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ORIGINAL ARTICLE

Insulinoma misdiagnosed as epilepsy in 44 Chinese patients

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Abstract

OBJECTIVE: Insulinoma is a rare pancreatic neuroendocrine tumor that can spontaneously produce excess endogenous insulin, resulting in recurrent and serious hypoglycemia. Patients with insulinoma always have intermittent neuroglycopenia, which has been frequently reported as being misdiagnosed as epilepsy. In this report, we analyzed the clinical data of patients with confirmed insulinoma who had ever been misdiagnosed to have epilepsy.

METHODS: The retrospective review was performed on 266 patients with confirmed insulinoma at the First Medical Center of Chinese PLA General Hospital between January 2000 and July 2020.

RESULTS: 1. The diagnosis of insulinoma was confirmed in 266 patients. Forty-four patients [male/female=1/1.8, aged (41.25±12.30) years old] were misdiagnosed to have epilepsy, with a misdiagnosis rate of 16.5%. 2. Thirty-eight patients presented with consciousness disorder. Eleven patients presented with palpitation, sweating, and anxiety. Five patients presented with convulsion and 6 patients presented with abnormal behavior and delirium. 3. Twenty-two patients underwent EEG examination. EEG showed spike wave or spike-slow complex wave in 5 patients, decreased α wave and increased slow wave in θ and δ band in 7 patients, and was normal in 10 patients. 4. Thirty-five patients were incorrectly prescribed with AEDs and 22 patients were even misdiagnosed to have refractory epilepsy. 5. All these 44 patients underwent successful surgery, and hypoglycemia symptoms were relieved after insulinoma resection.

CONCLUSION: Patients with insulinoma sometimes share common clinical characteristics with epilepsy. To patients with epilepsy or suspected epilepsy, especially with poor response to ADEs, hypoglycemia caused by insulinoma should be emphasized in the differential diagnosis.

INTRODUCTION

Insulinoma is a rare neuroendocrine tumor, with an estimated incidence of 1-4/million people every year. The tumors can spontaneously produce excess endogenous insulin, resulting in recurrent and serious hypoglycemia. Patients with insulinoma always have intermittent neuroglycopenic symptoms, for example, conscious disorder, abnormal behavior, psychiatric symptoms, or convulsion. Such presentations are usually complex, which may cause misdiagnosis and delayed therapy for a long time. In one series, it was documented that 64% of patients with insulinoma had ever been misdiagnosed as having neurologic disorders, and 12% of these patients were incorrectly treated with antiepilepsy drugs (AEDs). Such misdiagnosis can cause fatal outcomes and should be emphasized in clinical practice (Sauvanet 2019; Murakami *et al.* 2017).

In this report, we analyzed the clinical data of 44 patients with confirmed insulinoma who were misdiagnosed to have epilepsy and wrongly treated with AEDs, and summarized the reasons causing such misdiagnosis.

METHODS

Patients

The retrospective review was performed in patients with confirmed insulinoma at the First Medical Center of Chinese PLA General Hospital between January 2000 and July 2020. With a standardized data extraction form, we collected information about the diagnosis and therapy of insulinoma from the medical records.

We analyzed the detailed clinical information, including 1) general information, such as gender, age at symptoms onset, family history, clinical presentations caused by insulinoma. 2) diagnosis of insulinoma and tumor localization. 3) electroencephalography (EEG). 4) incorrect treatment with AEDs. 5) surgery and other targeted treatments.

The diagnosis of insulinoma was established using the following items (1) Whipple triad; (2) presence of hyperinsulinemic hypoglycemia (plasma glucose concentrations <2.8mmol/L meanwhile plasma insulin concentrations ≥3 μU/mL); (3) symptom relieved after meals or sugar supplement; (4) tumor(s) detected in pancreases. (5) confirmed insulinoma findings in pathology examination or/and immunochemical examination.

This study protocol was approved by the Institutional Review Board of Chinese PLA general hospital and was in accordance with the ethical guidelines for epidemiological research.

