

Cognitive Impairment in Insulinoma, Consequence of a Delayed Diagnosis: A Case Report

Gecikmiş İnsülinoma Tanısına Bağlı Kognitif Bozukluk: Bir Olgu Sunumu

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Abstract

The diagnosis of insulinoma is often delayed and this usually results with complications such as cognitive impairment. A 60 year old man who had history of aggressive behaviour and attacks of unconsciousness was evaluated for hypoglycemia. He was diagnosed as insulinoma biochemically. Spiral computed tomography of the abdomen revealed a 2 cm mass which was operated. The pathology of the tumour was consistent with an insulinoma. Mini mental status examination and neuroimaging revealed abnormalities which were attributed to severe repetitive hypoglycemia attacks. His postoperative course was complicated with a pancreatic fistule and he died following a massive gastrointestinal bleeding 18 days after operation. This report demonstrates that serious cognitive and neurological complications may occur due to hypoglycemia in patients with insulinoma. Physicians must keep in mind neuroglycopenic symptoms to reach the correct diagnosis to prevent consequences of delayed diagnosis. *Turk Jem 2007; 11: 108-10*

Key words: Hypoglycemi, insulinoma, cognitive function

Özet

İnsülinomalı hastalardaki tanı gecikmeleri tekrarlayıcı, şiddetli hipoglisemi ataklarına ikincil geri dönüşümsüz kognitif bozukluğa ve nörolojik komplikasyonlara neden olabilir. 60 yaşında, hipoglisemi etiyolojisi araştırılan erkek hastada 2 cm lik pankreatik kitle saptandı. Opere edilen hastanın tümör patolojisi insülinoma olarak rapor edildi. Hastada mini mental test ile kognitif bozukluk ve beyin MR ile beyinde multipl lezyonlar saptandı ve bu bozuklukların tekrarlayan hipoglisemi ataklarına bağlı olabileceği düşünüldü. Hastada pankreatik fistül gelişti ve hasta postoperatif 18. günde masif gastrointestinal kanamaya bağlı öldü. İnsülinomalı hastalarda tekrarlayan hipoglisemi ataklarına bağlı ciddi kognitif ve nörolojik komplikasyonlar meydana gelebilir. Doğru tanıya ulaşmak ve gecikmiş tanıya bağlı komplikasyonları önlemek için nöroglikopenik semptomların akılda tutulması gereklidir. *Turk Jem 2007; 11: 108-10*

Anahtar kelimeler: Hipoglisemi, insülinoma, kognitif fonksiyon

Introduction

Patients with insulinoma have symptoms of neuroglycopenia and increased catecholamine release in response to hypoglycemia. Neuroglycopenic symptoms such as anxiety, dizziness, personality changes, unusual behavior, confusion, incoherence, blurred vision, seizures and coma are observed more commonly than sympathoadrenal symptoms such as palpitations, tremulousness, diaphoresis and tachycardia (1).

The preponderance of neurologic symptoms often lead to delay in diagnosis. Patients with insulinoma are described as the patients who were misdiagnosed for many years as psychiatric subjects or

adult onset seizures (2). Delayed diagnosis in patients with insulinoma may cause irreversible cognitive impairment as a result of recurrent severe hypoglycemic episodes (3).

We report on a patient who had attacks of unconsciousness and agitation for many years. Despite the symptoms, he has not been evaluated for psychiatric or metabolic conditions. He has been admitted for hypoglycemia in a local hospital for several times. Four years after beginning of the symptoms, he was diagnosed as insulinoma. Cognitive impairment and abnormalities at brain magnetic resonance imaging (MRI) were found which were attributed to recurrent severe hypoglycemia due to delayed diagnosis.

Case Report

A 60 year old man was referred to our hospital for evaluation of hypoglycemia. He had a four year history of episodic dizziness, confusion and unconsciousness without seizures. His wife complained of his aggressive behaviour and hostile attitude. He had been seen in the emergency department in a local hospital with the same complaints for several times. At these admissions his plasma glucose levels were low and each time he was given glucose solutions and was discharged after the symptoms resolved. The etiology of hypoglycemia had never been investigated.

His past medical history was significant for chronic obstructive pulmonary disease. He was using inhaled bronchodilators. There was no history of diabetes, ulcer disease, insulin, sulphonylurea medication or drinking alcohol. His two sisters had diabetes mellitus. There was not a family history of thyroid, parathyroid and pituitary disease.

Physical examination revealed, decreased breath sounds and wheezing. Thyroid palpation was normal. Plasma glucose level was 16 mg/dl. Whipple's triad which consist of symptoms of hypoglycemia, documentation of a low plasma glucose concentration, and reversal of the symptoms by administration of glucose was observed.

