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Focal epileptic seizure induced by transient hypoglycaemia in insulin-treated diabetes

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ABSTRACT – Hypoglycaemia, common in diabetic patients treated with insulin, can induce various neurological disturbances. Of these, seizures are the most common acute symptom, mainly of the generalised tonic-clonic type, with focal events only exceptionally being reported and documented. Hypoglycaemia can modify cortical excitability by determining an imbalance between excitation and inhibition; some brain structures, such as the temporal lobe and hippocampus, appear to be particularly susceptible to this insult. We describe a case of a 61-year-old diabetic patient in whom insulin-induced transient hypoglycaemia triggered a focal seizure of temporal origin that was well documented by EEG during 24-hour ambulatory monitoring. This is, to our knowledge, one of the few, well-documented cases of this type of seizure.

Key words: hypoglycaemia, epileptic seizure, acute symptom, diabetes

Hypoglycaemia is a common problem in diabetic patients treated with insulin (Varghese *et al.*, 2007). Hypoglycaemia-induced neurological disturbances include epileptic seizures, which represent a relatively common acute symptom. The relationship between hypoglycaemia and epileptic phenomena is complex and has not yet been fully understood. A critical low glucose level can modify cortical excitability by determining an imbalance between excitation and inhibition. Indeed, several experimental studies have shown that the loss of high-energy substrates leads to the release of excitatory amino acids that result in hyperexcitability and consequent excitotoxicity (McCall, 2004). These effects may be more pronounced in some brain regions than in others, the temporal lobe and hippocampus appearing to be particularly susceptible (Auer, 2004). Although these data provide a convincing explanation for the possible occurrence of focal epileptic events associated with hypoglycaemia, this seizure type has rarely been reported and documented (Buckley, 1963; Penfield and Kristiansen, 1951; Lahat *et al.*, 1995; Caraballo *et al.*, 2004).

In the case study reported here, we describe a diabetic patient presenting a symptomatic focal epileptic seizure during an insulin-induced episode of hypoglycaemia.

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Case study

A 61-year-old woman had a 30-year history of insulin-treated diabetes, complicated by distal neuropathy and non-proliferative retinopathy. Although she had been referred to an endocrine unit, her glycaemic profile could not be satisfactorily controlled by insulin therapy. The patient experienced recurrent, mainly nocturnal, episodes that had begun some years earlier and had become more frequent in the last two years, consisting of extreme weakness, cold sweat, slight drowsiness and confusion, followed by loss of consciousness lasting from minutes to an hour. She sometimes fell and hurt herself during these episodes. No other objective clinical signs were reported while she was in an unresponsive state. The glucose finger-stick test, which was usually performed during these episodes, often documented a below-normal blood glucose concentration (mean 30 mg/dL). Hypoglycaemic attacks were usually terminated with a 1 mg intramuscular administration of glucagons or with some sweet food.

The patient's medical history was poor. In addition to insulin therapy, she had been taking 325 mg/day aspirin, 300 mg/day irbesartan for 15 years for essential hypertension and 20 mg/day atorvastatin for dyslipidaemia. She had been treated for depression two years before with 20 mg/day escitalopram.