Statistical analysis

Continuous data were presented as median, range, and/or mean ± standard deviation (SD). Statistical analyses were performed using IBM SPSS Statistics Version 22.0 (Chicago, IL, USA).

RESULTS

General information

From January 2000 to July 2020, a total of 266 patients (male 95, female 171) were diagnosed with insulinoma. The average time from symptom onset to diagnosis was (3.86±4.34) years. Various techniques were applied for tumor localization. Single insulinoma were detected in 257 patients and multiple insulinomas were detected in 9 patients. Nine patients (male 1, female 8) aged (23.7±5.6) years old were confirmed with multiple endocrine neoplasia 1(MEN1) according to their clinical presentation and *MEN1* gene mutation.

Ultrasound examination, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Endoscopic Ultrasonography (EUS), contrast-enhanced ultrasound examination, Digital subtraction angiography (DSA), PET18F-FDG PET/CT, and 68Ga-DOTA-TATE PET/CT were performed in tumor localization. The positive findings were 27.3% (48/176) with ultrasound examination, 76.2% (163/214) with CT, 83.8% (129/155) with DSA, 87.1% (108/124) with contrast-enhanced ultrasound examination, 92.9% (131/141) with MRI, 96.4% (134/139) with EUS, 83.33% (10/12) with PET18F-FDG PET/CT and 75.0% (3/4) with 68Ga-DOTA-TATE PET/CT, respectively.

Medical history

Forty-four patients [male/female=1/1.75, aged (41.25 ±12.30) years old] had ever been misdiagnosed to have epilepsy in local hospitals. The misdiagnosis rate was 16.5% and the average time of misdiagnosis was (3.6±4.1) years. Thirty-eight patients mainly presented with consciousness disorder, including 10 patients with repeated syncope and 11 patients with palpitation, sweating, and anxiety. Five patients presented with convulsion and six patients presented with abnormal behavior and delirium. In all these 44 patients, the blood glucose had never been monitored previously, also symptom relief after meals or sugar supplement had not been paid attention to.

Twenty-two cases underwent EEG examination. EEG showed spike wave or spike-slow complex wave in 5 patients, decreased α wave and increased slow wave in θ and δ band in 7 patients and were normal EEG in 10 patients. Twenty patients underwent skull CT or MRI scan, without abnormality detected (for example ischemia, bleeding, tumor and infection).

Thirty-five patients were incorrectly prescribed with AEDs and 22 patients were even misdiagnosed to have refractory epilepsy. The therapeutic medication included one AED in 8 patients, two AEDs combination in 3 patients, three AEDs combination in 3 patients, and even four AEDs combination in 1 patient, respectively. The AEDs included carbamazepine in 8 patients, sodium valproate in 7 patients, phenytoin sodium in 3 patients, phenobarbital in 1 patient, topiramate tablets in 1 patient, lamotrigine in 1 patient and traditional

Chinese medicines in 4 patients, respectively. In other 19 patients, the details of AEDs were unclear.

Diagnosis and therapy

After admission, all the AEDs were withdrawn. During hospitalization, more than 2 spontaneous hypoglycemic episodes in fasting time or 72h-fasting glucose test were detected in all the patients. When hypoglycemia attacked [plasma glucose concentration (1.89±0.59) mmol/L (normal range 3.4-6.1mmol/L)], plasma insulin concentration [(39.59±30.14) mU/L, normal range (2.6-24.9mU/L)] and insulin releasing index [(1.23±1.05) mIU/L/(mg/dL), normal range <0.3 (mIU/L)/(mg/dL)] were still at much higher level. So the diagnosis of insulinoma was clearly established in all these patients.

Later, various techniques were performed to localize the tumors, as prescribed in Methods. Two hundred sixty-seven patients with single or multiple tumors (including all these 44 patients being misdiagnosed with epilepsy) underwent surgical treatment and the hypoglycemia symptoms relieved after tumor resection. For other patients with unresectable metastatic disease, medical management was reserved. Diazoxide and transarterial embolization/chemoembolization were carried out in 2 patients respectively. After debulking surgery, three patients with progressive insulinoma were prescribed with long-acting somatostatin analogue. With these targeted therapies, the severity and frequency of hypoglycemia events also reduced obviously.