Plasma basal cortisol was between normal ranges with a level of 9.73 µg/dl. Rapid ACTH stimulation test by using 250 µg cosyntropin showed 60-minute and 120-minute values of 26.71 and 34.44 µg/dL, respectively. Serum TSH, growth hormone and calcium levels were in normal ranges with a level of 0.16 µIU/ml, 2.6 ng/ml and 9.7 mg/dL respectively.

During 72 hours fasting test, blood samples of the second hour showed low plasma glucose level of 37mg/dl with a failure of insulin and C peptid suppression which remain at the level of 47.15 µU/ml and 3.20 pmol/ml, respectively. Insulin/glucose ratio was 1.27. The diagnosis of insulinoma was made biochemically (Table 1).

Both CT and MRI of the abdomen did not show any abnormality of pancreas. Dynamic spiral CT of the abdomen identified a 25x16x12 mm hypervascular mass in the head of the pancreas (Figure 1).

In the clinical course, his plasma glucose was maintained with a continuous infusion of 20% dextrose. Agitation attacks were observed during hospitalization.

A 2 cm. tumour localized in the head of pancreas was enucleated. There was no evidence of gross invasion, abnormal lymph nodes, or liver metastases. Histopathology revealed an islet cell tumour. Immunostaining was positive for synaptophysin, chromogranin, neuron specific enolase and proliferative marker Ki 67 was positive in 1% of the tumour cells. Angioinvasion was observed. The tumour was classified as an insulinoma of uncertain biological behavior (Figure 2).

Brain MR revealed multiple lesions in brain stem, pons, basal ganglia and periventricular white matter representing infarction.

Diffuse ischemic white matter changes in frontal lobe were observed. Corpus callosum, lateral ventricles and cerebral sulcus were atrophic.

Mini mental status examination showed impairment in attention, repetition, memory and calculation with a total score of 16/30. Postoperatively his blood glucose levels were greater than 100 mg/dl. His postoperative course was complicated with a pancreatic fistula and he died due to massive gastrointestinal bleeding 18 days after the operation.

Discussion

Spontaneous fasting hypoglycemia in an otherwise healthy adult is most commonly due to an insulinoma, an insulin secreting tumour of the islets of Langerhans. 80% of these tumours are single and benign, 10% are malignant; and the remainder are mul-



Figure 1. Dynamic spiral computed tomography of the abdomen; demonstrating a 25x16x12 mm hypervascular mass in the head of pancreas

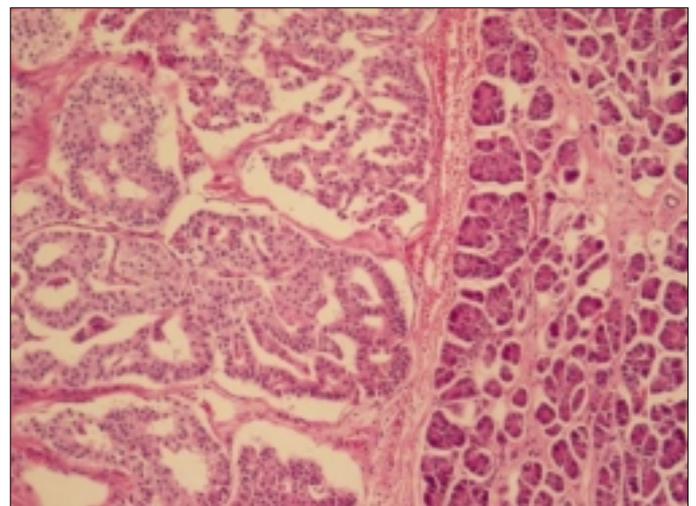


Figure 2. Microscopic features of the excised insulinoma. Tumor cells in tubular pattern and pancreas (x400 magnification)

Table 1. 72 hour fasting test results

	Basal	72 hour fasting
Glucose(mg/dL)	75	37
Insulin(µU/mL)	45.10	47.15
C peptide(ng/ml)	3.20	3.50

tiple, with scattered micro or macroadenomas interspersed within normal islet tissue. These adenomas may be familial and have been found in conjunction with tumours of the parathyroid glands and the pituitary (multiple endocrine neoplasia type 1). 99% of them are located within the pancreas and less than 1% in ectopic pancreatic tissue. These tumours may appear at any age, though they are most common in the fourth to sixth decades, there is no sex predilection. Insulinomas are rare lesions with a reported incidence of four cases per 1 million patient-year (4).

