Causes and Evaluation of Tumor-Induced Hypoglycemia

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We treated four patients who had hypoglycemia and non-pancreatic tumors. Two had pleural mesothelioma, one had primary fibrosarcoma of the liver, and one had pheochromocytoma metastatic to the liver. We propose four mechanisms for this syndrome: (1) insulin or insulin-like activity produced by the tumor, (2) decreased gluconeogenesis, (3) disruption of glucagon metabolism, and (4) increased utilization of glucose by the tumor. The local effects of the tumor in hepatic parenchyma may also play an important role. The important diagnostic tests are an insulin-glucose ratio, to rule out insulinoma, and fasting glucose levels. An assay of nonsuppressible insulin-like activity can be performed and is of investigative interest, but does not aid in individual patient therapy. Treatment consists of control of the tumor.

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Hypoglycemia induced by malignant disease is unusual, but it is important to recognize the syndrome when it occurs. Knowledge of the pathophysiology of carbohydrate metabolism is essential in the evaluation of tumor-induced hypoglycemia. We report four cases that demonstrate the mechanism of tumor-induced hypoglycemia, and outline the use of readily available laboratory tests for determining its cause.

PATHOPHYSIOLOGY OF HYPOGLYCEMIA

Several mechanisms have been proposed to account for tumor-induced hypoglycemia. It has been well established that various tumors have the ability to secrete hormones, particularly tumors of the APUD cell line. Islet cell tumors of the pancreas secrete insulin, which produces hypoglycemia. However, the causes of hypoglycemia associated with nonpancreatic tumors are less understood. Although there are reports of nonpancreatic tumors capable of producing insulin, such tumors are very uncommon. Because many of these patients have characteristics of hyperinsulinism, the concept of an insulin-like substance was postulated.

In 1974, Megyesi et al. developed a radioreceptor assay for an insulin-like peptide called nonsuppressible insulin-like activity (NSILA) and demonstrated elevated concentrations of NSILA in the serum of five of seven patients with nonpancreatic malignancy and hypoglycemia. However, subsequent reports of cases of tumor-induced hypoglycemia suggest that this assay does not effectively identify the humoral factor in many cases.

Precise analysis of carbohydrate metabolism in these patients shows several consistent abnormalities. Suppression of gluconeogenesis has been demonstrated in hepatoma, leiomyosarcoma, and mesothelioma, and is generally believed to be a major cause of hypoglycemia in these cases, possibly mediated by metabolites of tryptophan. Depression of glucagon secretion and activity has also been implicated in the development of hypoglycemia.

If the tumor is growing within the liver itself, there is destruction of functioning hepatic parenchyma and decreased liver function. It has been shown in dogs that approximately 85% of the liver must be destroyed before hypoglycemia ensues. In patients with massive liver destruction due to benign disease, this alone is the cause. If a large tumor in the hepatic parenchyma is producing small amounts of an insulin-like substance, both mechanisms contribute to the hypoglycemia. If the tumor is not within the liver, these metabolic defects must be due to humoral factors, including insulin and NSILA.

These tumors are invariably large, supporting the hypothesis that increased utilization of glucose by the tumor causes hypoglycemia. Calculation of glucose balance
in these patients often suggests that there is a glucose "sink." Increased glycolytic activity and lactic acidosis have also been demonstrated. Depleted hepatic glycogen storage depots in conjunction with a tumor heavily laden with glycogen storage granules have been described and support the hypothesis that substrate is diverted from the host to the tumor. Glycogen stored within the tumor is not available to the body, as suggested by abnormal reactions to epinephrine stimulation.17

REPORT OF CASES

Case 1.—A 69-year-old man was admitted unconscious to the Evanston (III) Hospital emergency room with a blood glucose level of 30 mg/dL. He had been having episodes of weakness for two weeks. Physical examination findings were unremarkable except for decreased breath sounds at the apex of the right hemithorax. His condition improved with intravenous (IV) administration of glucose. A chest roentgenogram showed a right upper-lobe mass, and an arteriogram more precisely defined a pleural mass. Results of a glucose tolerance test, tolbutamide test, epinephrine stimulation test, glucagon stimulation test, and leucine stimulation tests were all normal. Serum insulin, glucocorticoid, and growth hormone levels were normal, and findings from the assay for NSILA were normal. Exploratory thoracotomy was performed, and a 1,060-g malignant fibrous mesothelioma of the pleura was removed. The hypoglycemia was resolved and the patient is alive and without disease nine years later.

