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Case Report:

An insulinoma with clinical and electroencephalographic features resembling complex partial seizures*

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Abstract: We described a female patient with insulinoma who experienced recurrent episodes of automatism, confusion and convulsion. Furthermore, her electroencephalography (EEG) findings resembled the pattern in complex partial seizures with secondary generalization. The interictal EEG showed spikes and sharp waves, as well as focal slowing over the left temporal lobe, and the ictal EEG revealed generalized spikes and sharp waves associated with diffused slowing. She was initially misdiagnosed as pharmacoresistant epilepsy. After the insulinoma was found and surgically removed, her EEG turned normal and she was seizure-free during the 4-year follow-up. This report highlights the need for careful reassessment of all seizures refractory to medication, even for the patients associated with epileptiform discharges on EEG.

Key words: Insulinoma, Hypoglycemia, Electroencephalography (EEG), Seizure
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INTRODUCTION

Epileptic seizures can be mimicked by many conditions including hypoglycemia. Insulinoma is a rare neuroendocrine neoplasm deriving mainly from pancreatic islet cells. It can secrete insulin in short bursts and cause fluctuation of blood glucose level correspondingly, and then the patients will have intermittent neuroglycopenic symptoms, such as conscious disorder, abnormal behavior, psychiatric symptoms or convulsion (Dizon *et al.*, 1999). Therefore, insulinoma is frequently misdiagnosed as epileptic seizures (Bazil and Pack, 2001; Akanji *et al*., 1992). Electroencephalography (EEG) is a critical diagnostic tool for seizures. The EEG for hypoglycemia usually shows diffuse or focal slowing and enhanced response to hyperventilation (Gellhorn and Kessler, 1942). However, the EEG in our patients with insulinoma showed focal slowing (over the left mesial temporal lobe) and later generalized spikes and sharp waves as well as slow waves. The EEG pattern further misled us to interpret her symptoms as complex partial seizures.

CASE REPORT

A 53-year-old woman with unremarkable family history and personal history was referred to our department for evaluation of recurrent seizures. She was married and had two sons. None in her family had neurological symptoms. Five months ago, she began to experience recurrent attacks of altered consciousness and convulsion. In the attacks she firstly exhibited stereotyped behaviors and blank expression, and was unresponsive for several minutes. The periods were then followed by convulsions, urinary incontinence and a drowsy and confused state which lasted for about 1 h. She was also found to be diaphoretic and tachycardiac during the attacks. The seizures occurred every 2 weeks in the first few months. Later the frequency of seizures gradually increased up to

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twice a week.

In our outpatient department, the physical and neurological examinations of the patient were normal. Magnetic resonance imaging (MRI) of the brain was also normal. The awake EEG with sphenoidal electrodes revealed phase reversal of sporadic spikes and sharp waves as well as focal slowing over the left mesial temporal lobe. The EEG findings were interpreted as interictal activity. The diagnosis of complex partial seizures with secondary generalization was considered and carbamazepine 300 mg/d was introduced. However, the seizures were not controlled even after the patient administered higher dosages of carbamazepine and was co-treated with topiramate later. Meanwhile, the ambulatory EEG recorded a typical seizure in the patient. In ictus high-voltage theta and delta waves gradually built up in all leads, then sporadic spikes and sharp waves were found as well as the diffused slowing (Fig.1), and in the interictal period sporadic spikes and sharp waves were localized in the left temporal lobe.

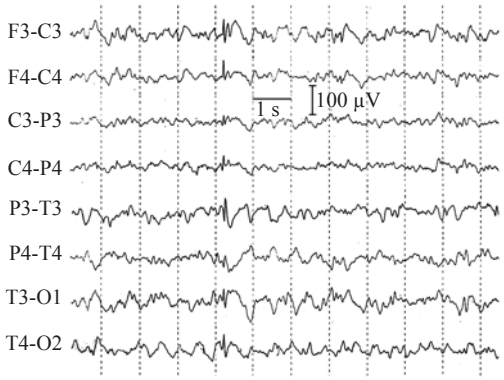

Fig.1 Ictal EEG recorded on awakening: sporadic spikes and sharp waves as well as diffuse high-voltage slow waves

Four months later (9 months after the onset of seizure), the seizures occurred every day, and the patient's confusion state became more profound and lasted longer. She was soon hospitalized. The routine testing was normal except that fasting blood glucose was 2.7 mmol/L. A fingerstick glucose level during a seizure was 1.5 mmol/L. An intravenous glucose infusion dramatically terminated the seizures. On further questioning, it was apparent that her previous seizures tended to occur in the early morning or several hours after meal, and that the post-seizure confusion state could be shortened if she ate something during the confusion period and she had gained 10 kg weight before seizure onset. The subsequent endocrine evaluation suggested insulinoma. Contrast-enhanced computed tomography (CT) scan revealed an enhanced mass in the head of the pancreas (Fig.2). After surgical removal of the neoplasm, the blood glucose level and insulin level turned normal. A benign insulinoma was also confirmed by histopathological evaluation. No abnormality was found in her EEG examination taken 50 d, 90 d, 1 year and 2 years after the surgery. The patient remained seizure-free during the 4-year follow-up.

