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Clinical letter

An unusual behavioural and motor paroxysmal disorder caused by insulinoma-related hypoglycemia: A possible cause of epilepsy misdiagnosis

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1. Introduction

Insulinoma is a common cause of hypoglycemia in patients without systemic illness. The clinical diagnosis of hypoglycemia is generally based on Whipple's triad: i.e. neuroglycopenic and autonomic symptoms, a low plasma glucose concentration at the time of symptoms, and symptom relief when the hypoglycemia is corrected. Neurological disorders are frequently misdiagnosed,[1] thus delaying a correct diagnosis and leading to undue drug treatment, particularly with anti-epileptic drugs (AEDs).

We report the case of a patient who experienced hypoglycemic episodes that had an unusual neurological presentation and a very protracted clinical course.

2. Case report

A 59-year-old woman with unremarkable personal and family history was admitted to our Epilepsy Monitoring Unit (EMU) with a diagnosis of refractory temporal lobe epilepsy. Upon admission, she reported more than daily "seizures" despite AED polytherapy. The results of routine blood tests and general and neurological examinations were normal. Her BMI was 16.81 kg/m^2, and she reported significant weight loss during the previous eight months.

The paroxysmal episodes were described as being variable in duration (ranging from a few minutes to several hours) without any strong circadian pattern or relationship with meals. They were clinically characterised by confused and aggressive behaviour, agitated wandering followed by unresponsiveness and facial grimacing, bizarre "chaotic" posturing of the limbs, and opisthotonus. Vegetative signs were rarely observed. No sleep-related episodes were reported.

The history of the patient started with very sporadic confusional states at the age of 51 years. The findings of repeat electroencephalography (EEG) and magnetic resonance imaging (MRI) were normal. A diagnosis of temporal lobe epilepsy was subsequently suggested on the basis of the presence of bi-temporal, slow and sharp EEG abnormalities, and treatment with carbamazepine was started.

However, despite the use of various AED schedules, the episodes increased in frequency and became more clinically complex with bizarre motor and behavioural signs.

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A number of paroxysmal episodes were recorded by means of video-EEG monitoring (Fig. 1), and recognised as her "usual seizures". They had a mean duration of 3 h, and were observed throughout the day but with some preference for the early afternoon; they were heralded by sleepiness and slowly progressive confusion alternating with phases of disinhibited and aggressive behaviour. The acme was reached after about 2 h, with loss of contact and continuous involuntary movements. During the episodes, the patient showed a combination of involuntary dyskinesias encompassing stereotypies, dystonia, and sustained limb and axial postures (Fig. 2), which developed with a fairly prototypical chronological pattern, and were beyond the patient's control. The episodes stopped spontaneously in a slowly progressive manner. Before and after each episode, the findings of neurological examination were normal.

The EEG findings during the episodes were characterised by a slowing in background activity, followed by the appearance of diffuse, irregular high-amplitude theta/delta activity, that occurred initially in short bursts and subsequently became continuous (Fig. 1). There was an overall increase in slow-wave components between the basal and acme EEGs. Although diffuse, the increase in delta activity was more prominent on the posterior derivations.

This EEG pattern suggested a metabolic condition. Blood sampling during one episode revealed severe hypoglycemia (21 mg/L in the first sample) that was progressively reversed over about 10 min by the intravenous administration of a 10% glucose solution. During one episode of hypoglycemia (35 mg/dL), the patients insulin level was 19 μIU/L (reference values 6–29 μIU/L) and her C peptide level was 3.9 pg/mL (reference values 0.4–4 pg/mL), thus suggesting hyperinsulinemia due to an insulinoma. The abdominal CT and pancreatic angiography findings were negative, but a gluconate-calcium load stimulus test induced an increase in insulin and C peptide secretion in the body and tail areas of the pancreas. The patient underwent abdominal surgery and, immediately after the removal of a 3.5 cm encapsulated insulinoma, the paroxysmal episodes disappeared.

At the time of her last evaluation (70 months after surgical treatment), the patient was still symptom free.