Case 2.—A 31-year-old woman was admitted to Evanston Hospital one week post partum, with symptoms of obtundation and delirium. Her medical history was unremarkable except that she was taking thyroid extract to suppress a multinodular goiter. She had also had an elevated right hemidiaphragm on a chest roentgenogram taken several years earlier. Examination found an enlarged nodular thyroid, decreased breath sounds, and dullness to percussion of the right hemithorax. A chest roentgenogram demonstrated a tumor mass above the right hemidiaphragm. The serum glucose level on admission was 30 mg/dL. Her condition rapidly improved with IV administration of glucose. She continued to have hypoglycemic episodes and had to receive IV maintenance therapy with 10% glucose. Laboratory examinations showed a normal insulin level, normal glucocorticoid levels, normal thyroid function, and normal findings on an assay for NSILA. Exploratory thoracotomy discovered a 1,300-g fibrous mesothelioma in the right pleural space. The patient recovered from the operation and is well two years later.

Case 3.—A 59-year-old man was comatose on admission to the emergency room of Evanston Hospital, with a blood glucose level of 29 mg/dL. He quickly regained consciousness with the IV administration of glucose. He had been experiencing generalized weakness for a month, and abdominal fullness and tenderness for three months. His medical history was unremarkable and he was taking no medication. Physical examination found an enlarged, firm liver extending 13 cm below the right costal margin. Open liver biopsy was done and a mesenchymal neoplasm of the liver was found. An extensive radiologic evaluation including liver scanning, computed tomography (CT) of the abdomen, and arteriography, demonstrated a large tumor involving the entire right lobe of the liver and the medial segment of the left lobe. The serum insulin level was normal, along with the glucagon level and the results of a glucagon stimulation test. Surgical resection of the tumor was attempted, but because of technical problems and coagulopathy the patient died. Pathologic examination of the tumor showed a huge spindle cell fibrosarcoma of the liver. The tumor replaced almost the entire right lobe and the medial segment of the left lobe of the liver, as had been suspected.

Case 4.—A 62-year-old woman with a pheochromocytoma was found to have episodic hypertension confirmed by elevated levels of urinary catecholamines. A 100-g pheochromocytoma was removed through a right flank incision, with an uneventful postoperative course. Three months later the patient began to experience episodes of diaphoresis and palpitations. She was brought to the Evanston Hospital emergency room because she was found unarousable in her bed. Her blood glucose level was 10 mg/dL. The liver span was 13 cm in the midclavicular line, and there was an 8-cm mass below the liver. A chest roentgenogram showed multiple pulmonary nodules. The alkaline phosphatase level was 450 IU/L, the lactate dehydrogenase (LDH) level, 461 units/L, and the SGOT level, 97 units/L. She had a normal insulin-glucose ratio. Urinary catecholamine levels were markedly elevated and the liver scan demonstrated multiple filling defects. Her hospital course from that time on consisted of rapidly rising liver enzyme levels, sepsis, and disseminated intravascular coagulation, and ended in her death. The autopsy revealed almost complete replacement of the liver by a confluece of metastatic nodules, in addition to multiple pulmonary and para-aortic metastases.

COMMENT

Three mechanisms have been postulated to explain the well-known association of mesotheliomas with hypoglycemic syndrome.18,19 First, mesothelioma is one of the few tumors known to produce NSILA.20 Second, Silbert et al demonstrated decreased glucagon secretion resulting in decreased glycogenolysis in a patient with a large benign mesothelioma. Their patient did not have elevated serum insulin or NSILA levels, or increased insulin-like activity. Chowdhury and Bleicher also found this relative glucagon deficiency in a patient with mesothelioma. That tumors can grow to substantial size within the pleural space without causing local symptoms certainly contributes to the pathogenesis of this syndrome. A critical tumor mass must be reached to produce enough humoral substance to cause symptoms of hypoglycemia. Third, increased utilization of glucose by these large tumors has been suggested as an additional cause of hypoglycemia.13

Patient 2 demonstrated the same basic hypoglycemic mechanism as patient 1, but several factors may account for the postpartum onset of her symptoms. It is well known that pregnancy produces an insulin-resistant state. Plasma insulin responses to glucose tolerance tests are elevated.21,22 Whether this resistance is secondary to decreased insulin binding to receptors23 or a decreased number of functional insulin receptors per cell24 is controversial. Progesterone also decreases insulin binding,25 and progesterone levels are elevated during pregnancy. The change in the hormonal milieu after delivery created a relative increase in insulin sensitivity, and hypoglycemic symptoms appeared. In addition, normal pregnant women have been shown to have elevated NSILA levels,26 and this may have been a contributing factor.

Fibrosarcoma is one of the tumors most commonly associated with hypoglycemia. Papaioannou's extensive literature review in 196627 found 47 patients with fibrosarcoma causing hypoglycemia. Of the various mechanisms proposed for hypoglycemia, evidence suggests that many...
mesenchymal tumors produce insulin or an insulin-like substance. In 1960, Bousvaros described a patient with metastatic fibrosarcoma to the liver and hypoglycemia. Although there was massive involvement of the liver, there did not appear to be enough parenchymal destruction to account for the metabolic effects. Therefore, insulin production by the tumor was proposed as a possible mechanism, as it was by August and Hiatt, who found insulin activity in a similar tumor. This hypothesis was substantiated when Oleesky et al. reported a spindle cell fibrosarcoma of the retroperitoneum associated with hypoglycemia and an elevated serum insulin level of 869 µU/mL (normal, 0 to 70 µU/mL), which decreased to normal levels after successful radiation therapy. More recently, Lindkaer et al. showed that an extract from a liver tumor composed of spindled fibroblasts in a patient with normal insulin levels greatly decreased the glucagon secretion of an isolated, perfused porcine pancreas. Mesenchymal tumors may each produce different humoral agents, some of which we can identify by insulin or NSILA assay, and others of which we can only be aware indirectly. The humoral substances affect glucagon secretion and, therefore, glycogenolysis.

