Factitious Hyperinsulinism Leading to Pancreatectomy: Severe Forms of Munchausen Syndrome by Proxy

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ABSTRACT. Clinical history and inappropriate insulin secretion during hypoglycemic episodes permit the diagnosis of hyperinsulinism. We report 2 cases of factitious hyperinsulinism leading to partial pancreatectomy. Case 1 was an 8-year-old girl who presented with severe hypoglycemia and elevated insulin and C-peptide levels. Catheterization of pancreatic veins was performed to localize the excess insulin secretion. Insulinoma was suspected, and partial pancreatectomy was performed. Ten days after surgery, severe hypoglycemia recurred with severely elevated plasma insulin levels (×100) but very low C-peptide plasma levels, suggesting factitious hyperinsulinemia. Hypoglycemic episodes before surgery were provoked by oral sulfonamides; postoperative episodes were caused by parenteral insulin. Falsified prescriptions for sulfonamides and insulin by the mother, a nurse, were found. Case 2 was a 6-month-old girl who presented with seizures and hypoglycemia but had a symptom-free interval of many months afterward. At 2 years of age, repeated hypoglycemic seizures and elevated insulin plasma levels suggested congenital hyperinsulinism. C-peptide plasma level, measured once, was normal, but blood sampling was performed 15 minutes after a hypoglycemic episode. Partial pancreatectomy was performed. Two weeks after surgery, hypoglycemic seizures recurred, and the patient was admitted for pancreatic vein catheterization. This investigation was performed during hypoglycemia and revealed high insulin levels and undetectable C-peptide levels, suggesting factitious hypoglycemia. Insulin/C-peptide ratio analysis is crucial to assess factitious hypoglycemia, although sulfonamide-induced hypoglycemia is not thereby detected. One percent (2 of 250) of all cases of hyperinsulinemic hypoglycemia in our unit have been identified as Munchausen syndrome by proxy. Atypical disease history should raise the question of factitious hypoglycemia. Pediatrics 2005;116:e145－e148. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2331; hyperinsulinemia, partial pancreatectomy, Munchausen syndrome by proxy, factitious hypoglycemia.

ABBREVIATIONS. PHHI, persistent hyperinsulinemic hypoglycemia of infancy; CHI, congenital hyperinsulinism; PVS, pancreatic venous sampling; MSP, Munchausen syndrome by proxy; LC-MS, liquid chromatography–mass spectrometry.

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a profound hypoglycemia resulting from excess insulin secretion. The diagnosis of PHHI is based on the combination of the clinical history and the laboratory findings. The clinical presentation of PHHI varies with the age at onset of hypoglycemia. The neonatal form (~60% of all patients) is characterized by hypoglycemia within 72 hours after birth, with ~50% of the patients exhibiting seizures. Irreversible brain damage may occur. Infantile-onset PHHI (35% of patients) occurs between the 1st and the 12th months of life, and, again, seizures occur in 50% of the patients. Approximately 5% of pediatric patients with PHHI present after 1 year of age. Laboratory findings of PHHI include fasting and postprandial hypoglycemia (<3 mmol/L) with hyperinsulinemia (plasma insulin concentrations >3 mU/L) and elevated C-peptide levels, requiring high rates of intravenous glucose (>10 mg/kg/min) to maintain blood glucose >3 mmol/L. Plasma glucose concentration increases by 2 to 3 mmol/L in response to 0.5 mg of glucagon injection. In the absence of clearly abnormal insulin levels during hypoglycemia, a 4- to 6-hour fasting study may reveal inappropriately low plasma levels of ketone bodies, free fatty acids, and branched-chain amino acids.

The causes of PHHI include congenital hyperinsulinism (CHI) and insulinoma. CHI is caused by 2 distinct histologic anomalies: focal adenomatous hyperplasia and diffuse pancreatic insulin hypersecretion,1–3 which share a similar clinical presentation4 but result from different molecular mechanisms.5–9 The distinction between the 2 forms is important because treatment is different.4,10 Diffuse CHI requires near-total pancreatectomy, with a high risk for iatrogenic diabetes and pancreatic insufficiency, whereas focal CHI can be cured by partial pancreatectomy limited to the focal lesion.2,11 Hypoglycemia that occurs later in childhood is most often attributable to pancreatic insulinoma.

In the absence of any distinctive clinical feature and because preoperative classical radiology of the pancreas, including sonography, CT scan, and MRI cannot discriminate between focal and diffuse dis-
ease, pancreatic venous sampling (PVS) was, until recently, the only preoperative procedure available for locating the site of insulin secretion. Venous blood samples were collected from the head, isthmus, body, and tail of the pancreas for measurements of plasma glucose, insulin, and C-peptide levels. Patients with a focal lesion had high plasma insulin and C-peptide levels in 1 or several contiguous samples, with low concentrations in the remaining pancreatic samples. Patients with diffuse hyperinsulinism had high plasma insulin and C-peptide concentrations in all pancreatic samples.

