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The Association between Tuberous Sclerosis and Insulinoma

Han Kim, Andrew Kerr, and Helen Morehouse

Summary: We describe a patient with tuberous sclerosis and an insulinoma. The neurologic abnormalities typically present in patients with tuberous sclerosis may, in rare cases, be manifestations of hypoglycemia. We discuss a possible association between tuberous sclerosis and multiple endocrine neoplasia type I.

Index terms: Sclerosis, tuberous; Adenoma

Pancreatic insulinomas are tumors arising from islets of Langerhans and are associated with multiple endocrine neoplasia type I syndromes (1). Neurologic manifestations of insulinoma include seizures, tremor, irritability, weakness, diaphoresis, and tachycardia, as well as personality change, confusion, and coma (2). Association between tuberous sclerosis and pancreatic insulinoma is rare but known (3). We report a patient with tuberous sclerosis whose sudden change in behavior ultimately led to a diagnosis of insulinoma.

Case Report

The patient is a 28-year-old mentally retarded man with a known history of tuberous sclerosis and seizures. Computed tomography scan of the head demonstrated multiple calcified masses lining the ependymal surfaces of both lateral ventricles. No cortical tubers, white matter alterations, or enhancing subependymal lesions were present, (Fig 1A). The patient had been in his usual state of health until 7 months before admission, when he started to show behavioral changes characterized by episodes of agitation and, at other times, lethargy. On a routine examination, the patient's serum glucose level was found to be 23 mg/dL. The serum insulin and proinsulin levels at this time were elevated; the serum insulin measured 3.2 ng/mL, (normal is less than 0.1 ng/mL.) Proinsulin level was 2.1 ng/mL (normal proinsulin should be no more than 20% of the serum insulin level.) Computed tomography and magnetic resonance scans of the abdomen demonstrated bi-

lateral angiomyolipomas (Fig 1B) but did not demonstrate an insulinoma. Celiac angiography was performed. This revealed a hypervascular lesion 2 cm in diameter in the tail of the pancreas (Fig 1C). Partial pancreatectomy was performed. Pathologic analysis revealed a well-circumscribed insulinoma. After surgery, the patient's glucose level returned to normal, and his agitation and lethargic episodes resolved.

Discussion

Tuberous sclerosis is a congenital abnormality of autosomal dominant inheritance, variable expressivity, and high penetrance. It may involve one or more organs, notably the skin; the central nervous system including the retina; the kidneys; and the heart. In addition to these common manifestations, a multitude of other associated abnormalities have been described affecting bone, lung, adrenals, retina, thyroid, gonads, pituitary, gut, and parathyroid (3). Involvement of the pancreas is very rare, with four reported cases (4–7). One of these cases was a nonfunctioning islet cell tumor; the remaining three cases were insulinomas, similar to that in our patient. In the case described by Gutman et al (4), the new onset of grand mal seizures in a patient with tuberous sclerosis led to detection of hypoglycemia, and the diagnosis of insulinoma was established. After the excision of the tumor, the seizures did not recur. Thus, although seizures or mental status changes in tuberous sclerosis patients are considered to be attributable to cortical and subependymal tubers, hypoglycemia induced by insulinomas also should be considered.

Tuberous sclerosis and its association with various endocrine adenomas have been reported in the past. In addition, the patient described by Ilgren et al (5) also had multiple

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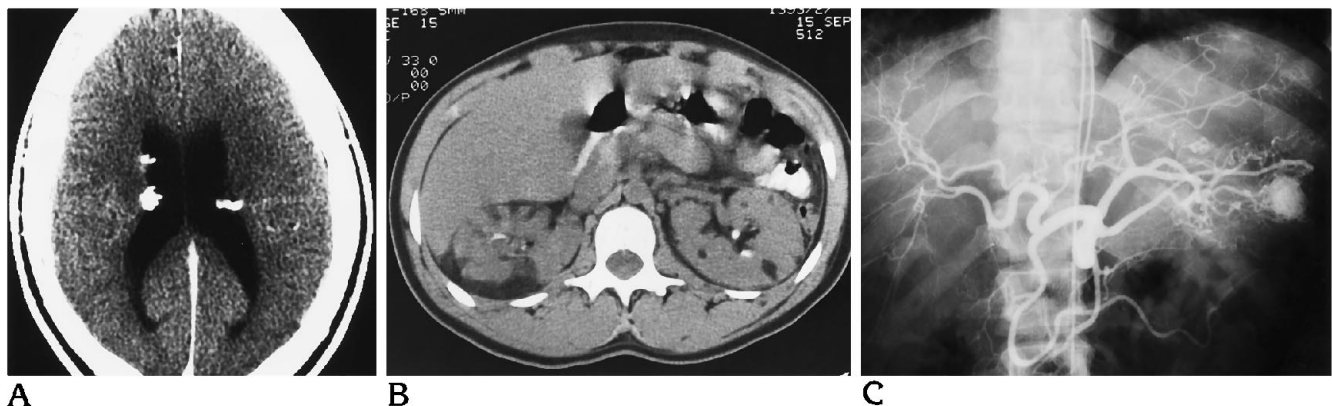


Fig 1. A, Axial computed tomography scan of the head shows multiple calcified subependymal tubers.
 B, Axial computed tomography scan through midabdomen shows multiple bilateral renal angiomyolipomas.
 C, Celiac artery angiogram shows an intense blush in tail of pancreas.

endocrine neoplasia, which, in addition to pancreatic islet cell tumor, affected the pituitary gland, the adrenal glands, and the parathyroid glands. Our case and those previously reported suggest the possibility of association of multiple endocrine neoplasia type I and tuberous sclerosis. Tuberous sclerosis has been linked to chromosome 9 (3). Although multiple-endocrine neoplasia type II has been linked to chromosome 10 (8), the genetic linkage of multiple endocrine neoplasia type I has not yet been delineated. Thus, the association of tuberous sclerosis to multiple endocrine neoplasia type I suggests the possibility that multiple endocrine neoplasia type I also may be linked to chromosome 9.

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