Although not all tumors related to hypoglycemia involve the liver, most of them do. The tumor may remain localized and grow to a substantial size within the liver without causing local symptoms. As it enlarges further, causing local symptoms, the glycogen storage and gluconeogenic capacity of the liver is decreased.

Approximately 85% of the liver parenchyma was replaced by tumor in patient 3, and we think that the loss of functioning hepatocytes was severe enough to cause hypoglycemia, independent of any other factors. Insulin levels were not elevated in this patient and, unfortunately, NSILA levels were not determined. We believe, however, that this patient's tumor was producing a humoral substance that decreased glucagon release and gluconeogenesis.

Megyesi et al. demonstrated elevated concentrations of NSILA in two patients with pheochromocytoma, in their original work. To our knowledge, there has been no previous report of pheochromocytoma metastatic to the liver causing hypoglycemia. In fact, removal of pheochromocytomas has resulted in hypoglycemia in some instances. Because of the common embryologic origin of tumors derived from the APUD cell line, production of insulin by the tumor seemed likely in case 4. However, serum insulin levels were not elevated in this patient. Therefore, one must hypothesize that either the tumor was producing an insulin-like substance, possibly NSILA as demonstrated by Megyesi et al., or there were other factors involved. Aside from the work of Megyesi et al., other evidence suggests that not all tumor-associated hypoglycemia is produced by the same mechanism and that there are often several different mechanisms operative in a single patient, particularly in one with nonmesenchymal tumors. In patient 4, we think the causes of hypoglycemia were cachexia with depletion of substrate for gluconeogenesis, impaired liver function with decreased capacity for gluconeogenesis, and increased utilization of glucose by the tumor. There also may have been a humoral substance augmenting these metabolic defects.

**DIAGNOSIS AND TREATMENT**

The evaluation of these cases consisted of a straightforward series of diagnostic tests. Such patients usually are initially in a coma, with low serum glucose level. Medical history usually excludes exogenous administration of insulin as a possible cause. Chest roentgenogram, medical history and physical examination may suggest the presence of the malignant tumor, since the tumors are often large. If the patient has symptoms of hypoglycemia and a normal serum glucose level, it may be necessary to obtain several fasting glucose levels until the hypoglycemia is proved. In some patients a prolonged fast of up to 14 hours is required to demonstrate a reduction of plasma glucose level below 50 mg/dL.

Once the hypoglycemia is confirmed and thought to be tumor associated, insulinoma must be considered. The diagnosis of excess insulin production is made by determining the serum insulin-glucose ratio. Insulin is measured as immunoreactive insulin (IRI) and should be compared with a simultaneously obtained serum glucose (G) level. A fasting IRI/G ratio greater than 0.3 is abnormal. In normal persons there is no measurable insulin when the fasting blood glucose level is less than 30 mg/dL. This consideration has been incorporated into an amended IRI/G ratio: (IRI × 100)/(G - 30), with IRI measured in microunits per milliliter. With this ratio, values greater than 50 are considered abnormal for nonobese patients. Both the original and amended ratios apply to an obese person if the serum glucose level is less than 60 mg/dL. If results of this test are positive, the provisional diagnosis of an insulinoma is made, and radiologic evaluation of the pancreas should be performed. The recently reported accuracy of CT scanning of pancreatic tumors facilitates evaluation.

Serum NSILA levels should be determined. At the present time, knowledge of elevated NSILA levels will not help in individual patient therapy, but if this substance is consistently found in the serum of patients with certain tumors, specific inhibitors may be developed that will help palliate their symptoms until the tumor is controlled. If an insulinoma or a nonpancreatic insulin-secreting tumor is found, diazoxide may help control hypoglycemia by inhibiting insulin release. There are currently no medications available to aid in the management of serum glucose level in hypoglycemic patients without hyperinsulinemia.

If hypoglycemia associated with a nonpancreatic tumor is diagnosed, the next step is aggressive treatment of the tumor. In many cases, the symptoms of hypoglycemia have completely resolved with surgical, radiologic, or chemo-therapeutic control of the tumor. Prognosis is poor if control of the tumor cannot be obtained. A high carbohydrate intake must then be initiated either orally or IV to maintain normal serum glucose levels. Streptozocin has also been used along with fluorouracil in the management of pancreatic islet cell tumors.
References