Diagnosis of insulinoma is confirmed biochemically in symptomatic patients who demonstrate an increased concentrations of insulin and C peptide despite hypoglycemia during 72-hour fasting(5). In this patient, low plasma glucose level with a failure of insulin and C peptid suppression is detected and insulinoma diagnosis is made biochemically.

After the biochemical diagnosis is established, the localization studies are done. Imaging techniques are frequently unable to detect a significant percentage of insulinomas. Since the mean size of insulinomas is less than 15 mm, preoperative imaging techniques such as ultrasonography (US), CT, magnetic resonance imaging(MRI) , radionuclide scanning and angiography are inadequate to detect about 40-60% of the tumours. Intraoperative palpation and endoscopic US are the gold standarts for localizing insulinoma with 90 to 100% sensitivity(6). In this patient abdominal preoperative localization is managed using dynamic spiral CT although reported sensitivities are suboptimal ranging from 20-40%. Despite CT and MRI could not detect the tumour , dynamic spiral CT of the abdomen identified a 25x16x12 mm hypervascular mass in the head of the pancreas. The liver was normal.

Surgical excision of the lesion is curative in most cases. The majority of these lesions are solitary, equally distributed throughout the pancreas, and less than 2 cm in diameter (7). The surgical procedure performed in our patient.was enucleation of the tumour .

The human brain is dependent on glucose exclusively. Therefore, glucose deprivation results with deterioration in brain functions. Hypoglycemia, may cause serious neurological sequeales such as cognitive impairment and peripheral neuropathy and, coma and death may occur. In adults, rarely a prolonged, single episode of severe hypoglycemia may result with cognitive deficits. However, less severe repetitive hypoglycemic episodes, may also cause subclinical brain damage and lead to cognitive impairment over time. Adults with insulin dependent diabetes who had severe hypoglycemia attacks scored lower on some neuropsychological tests than matched groups of diabetic patients who had never experienced severe hypoglycemia(3). Our patient has experienced severe hypoglycemia attacks for several times before and during hospitalisation. Mini mental test showed cognitive impairment and it was concluded that severe hypoglycemic attacks resulted with deterioration of cognitive functions .

There are few reports on structural changes associated with hypoglycemia. Neuroimaging studies following severe nonfatal hypoglycemia have revealed areas of cortical injury, particularly in the frontal lobes and hippocampus. It is also reported that, patients with type I diabetes mellitus with a history of frequent exposure to severe hypoglycemia have more prevalent cortical atrophy(9). Brain MRI of this patient showed multipl infarction in brain stem, pons, basal ganglias and periventricular white matter and atrophy in corpus callosum, lateral ventricles and cerebral sulcus.

Hyperinsulinemic hypoglycemia diagnosis is often delayed due to insidious presentation with neuroglycopenic symptoms. In the Cleveland Clinic series 64% of patients were misdiagnosed as neurologic disorders . It is reported that, insulinoma diagnosis is made with an interval which ranges from 10 days to more than 20 years from the onset of the symptoms(10). In this patient, the interval between the onset of the symptoms and the diagnosis was four years. He has been seen in the emergency service for several times and diagnosed as hypoglycemia, but has never been evaluated for this reason. Irritability and aggressiveness were reported by his wife but a psychiatric evaluation was not done. Therefore, the delay in the diagnosis of insulinoma resulted in cognitive impairment and abnormalities in neuroimaging.

Insulinoma should be suspected in all patients who present with symptoms of neurological (recurrent seizures, especially when multiple and without response to anticonvulsive drugs) and psychiatric symptoms with a fluctuating course and psychotic attacks. There are reported cases of insulinoma who presented with behavioral abnormalities and psychiatric manifestations. Piccillo et al reported 73 and 41 years old patients with insulinoma, misdiagnosed for many years as psychiatric subjects who have not been responsive to benzodiazepins, antidepressants and antiepileptics. After surgical therapy they recovered totally(10). In this patient there were psychiatric symptoms such as aggressive-ness and unconciousness, but he has never been evaluated for the psychiatric condition. During the hospital course he attacked his wife and the other patients. He received a psychiatric consultation and his aggressive behavior was attributed to hypoglycemia.

In conclusion, although insulinoma is an uncommon disorder, prompt diagnosis is necessary to prevent complications of hypoglycemia. Neuropsychiatric symptoms of the hypoglycemia must be kept in mind to reach the correct diagnosis. Although the mass was big enough for to be observed, CT and MRI could not detect the tumour in our patient. Also dynamic spiral CT of the abdomen can be used as an alternative imaging technique in cases which the mass could not be localised with US, CT and MRI

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