

Insulinoma misdiagnosed as juvenile myoclonic epilepsy

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Abbreviations

EEG electroencephalography
GTCS generalized tonic-clonic seizure
JME juvenile myoclonic epilepsy
MRI magnetic resonance imaging

We report a girl presenting with drug-refractory myoclonia and generalized tonic-clonic seizure (GTCS) on awakening who, initially, was misdiagnosed as having juvenile myoclonus epilepsy (JME) before insulinoma was detected.

Many conditions may mimic or cause epileptic seizures, including psychiatric and movement disorders, cardiac arrhythmias and metabolic abnormalities. Toxic and metabolic causes are potentially curable, are refractory to antiepileptic drugs, and may be fatal if untreated. Insulinoma is a rare and treatable cause of hypoglycemic seizures which might be misdiagnosed as intractable epilepsy.

Case report

In May 2001 a 13-year-old girl was referred to the hospital because of GTCS on awakening. The family history was unremarkable and her personal history revealed one simple febrile seizure at age 3 years. One month before admission two episodes of confusional states were reported which lasted 5 and 30 min and were characterized by unresponsiveness and psychomotor slowing.

Physical and neurological examinations were normal, weight was 62 kg (97th centile), height 162 cm (90th centile), and menarche was at age 13 years (March 2001, 1 month before the first seizure). Awake EEG the day after GTCS revealed normal background activity, bilateral synchronous and asynchronous high-amplitude delta waves over the parietotemporal regions, and right frontal sharp-slow waves. Blood count, blood chemistry (glucose 4.5 mmol/l, calcium 2.4 mmol/l, potassium 4.0 mmol/l), and magnetic resonance imaging (MRI) of the brain were normal. Confusional states were interpreted as complex partial seizures and GTCS as a secondary generalization. Low-dose carbamazepine (6.3 mg/kg per day) was introduced. Two weeks later, a second GTCS on awakening occurred, followed by two short episodes of unresponsiveness before breakfast in front of the television. Another few days later, perioral and eyelid myoclonus and jerks in the arms and legs were noticed early in the morning. After sleep deprivation a series of myoclonic jerks at awakening in the morning and after several naps were registered coinciding with generalized low-amplitude spikes or polyspikes. JME was diagnosed and carbamazepine replaced by valproate (20 mg/kg per day) which was not effective. Blood glucose was normal (4.2 mmol/l 4 h after food intake). Two months later (August 2001) a second overnight long-term

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video-EEG revealed generalized discharges of spikes or polyspikes and slow waves in the second part of the night. Again myoclonic jerks in the hands and legs with a single generalized low-amplitude spike and slow waves were registered on awakening (Fig. 1).

In September 2001, 6 months after the manifestation of the first seizures, low preprandial blood glucose (1.8 mmol/l, normal 3.8–6.1) and high insulin (31 μ U/ml, normal 1.9–2.3) were detected because the patient was sluggish and dizzy (glucose and insulin were measured by routine methods). Inappropriate insulin secretion was suspected and confirmed by pre- and postprandial glucose and insulin measurements (preprandial: glucose 2.8 mmol/l, insulin 33 μ U/ml and 50 min after food intake: glucose 3.1 mmol/l, insulin 153 μ U/ml); therefore, a 72-h fasting test was not done. Abdominal ultrasound (US) and MRI revealed a round and circumscribed hypoechoic lesion (2.1×1.8×1.9 cm) with sharp but uneven borders in the pancreatic body without evidence of metastases. Insulinoma was suspected. Because multiple endocrine neoplasia type I syndrome (MEN I) is associated in 5–10% of the cases with insulinoma [5, 9], prolactin, thyroid-stimulating hormone, parathyroid hormone, and thyroxin (T3, T4) were determined, which were all normal; therefore, mutation analysis of exons 2–10 of the *MENIN* gene was not done. Valproate was stopped and the patient was advised to have food intake every 2 h and three times during the night. Since then she has been seizure free, but myoclonic jerks recurred occasionally when meals were delayed by >5 h during the night. Her