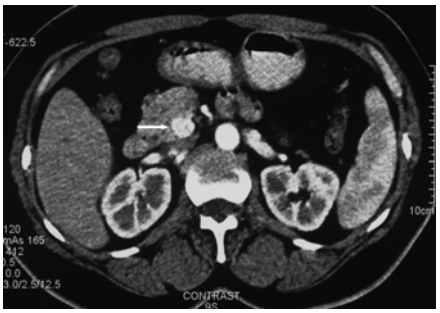

Fig.2 Helical CT scan of pancreas with contrast, axial slice and arterial phase (23~25 s after initiation of contrast injection). The left arm was used as the site of intravenous contrast administration. White arrow: an enhanced mass (2.0 cm×2.0 cm) in the head of pancreases

DISCUSSION

We reported the case of an insulinoma seen in the neurological department as adult onset pharmacoresistant epilepsy. In this patient, the symptoms of recurrent automatism, episodes of altered consciousness and convulsion combined with epileptiform discharges over the left temporal lobe on EEG were highly indicative of complex partial seizures. She received escalating doses of antiepileptic drugs due to the misdiagnosis. Four months after her first visit hypoglycemia was correctly recognized since her symptoms were rapidly exacerbated and she needed hospitalization. Insulinoma is very rare. The interval from presentation to diagnosis ranged from 1 month to 30 years (median 2 years) (Service *et al*., 1991). The delay in its diagnosis is caused by several factors. Firstly, the symptoms of insulinoma lack specificity, including various seizure disorders, per-

sonality change, bizarre behavior, amnesia, convulsions, and incidentally dystonia (Tan *et al*., 2002) and polyneuropathy (Striano *et al*., 2003); these symptoms are similar with many common neurological and psychiatric disorders. Secondly, fasting blood glucose level can be normal in some patients. Thirdly, hypoglycemia itself is able to decrease the counterregulatory hormonal responses to hypoglycemia and induce unawareness of autonomic and neuroglycopenic symptoms (Mitrakou *et al*., 1993).

Hypoglycemia can activate focal abnormality in the EEG in epileptic who have an old lesion in the cortex (Sperling, 1984); however, our patient was previously healthy and the MRI scan revealed that the left temporal lobe was normal. Therefore, the EEG change in our patient was caused by hypoglycemia as a result of hyperinsulinemia. According to the best of our knowledge, the epileptiform discharges on EEG are unusual manifestation in insulinoma. Jaladyan and Darbinyan (2007) described that a patient with insulinoma presenting as juvenile myoclonic epilepsy showed the generalized low-amplitude spike with simultaneous registration of myoclonic jerks of the hands and legs in the ictal EEG on awakening. In another case of insulinoma presenting as adult-onset complex partial seizures (Graves *et al*., 2004), EEG showed a gradual build-up of diffuse slow waves prior to the attack, and then a few sharp waves and spikes were seen; the EEG abnormalities were attenuated after glucagon was administered. In these cases including ours, it is obvious that the EEG change was closely related to the blood glucose level. In addition, epileptiform discharges induced by hypoglycemia are also occasionally found in patients with diabetes (Engel *et al*., 1954).

EEG slowing caused by hypoglycemia represents an inhibitory state and adaptive hypometabolism of the brain; additionally, the epileptiform discharges could reflect disarrangement of neuronal excitation and inhibition as a result of selective neuronal vulnerability to neuroglycopenic damage (Ratcheson *et al*., 1981). Recent experimental studies confirmed that severe hypoglycemia is able to induce spontaneous synchronic discharges in vitro and in vivo, thus even generate a hypermetabolic state and further deplete the brain energy reserve (Abdelmalik *et al*., 2007; Kirchner *et al*., 2006). This seizure-like event cannot be blocked by the common antiepileptic drugs. Interestingly, hypoglycemic seizure induced in animals tends to be originated in the mesial temporal lobe structures, such as amygdala and hippocampus, which have a low threshold for seizures (Tokizane and Sawyer, 1957). These findings are helpful to explain the phenomenon that hypoglycemic seizure in insulinoma is "pharmacoresistant" and can present as complex partial seizures with temporal origin.

Seizure caused by hypoglycemia is a benign and curable situation, but it may be fatal if unrecognized. Our report reiterates the importance of evaluating the metabolic cause of seizure disorders. Although sometimes insulinoma shares some common semiological and EEG features with complex partial epilepsy, there are some clues for diagnosis, such as close relationship of seizure attacks to food intake, weight gain, atypical attacks and poor response to antiepileptic drugs. A further 72-h fasting test to measure the blood level of insulin and glucose is convenient and reliable to confirm the diagnosis. Endoscopic sonography and MRI are useful in preoperative diagnosis of small pancreatic insulinomas (Noone *et al*., 2005). In several experienced centers endoscopic sonography is the initial and often the only preoperative imaging test performed. Conventional CT scan is usually unhelpful (McLean and Fairclough, 2005); however, multiphase thin slice enhanced CT greatly increases the detection rate, and small insulinomas can be readily found in arterial phase image.

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