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CASE REPORT

Insulinoma presenting as idiopathic hypersomnia

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Abstract We report the case of a 32-year-old woman with a history of increased sleep need and difficulty waking up; the diagnosis of idiopathic hypersomnia was hypothesized. During ambulatory polysomnography (PSG), the patient presented an episode characterized by loss of consciousness and jerking of the four limbs. A video-PSG monitoring was performed and the patient showed unresponsiveness and drowsiness at 7 a.m. During the episode, EEG showed theta–delta diffuse activity, and blood glucose level was 32 mg dl^{-1}. The diagnosis of insulinoma was then assumed; CT scan showed a hypodense mass into the pancreatic tail, and a partial pancreasectomy was performed. The described symptoms disappeared, and 5 years later the findings of a complete clinical and neurophysiological examination were negative. The clinical picture of insulinoma presenting with paroxysmal disorders has been previously described; however, whereas hypersomnia is uncommon, in the current case it represents the main symptom. Clinicians should keep in mind that neuroglycopenia should be considered in the differential diagnosis of patients with hypersomnia, particularly if the clinical scenario does not conform to standard criteria.

Keywords Hypoglycaemia · Sleepiness · Hypersomnia · Insulinoma

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Introduction

Many conditions could recall idiopathic hypersomnia, including medical, neurological and psychiatric disorders or medications [1]. Among medical diseases, hypoglycaemia that occurs with a large variability of signs and symptoms [2] should be considered. We report the case of a young woman who referred to our Sleep Disorder Centre for severe excessive daytime sleepiness related to insulinoma-induced hypoglycaemia.

Case report

A 32-year-old woman referred to our Sleep Disorder Centre with a history of 2 years of increased sleep need (patient slept a mean of more than 8 h daily) and extreme difficulty waking up in the morning. Moreover, mild sleepiness during daytime was reported. Symptoms suggesting restless legs syndrome or sleep apnea syndrome were not reported, while depression was excluded; body mass index was normal (22 kg m^{-2}).

Brain magnetic resonance imaging (MRI) and routine EEG had been already performed and did not show any abnormalities. Diagnosis of idiopathic hypersomnia was therefore hypothesized, and continuous ambulatory polysomnography (PSG) was undertaken. During PSG recording, the patient presented for the first time an episode characterized by loss of consciousness and muscular jerks of the four limbs. Ictal EEG showed monomorphic diffuse slow waves followed by artefacts due to muscular jerks and post-ictal amplitude reduction (Fig. 1a).

In order to clarify the episode, a video-PSG monitoring in the Sleep Laboratory was performed. PSG included a bilateral extended EEG montage (Fp2–F4, F4–C4, C4–P4,