The patient was admitted to hospital following a nocturnal episode with "atypical" features. The patient's husband, who was awoken during the night, described a "convulsive" episode. He found her sweating, moving her legs up and down and clapping her hands; the episode lasted two minutes, during which time she was unable to answer. She was drowsy and confused for up to one hour afterwards. The objective clinical signs were trismus and sialorrhea, with no lateralizing signs or urinary incontinence. The husband treated the patient with sweets and honey, suspecting a hypoglycaemic attack. No glucose finger-stick test was performed on this occasion. Following this atypical episode, the patient was admitted to hospital where she had some regular hypoglycaemic episodes (glucose level ranging from 30 to 40 mg/dL), which were treated with food and 3 cm^3 of glucose solution. Monitoring of capillary blood glucose levels over the following days revealed unpredictable oscillations following administration of the insulin dose. Since a "convulsive" event had been referred, a neurological evaluation in our epilepsy unit was requested. The patient's physical and neurological examinations were normal. There was no past or family history of epilepsy or febrile convulsions. A neuroimaging study (brain MRI scan) and a neurophysiological evaluation (video-EEG recording and 24-hour ambulatory EEG) were performed. The neuroimaging study was normal and the video-EEG monitoring did not reveal any abnormalities. However, the 24-hour ambulatory EEG recorded a focal epileptic seizure with a pattern characterized by monomorphic 5-6 Hz slow wave rhythmic activity involving the right temporal regions *(figure 1)*. During the recording when the focal seizure occurred, the patient noted on the self-reported diary "I felt ill… a blood glucose concentration level of 46 mg/dL...''; no other ictal symptoms or signs were reported. However, a revision of the clinical history, by means of a more targeted interview, revealed the occurrence, in the previous two years, of frequent events described as "… an empty feeling… it starts in the stomach and rises to the throat...". All these subjective phenomena, never accompanied by other evident signs, were considered to be related to regular hypoglycaemic episodes. When specifically asked, the patient was not able to state whether the symptoms during the recorded seizure were similar to those that had occurred during previous events. The ambiguous clinical symptoms, the normal MRI scan and the lack of any interictal abnormalities on the EEG do not yield a definite diagnosis of the nature of the previous episodes (hypoglycaemic attack or acute symptomatic seizures), nor do they allow us to clearly establish whether the EEG-documented episode was related to an acute symptomatic condition or was, instead, a hypoglycaemia-facilitated seizure within the context of "hidden" partial epilepsy.

Discussion

Glucose is known to play a critical role in brain functions because it represents the main source of metabolic energy generation. Hypoglycaemic episodes, particularly at night, are known to be a common problem in patients with insulin-treated diabetes (Varghese *et al.*, 2007). Hypoglycaemia can induce various neurological disturbances, ranging from transient autonomic signs (sweating, palpitations, etc.) to more serious conditions, such as stupor or coma (Eeg-Olofsson, 1977). Seizures, which are one of the most common acute symptoms, may be misdiagnosed because of their similarity to some of the clinical disorders induced by hypoglycaemia, particularly autonomic symptoms and loss/impairment of consciousness. The mechanisms underlying the epileptic phenomena during hypoglycaemia have not yet been fully understood, however, experimental studies suggest that the loss of high-energy substrates for the tricarboxylic acid cycle may cause a neurotransmitter imbalance that results in a massive release of excitatory amino acids and possible subsequent excitotoxic effects (McCall, 2004). Consequently, hypoglycaemia may, on the one hand, induce epileptic symptomatic seizures and, on the other, predispose to the development of epileptogenic processes. In this regard, data from experimental studies suggest that some brain structures, including the hippocampus, are more susceptible than others to hypoglycaemic brain damage (Auer, 2004).