We report here 2 cases of severe hypoglycemia, 1 with late onset in childhood (8 years) and the second with initial onset in infancy (6 months) followed by a long symptom-free period. C-peptide and insulin plasma levels were not found to be discrepant, and hyperinsulinism was diagnosed, leading to partial pancreatectomy in both patients. Severe hypoglycemia recurred after the partial pancreatectomy, and diagnosis of factitious hypoglycemia was suspected.

CASE REPORTS

Case 1
An 8-year-old girl presented with fever, severe vomiting, and headache, necessitating intravenous rehydration therapy. She left the ward 3 days later in stable condition. Five days later, she was readmitted to the hospital because of aggressive behavior and vomiting, pallor, and sweating. Laboratory studies revealed severe hypoglycemia (0.25 g/L). A subcutaneous glucagon injection was given and resulted in rapid normalization of blood glucose levels. Several episodes of hypoglycemia before and after eating occurred during the following days. Insulin plasma levels were elevated. The girl then was transferred to our unit for catheterization of pancreatic veins to localize the site of excess insulin secretion. PVS was performed under general anesthesia, and the patient was hypoglycemic during the investigation. Elevated insulin and C-peptide levels were observed in pancreatic isthmus and tail samples. Insulinoma was suspected because of the child’s age. Partial pancreatectomy was proposed, after which blood glucose and C-peptide levels were observed in pancreatic isthmus and tail. The patient was hypoglycemic during the investigation. Elevated insulin plasma levels were not found to be discrepant, and hyperinsulinism was diagnosed, leading to partial pancreatectomy in both patients. Severe hypoglycemia recurred after the partial pancreatectomy, and diagnosis of factitious hypoglycemia was suspected.

Case 2
A 3-year-old girl with the diagnosis of CHI was referred to our department because of recurrent hypoglycemia after partial pancreatectomy. Symptoms began at 6 months of age with hypoglycemic seizures. However, at that time, the plasma glucose levels and the fasting study performed in this hospital over 3 days were normal. At 2 years of age, hypoglycemic seizures and malaise reappeared. Hyperinsulinemia was repeatedly found. Plasma C-peptide level was measured once and was normal, but the blood sampling was done ~15 minutes after a hypoglycemic episode. Conservative treatment with diazoxide, 150 mg in 3 daily doses, was unhelpful. Radiologic investigations, including abdominal sonography, CT, and MRI, as well as octreotide uptake were normal. Partial pancreatectomy (tail) was performed at 2.5 years. Pancreatic histology was normal. Diagnosis was made preoperatively. During the 2 postoperative weeks, no hypoglycemic episodes occurred. On postoperative day 15, severe hypoglycemic seizures recurred, requiring continuous gastric tube feeding (glucose 13 mg/kg/min), oral diazoxide (20 mg/kg/day) and subcutaneous somatostatin.

The child was transferred to our unit for additional diagnostic evaluation and treatment. During hyperglycemic episodes, serum cortisol, insulin-like growth factor-I, ammonia, and transferrin electrophoresis were normal. Electroencephalogram and echocardiogram were also normal. Just before transhepatic catheterization with PVS, a severe hypoglycemic episode occurred, requiring high rates of intravenous glucose (10 mg/kg/min). Blood glucose levels were normalized by the end of the investigation. Selective pancreatic catheterization revealed high insulin levels (7–16 mU/L) and undetectable C-peptide. The patient was admitted to the ICU for continuous monitoring. She had no hypoglycemia during the 24 hours after catheterization. Factitious hypoglycemia was suspected. For evaluating this suspicion, the child was kept for 5 days in the ICU under continuous observation. No additional hypoglycemic episode occurred. The girl’s mother, who had received a diagnosis of type 1 diabetes at the age of 10 years, was suspected to have injected subcutaneous insulin into her daughter. Both parents denied administration of insulin. Several days later, during a psychological evaluation, the child imitated insulin injections to her teddy bear. Several months later, the mother admitted that she had repeatedly injected insulin into her daughter.

DISCUSSION
Munchausen syndrome was first described in 1951. The term Munchausen syndrome by proxy (MSP) was introduced by Meadow in 1977 to describe a form of child abuse involving the mother’s, a parent’s, or another guardian’s falsifying illness in a child. Diagnosis is difficult because caregivers are adept at deceiving medical and mental health professionals. The average length of time to establish a diagnosis of MSP generally exceeds 6 months. More than 400 articles related to MSP have appeared, with a wide variety of presentations among them: allergic disease, fever, dermatitis artefacta, bacterial infections, osteomyelitis, epilepsy, neurologic disease, autoerythrocyte sensitization, cystic fibrosis, gastrointestinal disease, renal disease, factitious bleeding, apnea, cardiorespiratory arrest, and death.

