INTRODUCTION

Insulinoma is the most common functioning pancreatic neuroendocrine tumor, occurring in about one person per million per year[1]. The leading symptoms in establishing the diagnosis of insulinoma are included in the Whipple’s triad: symptoms of neuroglycopenia, documented hypoglycemia (plasma glucose levels < 50 mg/dL), and rapid symptom relief following glucose administration, often within 5-10 minutes[2]. Symptoms can be classified as either adrenergic, i.e. resulting from a catecholaminergic response such as anxiety, tremor, nausea, sweating, and palpitations, or neuroglycopenic, such as headache, lethargy, amnesia, seizures and, in more severe cases, confusion or coma[3]. The mean length of symptoms is approximately three years due to the non-specific nature of neuroglycopenic symptoms. Transient hypoglycemic events are common, especially in diabetic patients, and are usually not life-threatening or associated with persistent neurological deficits or organ damage[4]. However, severe persistent hypoglycemia or recurrent mild hypoglycemia may cause long-lasting coma, seizures, and neurologic deficits[5,6]. This syndrome has been called hypoglycemic encephalopathy, but is not well defined in the literature and the pathophysiology is poorly understood[7]. Here, we report a case of insulinoma that went undiagnosed for 11 years and induced mild cognitive impairment with suspicious frontal lobe dysfunction, as confirmed by a Korean-Mini Mental State Examination (K-MMSE).

CASE REPORT

A 47-year-old male with recurrent abnormal behavior for ten years was referred to our clinic. He was diagnosed with insulinoma and cognitive dysfunction. Persistent hypoglycemia leads to a high risk of cognitive dysfunction in diabetic patients. However, cognitive dysfunction associated with insulinoma is rare. In this case study, cognitive dysfunction was confirmed by neurological testing. (J Korean Diabetes 2013;14:98-101)

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hypoglycemia (serum glucose 25 mg/dL). However, at that time, he refused further evaluation. He continued to experience similar symptoms almost daily for the next ten years, including dizziness, headache, slurred speech, and abnormal behavior (murmuring, drooling, and agitation) without consciousness. Symptoms usually occurred during sleep at night in addition to being aggravated by hunger and exercise, and were relieved by glucose intake. On admission, his body temperature and vital signs were normal. He appeared well and was not in acute distress, but reported slow speech and an impaired sense of direction.

All routine laboratory parameters were within normal ranges except for a low blood glucose level (53 mg/dL) and elevated levels of serum insulin (75.5 μU/mL), pro insulin (637.9 pmol/L), and c-peptide (8.17 ng/mL). We investigated for the possibility of accompanying multiple endocrine neoplasia type I. Basal pituitary hormone levels were within normal ranges (growth hormone 0.08 ng/mL, thyroid stimulating hormone 4.32 uU/mL, luteinizing hormone 6.12 mU/mL, follicle stimulating hormone 5.78 mU/mL, prolactin 21.45 ng/mL) except for an elevated level of adrenocorticotropic hormone (61.40 pg/mL). There were no features of multiple endocrine neoplasia type I in an overnight dexamethasone suppression test, or on a sellar magnetic resonance image or parathyroid scan. A pancreas computed tomography scan and transhepatic portal venous sampling were performed to localize the insulinoma. The computed tomography scan showed an enhanced 8-mm nodule in the superior aspect of the pancreatic body (Fig. 1A). Transhepatic portal venous sampling showed an elevated serum insulin level of 662.7 μU/mL in the body of the pancreas (Fig. 1B).

Surgical resection of the insulinoma at the body of the pancreas was performed. The mass was 2-cm in diameter, well-demarcated, and solid, with a pale yellowish color. Microscopic study demonstrated a solid, trabecular, and gyriform growth pattern. The tumor cells had small and relatively uniform nuclei with granular cytoplasm. Hyalinized stroma with calcification was evident (Fig. 2).