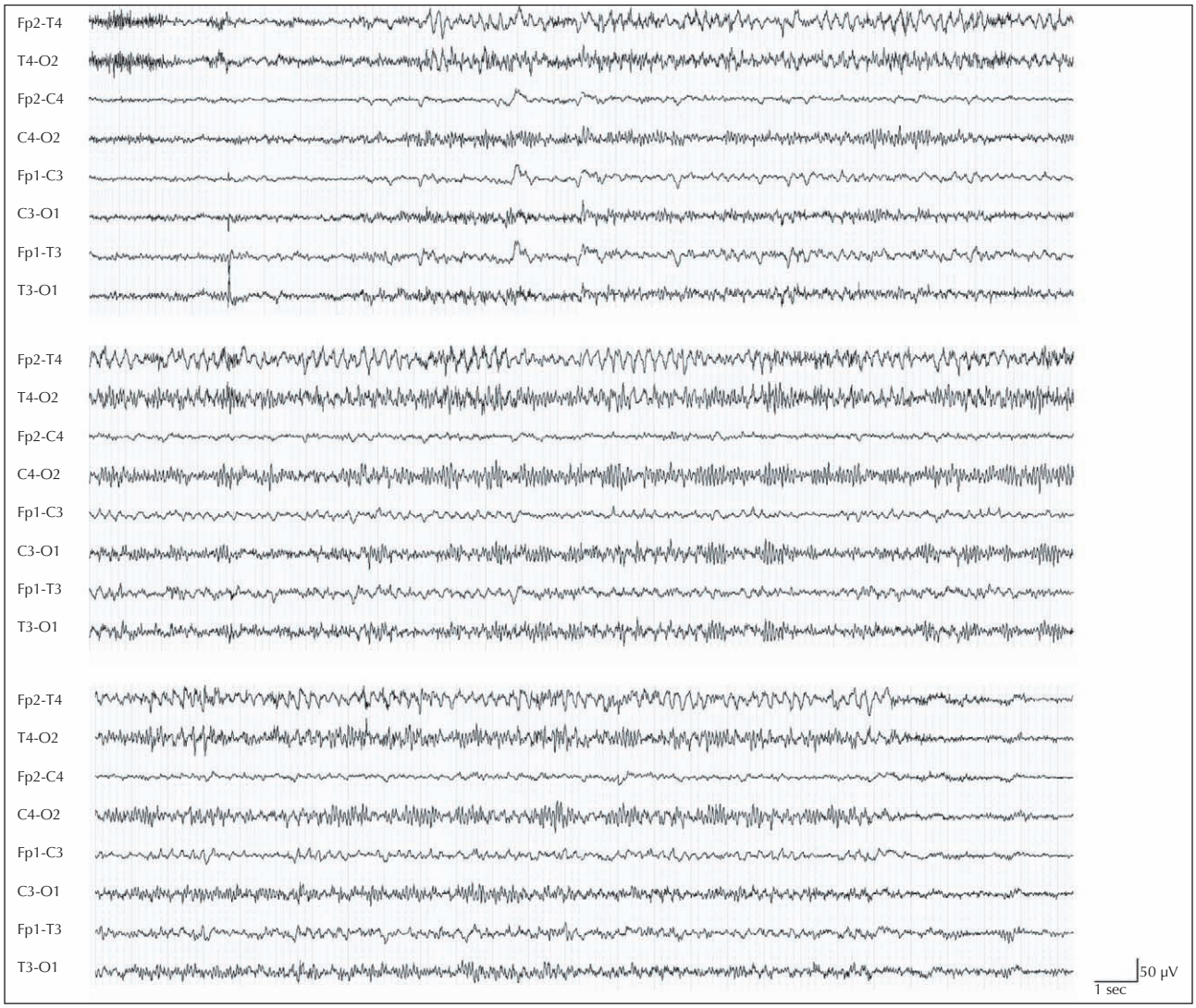

Figure 1. Hypoglycaemia-induced focal seizure recorded during a 24-hour ambulatory EEG. Ictal pattern consists of monomorphic 5-6 Hz slow wave activity involving the right temporal lobe. During the event, the patient noted on the self-reported diary "I felt ill... a blood glucose concentration level of 46 mg/dL". No other clinical manifestations were reported, although the artefacts of the EEG document the appearance of a rhythmic blinking.

The case we describe here may be regarded with considerable interest for several reasons. Although hypoglycaemia-induced seizures are fairly frequent, they are usually of generalised tonic-clonic type. By contrast, partial seizures, despite being reported by several authors, have rarely been documented by means of EEG (Buckley, 1963; Penfield and Kristiansen, 1951; Lahat *et al.*, 1995; Caraballo *et al.*, 2004). Indeed, the EEG changes induced by hypoglycaemia more commonly include theta and/or delta activity, which is often predominant in the fronto-temporal regions, reproducing findings of metabolic encephalopathy (Kaplan, 2004). From a speculative point of view, the well-localised expression of the discharge in the temporal lobe documented in our patient lends support to the aforementioned marked susceptibility of this structure to hypoglycaemia-induced dysfunctions. In keeping with this hypothesis, the autonomic symptoms reported by the patient may be the clinical expression of epileptic phenomena due to temporal lobe involvement and not merely a "direct" effect of hypoglycaemia. This curious observation may highlight the complex nature of some clinical manifestations in patients with unstable diabetes, which has obvious implications in the differential diagnosis. Lastly, this observation suggests that an EEG follow-up should be recommended to exclude the development of chronic epileptic disorder, at least in cases with ambiguous or less typical manifestations. □

Disclosure.

None of the authors has any conflict of interest to disclose.

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