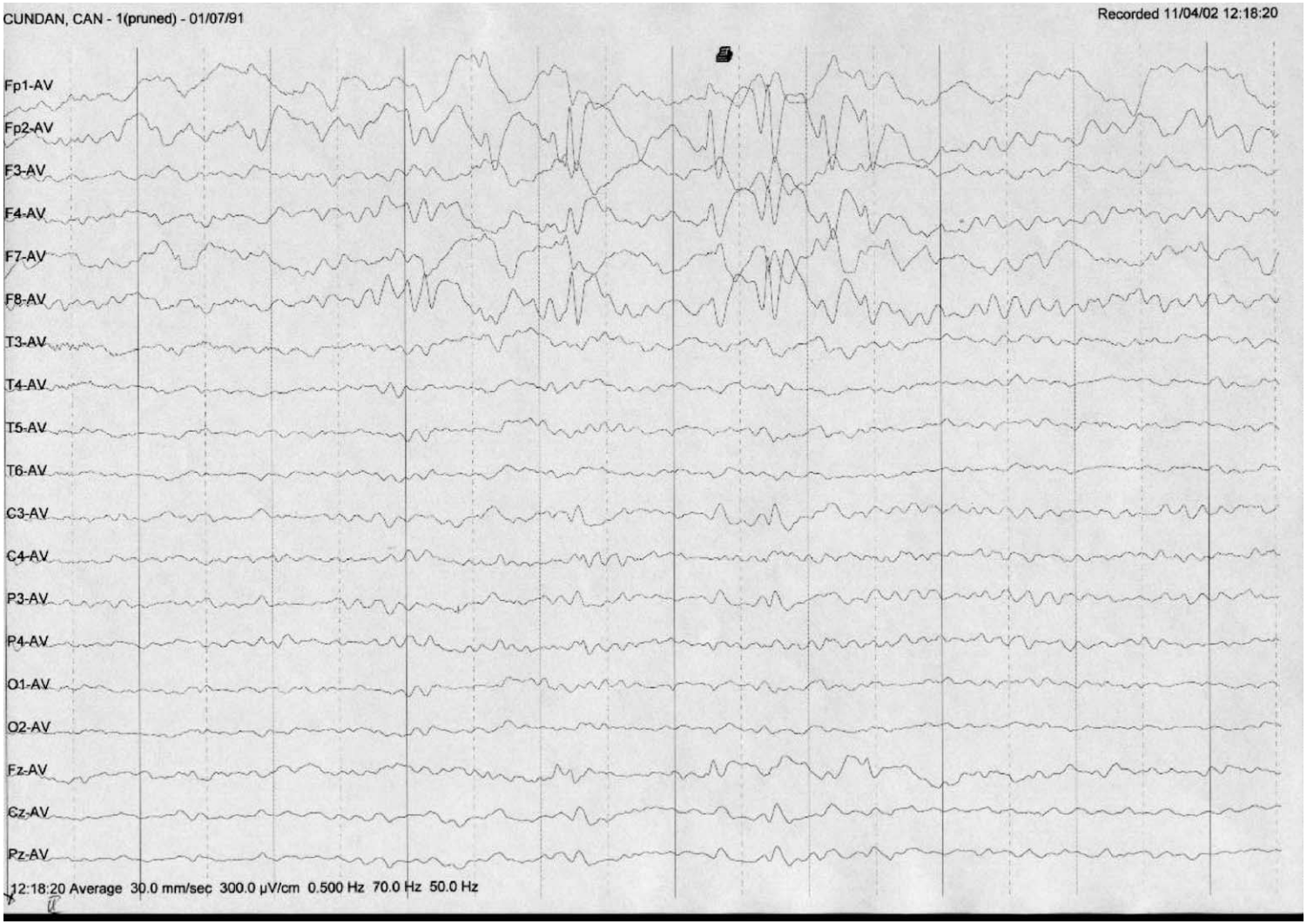

Fig. 2: EEG showing the right frontal hemisphere epileptic focus especially FP_2 and F_8 channels (average montage) with spike and slow wave complexes of 2–2.5 Hz (average, 30.0 mm second^{-1}, 300.0 μV cm^{-1}, 70 Hz).

There were reports that did not show elevation of TSH after seizure activity[11–13]. In contrast, Roa *et al.*[14] have noted elevated TSH levels that returned to baseline 2 hours after seizures only in epileptic patients. On the other hand, results of Kim *et al.*[15] demonstrated that thyroid hormone plays a modulatory role in the seizure-induced changes of neurotrophin-3 mRNA expression found in the dentate gyrus. Elevated TRH contents were demonstrated in rat brain of both electrical stimulated and kainic acid-induced seizure models[16]. Furthermore, radioimmunoassay measurements revealed an increased hippocampal TRH concentration after seizure activity[16,17]. This prolonged elevation of TRH following recurrent seizure activity may be indicative of a homeostatic response to convulsion, since TRH can selectively reduce glutamate-induced excitation of cortical neurones[17,18]. Since our patient has a central hypothyroidism most probably secondary to hypothalamic dysfunction, decreased TRH secretion due to L-thyroxine medication may not be the mechanism responsible for his L-thyroxine-induced seizures since he probably had decreased TRH even before L-thyroxine treatment.

Another proposed mechanism for L-thyroxine-induced seizures is that L-thyroxine has been found to decrease the number of cortical benzodiazepin receptors[19]. Since our patient was on phenobarbital while he was started on L-thyroxine, this mechanism may be responsible for the seizures of our patient precipitated by L-thyroxine medication.

Although the mechanism how L-thyroxine treatment induces HMS is not well known; it has been reported that in patients with petit mal status and JMCE, it may precipitate petit mal seizures[4,5]. This condition may be due to inadequate antiepileptic dosage when L-thyroxine medication has been started, possibly due to changes in pharmacokinetics or bioavailability without changing the serum concentration of antiepileptic medications.

In conclusion, we would like to emphasize that, L-thyroxine medication may precipitate seizures in epileptic patients and therefore, when L-thyroxine treatment is required in epileptic patients, it should be started in low dose and monitored very carefully to avoid precipitation of seizures and potentially of status epilepticus. Furthermore, the dosage of anticonvulsants may have to be increased, especially in patients with HMS, petit mal or JMCE.

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