Three days after the operation, the patient’s serum insulin and c-peptide levels returned to normal (serum insulin 8.4 μU/mL, serum c-peptide 1.80 ng/mL). However, his slow speech and the impaired sense of direction did not return to normal. To examine the cognitive dysfunction, a neuropsychological battery of tests (K-MMSE, Attention, Language fluency, Controlled Oral Word Association Test, and Seoul Verbal Learning Test)
was performed. Total percentile score on the K-MMSE was 0.02, implicating cognitive impairment, and spontaneous speech was non-fluent. The Seoul Verbal Learning Test (SVLT) revealed verbal memory dysfunction (immediate recall total percentile score of 10.38). Controlled Oral Word Association Test (COWAT) revealed frontal lobe dysfunction (phonemic total percentile score of 3.51). Considering the age and academic ability of the patient, generalized cognitive dysfunction and frontal lobe dysfunction were diagnosed. The patient was discharged without any surgical complications and follow-up neuropsychological tests were performed after five months. At that time, cognitive impairment was normalized (total percentile score on the K-MMSE of 36.32). Spontaneous speech was fluent, and both verbal memory and frontal lobe dysfunction had improved relative to the immediate post-surgery time point (immediate recall total percentile score of 31.92, phonemic total percentile score of 18.94).

**DISCUSSION**

Neuroglycopenic manifestations are common in patients with insulinoma, but are frequently misdiagnosed because of their unusual manifestations. Failure to recognize the presence of an insulinoma may result in permanent neurological damage, or even death[8]. The brain regions most vulnerable to hypoglycemia are cornu ammonis area 1, subiculum, dentate gyrus of the hippocampus, and the outer layers of the cortex. All of these regions are important for learning and memory[9]. Patients who recover from severe hypoglycemia may be left with cognitive dysfunction, particularly short-term memory[10].

The pathophysiology of hypoglycemic encephalopathy is poorly understood. However, it is known that hypoglycemic neuronal injury is precipitated almost entirely by sustained glutamate receptor activation (excitotoxicity), which is mediated by Poly ADP-ribose polymerase-1 (PARP-1)[11,12]. The only treatment for hypoglycemic brain damage is blood glucose repletion and, currently, there are no useful interventions to prevent the neuronal death that develops after correction of hypoglycemia. Pretreatment using glutamate receptor antagonists has been investigated in an attempt to reduce hypoglycemic neuronal death, but these agents are neurotoxic themselves and less effective when administered after hypoglycemia has occurred[13].

According to Suh et al. [14], PARP-1 activation has a pivotal role in the development of hypoglycemic neuronal death and these authors provide proof of...
principle that PARP-1 inhibition can rescue neurons that would otherwise die after severe hypoglycemia. However, these treatments are not yet available, so the early diagnosis of insulinoma is crucial in patients with atypical neuroglycopenic presentation.

According to Daggett et al. [8], the most common neuropsychiatric manifestations of insulinoma are confusion, coma, and convulsions: less common symptoms are blurred vision, paresthesiae, diplopia, paralysis including hemiplegia, monoplegia, and paraplegia. Therefore, blood glucose levels should always be checked in patients with neurologic deficits. When neurologic symptoms are recurrent and associated with hypoglycemia in non-diabetic patients, serum insulin levels must be checked to rule out insulinoma. Normally, when blood glucose levels decrease, insulin production is reduced. In β-cell adenomas, the production of insulin is elevated despite decreased blood glucose levels. In our study, the patient suffered from atypical neurologic symptoms for ten years. When he visited the Emergency Department ten years prior, insulinoma was suspected; however, he refused further evaluation and was discharged. Untreated insulinoma leads to cognitive dysfunction. According to Tam et al. [15], hypoglycemia is associated with a higher risk of adverse motor and cognitive outcomes at 12 months of age in infants with neonatal encephalopathy. A previous study also highlights the impact of hypoglycemia on cognitive function in diabetic subjects who developed the condition in childhood[10]. However, insulinoma accompanying cognitive dysfunction is rare. There have been many studies focusing on neuroglycopenic symptoms of insulinoma: however, as far as we aware, this is the first case documenting cognitive dysfunction and frontal lobe dysfunction caused by insulinoma.

References