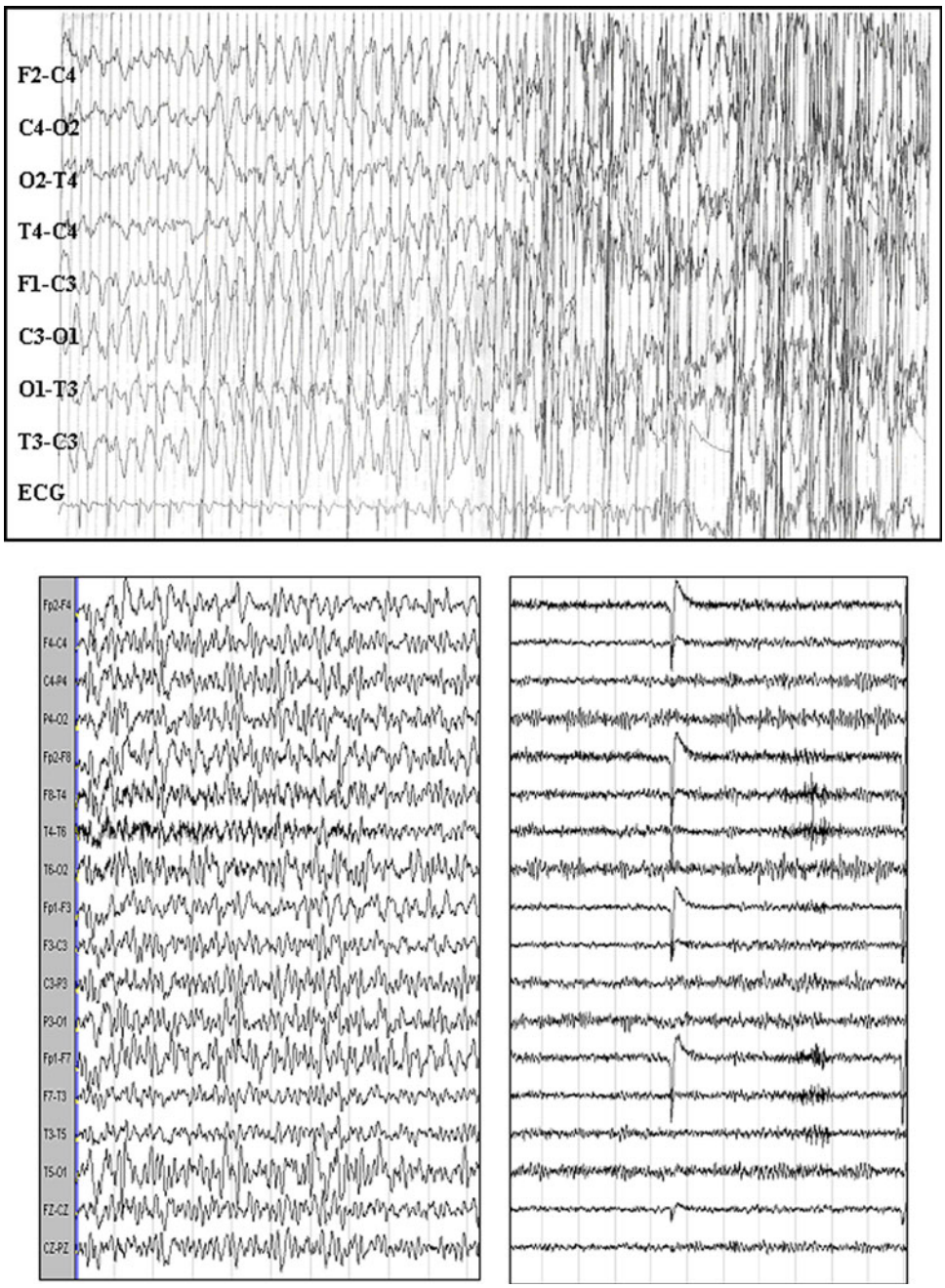

Fig. 1 EEG showing monomorphic diffuse slow waves, followed by muscular artefacts due to myoclonic jerks (**a**). EEG pattern during hypoglycaemia on awakening (7:30 a.m.; blood glucose level 32 mg dl^{-1}) (**b**) and after glucose administration (7:50 a.m.; blood glucose level 152 mg ml^{-1}) (**c**)

P4–O2, Fp2–F8, F8–T4, T4–T6, T6–O2, Fp1–F3, F3–C3, C3–P3, P3–O1, Fp1–F7, F7–T3, T3–T5, T5–O1), with the electrodes positioned according to the 10–20 International System, two electro-oculogram channels (right and left outer canthi), one chin-EMG channel, nasal-oral flow (thermistor), strain gauges for measuring thoracic and abdominal movement, one ECG lead, finger pulse oximeter, digital microphone, EMG tibialis anterior bilaterally and video recording. At 7 a.m., patient was unable to wake up, looked unresponsive, while EEG showed theta–delta diffuse activity (Fig. 1b) and blood glucose level was very low (32 mg dl^{-1}). Glucose solution (20%) i.v. infusion ended the episode (Fig. 1c).