DISCUSSION

Blood glucose homeostasis depends on the joint regulation of hormones and nerve system. Insulin, secreted by pancreatic islet β cells, is the only hypoglycemic hormone that can promote glucose uptake, storage and utilization by tissues (Murakami *et al.* 2017). Insulin secretion is precisely regulated by blood glucose and other islet hormones. So the plasma glucose concentration can be maintained within a relatively narrow range. When plasma glucose is lower than 4.4 mmol/L insulin secretion reduces significantly. When blood glucose decreases lower than 2.8 mmol/L insulin secretion nearly terminates, preventing blood sugar from further decreasing. However, the feedback mechanism nearly does not exist when insulinoma presents in patients. Spontaneous insulin oversecretion from insulinoma can lead to continuous and repeated hypoglycemia (Murakami *et al.* 2017). So Patients with insulinoma always present with intermittent neurological hypoglycemia symptoms. Poorly differentiated insulinoma can cause more serious hypoglycemia (Gao *et al.* 2019; Aupy *et al.* 2013).

Under physiologic conditions, glucose is the obligate metabolic fuel for the brain. As a result, brain is more susceptible to be affected by hypoglycemia. Hypoglycemic symptoms can be classified as neuroglycopenic symptoms and neurogenic symptoms. The former presents as a result of central nervous system glucose deprivation, while the latter is due to autonomic nervous system discharge. Neuroglycopenic manifestations appear as confusion, weakness, dizziness, fainting, convulsion, loss of consciousness, seizures and ultimately death when hypoglycemia gets worse and worse. Most of the complicated presentations may mimic neurological and psychiatric disorders, such as epilepsy (Ma *et al.* 2015; Suzuki *et al.* 2015; Deleo *et al.* 2014).

Insulinoma is the most frequent functional pancreas neuroendocrine tumor. It usually presents in middle aged patients, and 60% insulinoma occurs in female. 95% of insulinoma are sporadic and the other 5% insulinoma are MEN1-associated. In this report, a total of 266 patients (male 95, female 171) aged (45.55±15.25) years old got the confirmed diagnosis of insulinoma in our center. Since the prevalence was much lower and the presentations were complex, the average time from symptom onset to confirmed diagnosis had been delayed to (3.86±4.34) years. Nine patients (male 1, female 8) were confirmed with MEN1, with an average age (23.7±5.6) years. With multiple techniques as prescribed above, the insulinomas were clearly detected in all these patients.

Seizures are disorders characterized by temporary neurologic signs or symptoms resulting from abnormal, paroxysmal and hypersynchronous electrical neuronal activity in the brain. The electrical activity in the brain reflects the metabolic state of the brain cells and can be recorded with EEG. The EEG has been a helpful confirmatory test in distinguishing seizures. Specific EEG features of epilepsy include abnormal spikes, polyspike discharges, and spike-wave complexes (Naimo *et al.* 2019; Fox *et al.* 2015; de Paiva *et al.* 2012).

Hypoglycemic episodes are associated with measurable changes in the EEG. Overall, the earliest abnormalities in response to hypoglycemia is total EEG power increasing and a generalized slowing of the frequency, followed by the appearance of diffuse, irregular high-amplitude θ/ δ activity which occurs initially in short bursts and subsequently continuous. Occasional sharp waves can be seen, especially over the frontal regions. What should be emphasized is that all EEG abnormalities will be promptly resolved after glucose infusion, with the altered mental status episodes termination (Aupy *et al.* 2013; Suzuki *et al.* 2015; Naimo *et al.* 2019).