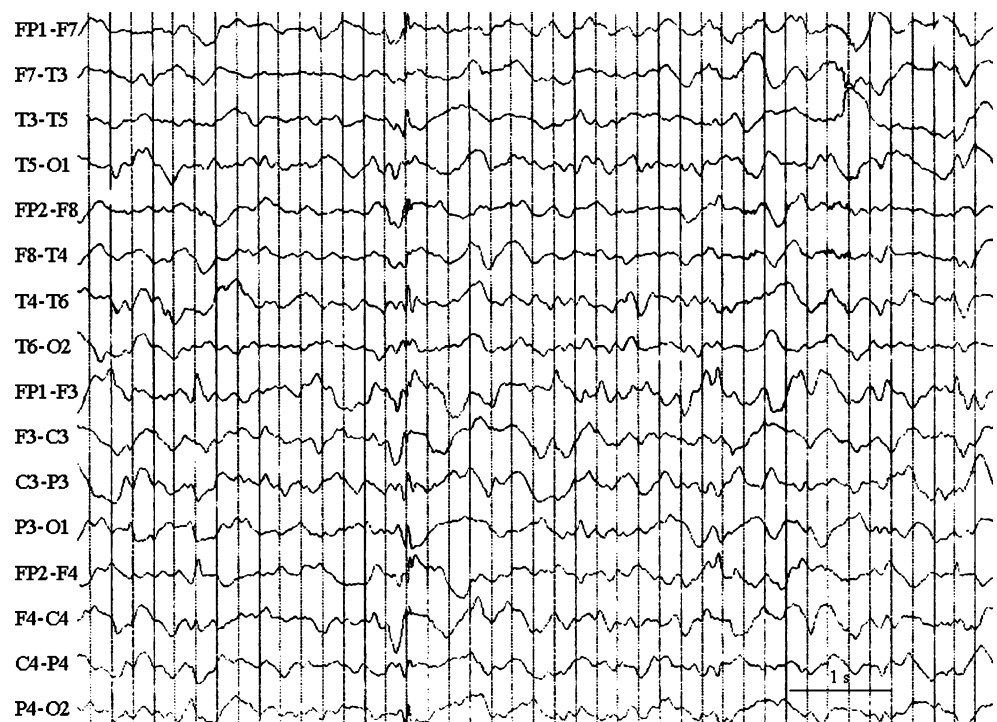
weight had increased from 62 to 84 kg within the last 10 months before surgery.

Surgery was performed 5 months later (March 2002) in Moscow and two insulinomas were revealed by intra-operative US: one located on the superior-posterior surface between the head and body (diameter 2.5 cm) and the other on the anterior surface of the pancreas (diameter 0.7–0.9 cm). Before the surgery, US and MRI disclosed only one lesion. Both insulinomas were removed in toto and the endocrine pancreas was suppressed by Sandostatin (octreotide) for 4 days. Histology confirmed the diagnosis of two benign beta-cell adenomas. The patient fully recovered, remained seizure free during the next 4 years, has a current weight of 62 kg (75th centile), and is mentally normal.

Discussion

Myoclonus and GTCS after awakening are hallmarks of JME, especially when adolescents are affected [2]. Hence, in our patient the interpretation of the clinical symptoms together with spike waves was indicative of JME. Confusional states and drug-refractory seizures on the other side are less compatible with the diagnosis of JME, but fit well with hypoglycemic events. The latter, however, were erroneously thought to be excluded by two normal blood glucose measurements. Furthermore, hypoglycemia in nondiabetic adolescents is much rarer than JME. Insulinoma, responsible for the profound hypoglycemia in our patient, has its onset usually in middle [10] or older age [4]

Fig. 1 Ictal EEG on awakening: generalized low-amplitude spike with simultaneous registration of myoclonic jerks of the hands and legs. Although the EEG pattern is not so typical for JME, together with the history and the clinical symptoms this EEG seemed compatible with this diagnosis



and is very rare in children [9]. Symptoms are prominent following prolonged fasting states, especially in the morning as in our patient, but also in the late afternoon [4]. Hypoglycemia can cause loss of consciousness, sluggishness, confusion, asthenia, deep coma, dizziness, disturbances in vision, and epilepsy. An international review of 1,067 cases [10] showed such neuropsychiatric symptoms in 92% of the patients. Irreversible damage of the central nervous system occurred in 6.8% of the cases [10]. Forty-one percent of the patients have amnesia during the hypoglycemic event [4]. Therefore, the history has to be obtained from family members or friends. Clinical details about the onset, duration, and type of symptoms as well as temporal association with fasting and the relief of symptoms after food intake are helpful information for making the diagnosis. Considerable weight gain as in our patient was reported in 39% of the patients [4]. Taking into account that an actually normal glucose level does not exclude episodes of hypoglycemia, a prolonged fasting test up to 72 h under close monitoring is recommended to assess inappropriate insulin secretion [3].

The median interval from the onset of symptoms to the diagnoses of insulinoma is 2 years, with a wide range of 1 month to 30 years [4]. Initial misdiagnosis is frequent. In a series of 59 patients with insulinoma, prior diagnosis included neurological disorders in 39 (64%) and especially epilepsy in 23 (39%) patients. Seven patients (12%) were treated with antiepileptic drugs [4]. The seizure symptoms are variable. During severe hypoglycemia generalized and focal seizures occurred in children [6]. In patients with insulinoma, shaking of all four limbs at night [8], jerking and twitching [1], and symptoms suspicious for partial and complex partial seizures with and without secondarily generalized seizures are reported [3, 5]. Varying degrees of EEG changes and sometimes massive spiking were recorded during hypoglycemia [7]. In patients with insulinoma, focal and widespread EEG slowing [1, 3] combined with epileptic activity [5] are mentioned.

Conclusions

The combination of seizures and episodic confusional states should prompt the search for hyperinsulinism, especially

when the episodes occur in fasting states and when they are refractory to antiepileptic treatment. Inappropriately high insulin with low blood glucose is diagnostic; this constellation has to be investigated resolutely (e.g., by the classic 72-h fasting test) but with caution under strict clinical and chemical monitoring. Timely diagnosis of an insulinoma is of paramount importance to prevent sequelae for such patients.

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