Sleep recordings were visually scored according to the criteria of Rechtshaffen and Kales [3] and examined with spectral analysis [colour density spectral arrays (CDSA)] [4]. With this method, using Fast Fourier Transform (FFT), the power spectrum of the EEG was obtained and the various frequencies were represented according to their power in different colours. PSG recording showed an abnormal sleep pattern in the second half of the night with absence of REM sleep, reduction of spindles and K

complexes, and an increased delta activity as well as loss of its dynamicity during sleep.

Thus, she was suspected to be affected by hypoglycaemic disorder and referred to the Department of Internal Medicine. Blood samples for routine laboratory tests, collected at 6 a.m. after an overnight fast, were within the normal limits a part from low plasma glucose level. Circadian analysis confirmed low plasma glucose level, especially at wake-up before breakfast (46 mg dl^{-1}) and 2 h after lunch (55 mg dl^{-1}). Urine sulfonylurea screening was negative. A prolonged (up to 300 min) 75 g-oral glucose tolerance test (OGTT) was performed, demonstrating low plasma glucose levels at baseline and at the last determination (39 and 42 mg dl^{-1} respectively); the corresponding insulin levels were 9.4 and 8.8 μIU ml^{-1}, with an insulin/glucose ratio of 0.2 for both times, not fulfilling the classical criteria for the diagnosis of insulinoma (>0.3) [5]. The contra-insulin regulatory hormone system was normal; moreover, the presence of a multiple neuroendocrine neoplasia was excluded. A 72-h fasting test was then performed: plasma glucose level fell to 26 mg dl^{-1} at the 17th h, when the patient developed neurological signs and symptoms (behaviour confusion, blurring of vision, drowsiness, tremulousness). Although during the hypoglycaemic episode the insulin/glucose ratio still showed a borderline value, the diagnosis of insulinoma was then assumed.

While abdominal ultrasound and ^{111}Indium-labelled octreotide scintiscan were negative, abdominal CT scan revealed a 1.5 cm hypodense mass into the pancreatic tail, consistent with insulinoma. The patient was therefore referred to the Department of Surgery for partial laparoscopic pancreasectomy. The histological and immunohistochemical examination of the surgical specimen demonstrated an adenoma originating from the pancreatic islet cells expressing insulin with a negative proliferation index. The patient remained asymptomatic, and a complete clinical examination (including standard OGTT and abdominal CT scan) was negative at 1-year follow up. Five years after surgery, video-PSG monitoring confirmed the absence of any EEG abnormalities (Fig. 2).

Discussion

Several case-reports of insulinoma presenting as seizures or paroxysmal disorders have been previously described [6–11]; in addition, a rare involvement of peripheral nerve has been reported [12]. However, in the current case hypersomnia was the main neurological symptom leading to medical consultation. To the best of our knowledge only one other case of insulinoma presenting as hypersomnia has been till now described [13].

We should underline that both in the present and previous case reports, sleepiness did not resemble the common somnolence and altered cognitive function usually described in hypoglycaemic episodes, but occurred as extreme difficulty at waking. The absence of autonomic signs,