When the initial AEDs get poor effect in epilepsy, other kinds of AEDs with different mechanisms, pharmacokinetics and even combination therapy are usually recommended (Naimo *et al.* 2019). In this study, 35 patients with insulinoma were incorrectly treated with AEDs, and 22 patients were even misdiagnosed as refractory epilepsy. Twenty-seven patients were treated with one or more AEDs. In particular, three patients in this series have initially had some response to phenytoin, one of the first-line AEDs. This drug

can inhibit the secretion of antidiuretic hormones and insulin, resulting in blood sugar elevating. It can alleviate the hypoglycemia symptoms in some patients with insulinomas, leading to delayed diagnosis (Murakami *et al.* 2017). The life quality of all these patients was seriously disturbed by "epilepsy" for a long time before they finally got the precise diagnosis and correct treatment in our center.

Some specific clinical features may aid the diagnosis of insulinoma, which include mental disturbances occurring mainly in the morning time or several hours after meals, relief of symptoms after food intake or sugar supplement, abnormal weight gain and poor response to ADEs. However, such manifestations have always been overlooked in the primary clinic.

Hypoglycemia can cause loss of consciousness, sluggishness, confusion, asthenia, deep coma, dizziness, disturbances in vision, and epilepsy. *Aupy J* reported that the median interval from symptom onset to confirmed diagnoses of insulinoma was nearly 2 years, with a wide range from 1 month to 30 years (Aupy *et al.* 2013). In a series of 59 patients with insulinoma, the previous diagnosis included neurological disorders in 39 (64%) and especially epilepsy in 23 (39%) patients. Seven patients (12%) were treated with AEDs. In our series, thirty-five patients were incorrectly prescribed with AEDs and 22 patients were misdiagnosed with refractory epilepsy because of poor response to AEDs. The therapeutic medication included one AED in 8 patients, two AEDs combination in 3 patients, three AEDs combination in 3 patients, and even four AEDs combination in 1 patient.

In this study, we retrospectively analyzed 44 patients with insulinoma who had ever been misdiagnosed to have epilepsy and incorrectly treated with AEDs for a long time. We summarized the factors causing such a misdiagnosis. Firstly, the symptoms of insulinoma are complex and similar to some common neurological and psychiatric disorders, especially epilepsy. Secondly, the relationship between symptom attacks and hypoglycemia was not recognized and blood glucose was not monitored during symptoms, causing hypoglycemia overlooked. Also, some patients with insulinoma have normal fasting blood glucose, so occasionally monitoring the fasting blood glucose may overlook the diagnosis of insulinoma. Thirdly, recurrent and prolonged hypoglycemic attacks can impair the neurogenic and neuroglycopenia response in some patients, leading to hypoglycemia more difficult to be identified. Fourthly, the EEG feature during hypoglycemia attacks is similar to epilepsy in some patients. Lastly, when AEDs had poor effects, the previous diagnosis of epilepsy was not analyzed and questioned. These factors may mask hypoglycemia and have the diagnosis of insulinoma delayed for a long time and even lead to fatal outcomes (Naimo *et al.* 2019; Fox *et al.* 2015; de Paiva *et al.* 2012).

More than 90 % of insulinoma is well differentiated and localized in the pancreas. Patients without distant organ or lymph node metastases could be completely cured with surgery (de Paiva *et al.* 2012; Liang *et al.* 2018; Burghardt *et al.* 2019; Sood *et al.* 2019; Leroy-Freschin *et al.* 2019). In this series, 264 patients with single or multiple insulinomas (including all these 44 patients misdiagnosed to have epilepsy) underwent a successful operation and no hypoglycemia was detected later. Two patients with multiple metastases underwent interventional palliative treatment. Three patients with progressive insulinoma were prescribed with long-acting somatostatin analogue after debulking surgery. Also, the frequency and severity of hypoglycemic attacks reduced significantly (Niitsu *et al.* 2019; O'Donohoe *et al.* 2019).

In conclusion, patients with insulinoma sometimes share common clinical characteristics with epilepsy which may cause misdiagnosis and incorrect therapy with AEDs for a long time. To patients with epilepsy or suspected epilepsy, many complex situations should be paid attention to in differential diagnoses, such as symptom attack in fasting time, symptom relief after sugar supplement, different EEG presentation between hypoglycemia and epilepsy, and patient's poor response to ADEs. In this way, the potential hypoglycemia caused by insulinoma can be identified in time and the misdiagnosis could be avoided.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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