3. Discussion

Although our patient partially satisfied the criteria of Whipple's classic triad, and her symptoms began in the fifth decade of life as may be expected, a number of atypical features delayed the correct diagnosis of insulinoma-related hypoglycemia. It is known that symptoms may last for many years before such a diagnosis is reached, and that up to 64% of patients are misdiagnosed as having neurological or psychiatric disorders, and 12% are mistreated with AEDs.[1]

Our patient's paroxysmal episodes were characterised by neuroglycopenic symptoms such as sleepiness, confusion and altered consciousness, but the most striking feature was the presence of a bizarre movement disorder associated with a

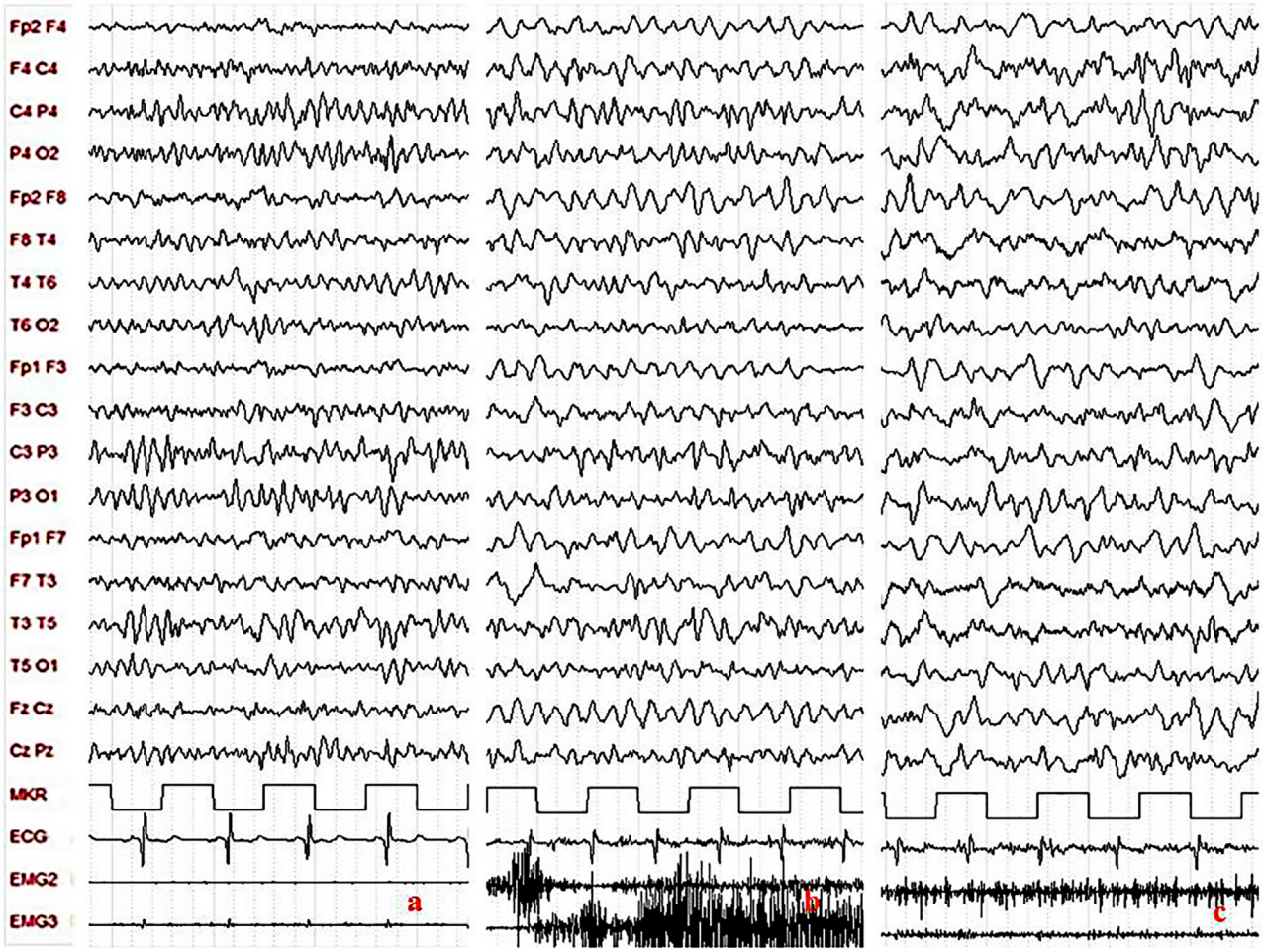

Fig. 1. Relationships between clinical and EEG findings. (a) Basal EEG with eyes closed. (b) Beginning of an episode. Background activity is slowed and theta/delta activity appears mainly in the anterior regions before spreading posteriorly when the acme of the episode is reached (c). (EMG 2 and EMG 3: right and left deltoid muscle, respectively).