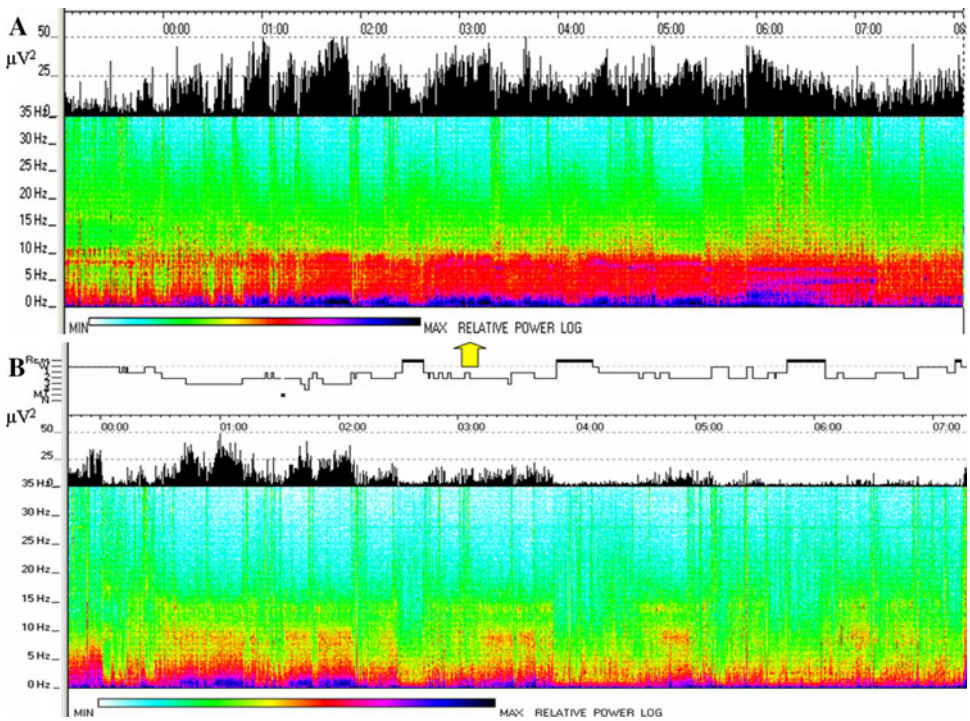

Fig. 2 Sleep analysis at baseline (**a**) and 5 years after surgery (**b**). Delta power absolute power (1–4 Hz, *above*), spectral power (colour-density spectral arrays, *below*) and hypnogram (only for the follow-up registration). EEG derivation C4-A1 was analysed with Analysis Manager Software (FFT analysis, windows length 5 s, overlap 50%, rectangular window). See *text* for further details

related to hypoglycaemia-associated autonomic failure is reported in diabetic patients and in our case could be related to a shift of the hypoglycaemic threshold for autonomic activation by recurrent hypoglycaemia [14]. On the other hand, both sympathetic tone and sympatho-adrenal responses to hypoglycaemia are reduced during non-REM sleep in normal subjects [15]. In our patient EEG recordings during hypoglycaemia showed increased delta waves without the physiological decrease during sleep cycles, suggesting a pathological rather than physiological slow wave activity [16]. It is noteworthy that an analogous reduction of REM sleep as well as a fragmentation of non-REM slow-wave activity during hypoglycemia has been reported in adult rats [17].

In the current case, the occurrence of post-awakening confusion recalled the sleep drunkenness of idiopathic hypersomnia, in which awakening procedures need to be vigorous and repeated [18]. Nonetheless, the presence of low plasma glucose levels at awakening (46 mg dl^{-1}) along with the improvement of sleepiness during daytime allowed us to hypothesize the metabolic pathogenesis of neurological signs. Moreover, an acute symptomatic seizure, characterized by unresponsiveness and jerking, occasionally recorded during PSG strengthens the hypothesis. Even if it was the only episode reported, and the EEG showed no spikes or sharp waves, the episode can be considered as an acute symptomatic seizure. Since hypoglycaemia, with levels of blood glucose less than 40 mg dl^{-1}, could lead to seizures some of the episodes described in patients with insulinoma have been defined as such [6, 8, 9, 19].

It should be underlined that differential diagnosis may be complex and intricate in this life-threatening disease, since psychiatric and neurological disorders are frequently hypothesized before the identification of the disease [2]. Indeed, in the case reported by Dhume et al. [13] brain MRI suggested encephalitis leading to a fatal delay in making the correct diagnosis of hypoglycaemic crises.

Conclusion

In conclusion, clinicians should keep in mind that several medical conditions could cause impaired alertness [1] and that neuroglycopenia should be considered in the differential diagnosis of patients with hypersomnia, particularly if the clinical scenario does not conform to standard neurological criteria [18, 20]. In these cases a complete medical workup and a multidisciplinary approach are required to make a correct diagnosis.

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