Cases of chronic surreptitious administration of insulin or antidiabetic drugs such as sulfonylamides to children and adults have already been reported. Nonetheless, factitious hypoglycemia continues to be misdiagnosed as PHHI, as it initially was in the 2 cases reported here. Distinguishing factitious hypoglycemia from PHHI depends on history and laboratory findings. Atypical histories of hypoglycemia were noted in both of our patients: long periods without hypoglycemia, severe hypoglycemic episodes, and relapse after event-free periods of several years.
days after partial pancreatectomy. Increased plasma insulin/C-peptide ratio that is coincident with an episode of hypoglycemia is useful in identifying factitious hyperinsulinism but is not inevitably present. It is crucial that, during hypoglycemia, plasma samples for both insulin and C peptide be sent for laboratory evaluation. In case 2, in which exogenous insulin was the sole hypoglycemic agent, although multiple blood tests that showed hyperinsulinemia were sent, only 1 C-peptide level was drawn before partial pancreatectomy. In case 1, the preoperative hyperinsulinism was caused by oral administration of sulfonamides. Therefore, increased insulin/C-peptide ratio was not seen and the atypical features of the history assume more diagnostic importance. In this case, postoperative surreptitious administration of insulin, resulting in hypoglycemia and in increased insulin/C-peptide ratio, precipitated suspicion of MSP. Importantly, intraoperative pancreatic frozen sections would have shown absence of either diffuse or focal CHI.2,4 For this reason, we strongly recommend intraoperative frozen sections to help to define clearly the localization and the type of abnormal histology, if any. In the rare event that hypoglycemia has been factitious, such procedures may help to avoid unnecessary partial or complete pancreatectomy.

Transhepatic catheterization with PVS was used to distinguish between diffuse and focal CHI. It can also help to distinguish organic from factitious hyperinsulinism, as it did in case 2, in which PVS samples showed an increased insulin/C-peptide ratio, although unfortunately not before a partial pancreatectomy. In the future, PVS will likely be replaced by [18F] Fluoro-L-DOPA PET scan.44 It is foreseen that [18F] Fluoro-L-DOPA PET scan will not show any dopamine fixation in the pancreas. In our experience, [18F] Fluoro-L-DOPA did not fix on histologic samples of healthy pancreas but did on histologic samples of diffuse or focal forms of PHHI (unpublished observations).

Several methods have been reported for the extraction and detection of antidiabetic drugs in human plasma or urine: micellar electrokinetic capillary chromatography with diode-array detection45 and high-performance liquid chromatography with ultra-violet detection.46 However, most of them are time-consuming, involving multiple extraction steps, and may provide false-positive results as a result of interferences with basal components of sample matrices or concomitant therapies. Application of liquid chromatography–mass spectrometry (LC-MS) for detection of antidiabetics has been reported recently.47 However, detection was optimized for only a few or just a single antidiabetic drug in serum. Very recently, an LC-MS method for the determination of antidiabetic drugs in equine plasma and urine was published.48 So far, none of these laboratory methods has been used currently in medical practice. The LC-MS method could be an interesting method for the detection of antidiabetic drugs in human serum and/or urine in the future. Therefore, it might become an interesting diagnostic tool to confirm sulfonamide-induced factitious hypoglycemia.

MSP can be devastating and sometimes fatal for children or infants.49,50 Paradoxically, it is in a hospital where ~75% of the MSP-related morbidity occurs as a consequence of continued illness fabrication by the perpetrator,14,51,52 the majority of whom are female (76%–95%).14,51,53 Typically but by no means inevitably, while creating or feigning the child’s illness, the parent seems to be “ideal” (ie, especially attentive, caring, supportive, and close to the medical staff). In our cases, both patients’ mothers had normal intelligence, seemingly normal behavior, and an excellent understanding of medical information. They were very interested in their children’s medical care. As it is difficult to prevent relapse of MPS, it is essential to detect the mother’s surreptitious abusive behavior in a timely manner, as they may change care teams frequently. The perplexing presentation and the mothers’ psychological structure are difficult not only to detect but also to treat. These individuals are often reported for child abuse, and their psychological follow-up is difficult. Additional psychosocial and medical studies have to be performed to optimize prevention and follow-up of affected families.

In summary, the clinical history and the insulin/C-peptide ratio should be assessed carefully in all cases of hyperinsulinemic hypoglycemia. An increased ratio can help to identify surreptitious exogenous insulin as the cause. Administration of sulfonamides will not have an increased insulin/C-peptide ratio, but the history may be odd because of some combination of long symptom-free intervals, late age of onset, extreme events, and, if subtotal pancreatectomy has apparently been successful, late recurrence of symptoms and signs. In the future, LC-MS will probably be an interesting method to detect antidiabetic drugs in human serum or urine and therefore an interesting diagnostic tool to confirm sulfonamide-induced factitious hypoglycemia. In all cases, competing diagnosis must be considered thoroughly. In our unit, <1% of all cases of hyperinsulinemic hypoglycemia have been identified as MPS (2 of 250). The frequency is low, but the individual morbidity is high, as represented by the 2 cases reported here, in which unneeded partial pancreatectomies were performed. MSP is surprising, even for experienced physicians.

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