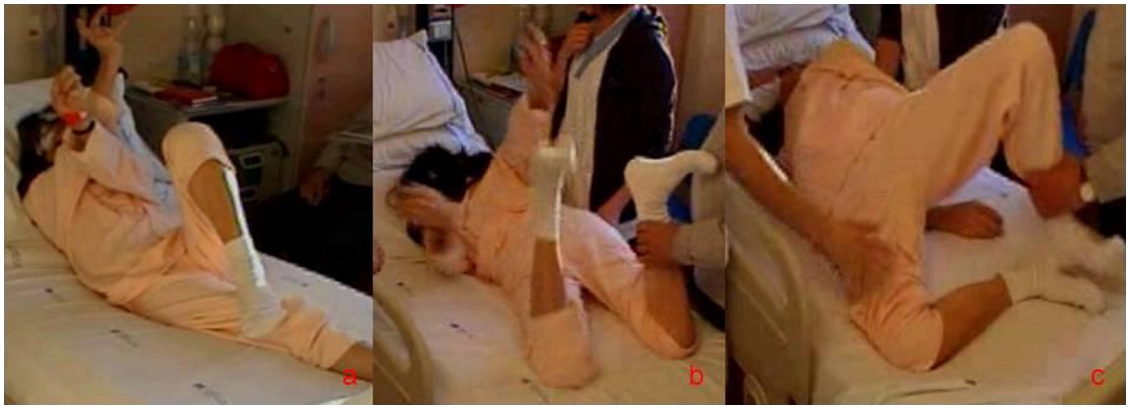

Fig. 2. Dyskinetic movements at different times during a video-EEG recorded hypoglycemic episode. Three frames showing sustained dystonic posturing and opisthotonus occurring about 2 h after the onset of an episode. The sustained posturing progressively involves the limbs (a and b), followed by the pelvis and trunk (c).

behavioural abnormality. Furthermore, there were no sleep-related convulsive seizures or autonomic disturbances such as sweating, tremors, skin pallor and palpitations, and the episodes lacked the typical circadian pattern due to prolonged nocturnal fasting, paradoxically occurred after meals, and always reversed spontaneously.

A relationship between hypoglycemia and movement disorders such as choreoathetosis or paroxysmal dyskinesias has been previously described,[2] and it is known that MRI scans of comatose patients with hypoglycemia may reveal hyperintense lesions in the basal ganglia, cerebral cortex, and other structures.[3] In our case, the striking movement disorder characterised by stereotypies, dystonia and choreoathetosis suggests particular vulnerability of the basal ganglia to hypoglycemic stress, but repeated MRI scans never showed any lesions in the basal ganglia or other brain regions. Other causes of secondary paroxysmal dyskinesias, such as vascular, degenerative, demyelinating or tumoral diseases, metabolic conditions, or factitious hypoglycemia, were also excluded.

A strict relationship between the time course of the EEG abnormalities, altered consciousness and motor symptoms was finally demonstrated by means of video-EEG.

Video-EEG monitoring, revealed the diffuse distribution of slow activity during the early phases of the episodes, and the increased delta activity in posterior regions at the acme of an episode was similar to that observed in diabetic patients with insulin-induced deep hypoglycemia,[4] suggesting the possible vulnerability of the posterior regions to hypoglycemia.

In conclusion, although rare, the possibility of insulinoma should be taken into account in the presence of prolonged paroxysmal events with very unusual motor and behavioural features, and a video-EEG recording may be a helpful, non-invasive diagnostic means of differential diagnosis.

Conflict of interest statement

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

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