Noninsulinoma pancreatogenous hypoglycemia syndrome

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INTRODUCTION — The noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS)[1] is a rare syndrome. The term 'nesidioblastosis' was originally conceived by George F Laidlaw (1938), common in neonate persistent hyperinsulinemic hypoglycemia(PHH) . Since the first reported case of an adult nesidioblastosis in 1975, less than 100 patients have been described in the literature findings different from those in patients with insulinomas[20].

DEFINITION — NIPHS is neoformation of islets of Langerhans from pancreatic duct epithelium. Formerly termed adult nesidioblastosis, is characterized by postprandial hypoglycemia with islet cell hypertrophy and negative prolonged fasts, and negative perioperative localization studies for insulinoma but positive intra-arterial calcium stimulation (IACS) . The pathologic findings are similar to those seen in neonates and infants with persistent hyperinsulinemic hypoglycemia

Epidemiology : 0.5-7% in hyperinsulinemic hypoglycemia

CLINICAL FEATURES

Symptoms —NIPHS is postprandial hypoglycemia, two to four hours after meals, and only rarely while fasting [2]. All patients had neuroglycopenic symptoms, and several lost consciousness or had generalized seizures. Forty percent of the patients had a history of upper gastrointestinal surgery (not gastric bypass) [3]. In smaller series and case reports, a similar preponderance of postprandial hypoglycemia, neuroglycopenic symptoms, and male predominance was noted. However, fasting hypoglycemia has also been reported. Some patients (4% of one series188) with fasting endogenous hyperinsulinemic hypoglycemia do not have an insulinoma but have islet hypertrophy, sometimes with hyperplasia[4]

Biochemical findings — During episodes of hypoglycemia, patients with NIPHS have similar to those of insulinoma, including elevated plasma insulin, C-peptide, and proinsulin concentrations, low plasma beta-hydroxybutyrate, and a negative sulfonylurea/meglitinide screen.

DIAGNOSTIC EVALUATION

●The initial evaluation of hypoglycemia includes measurement of glucose, insulin, proinsulin, C-peptide, beta-hydroxybutyrate, and sulfonylurea/meglitinide screening during an episode of hypoglycemia.

●In patients with endogenous hyperinsulinism, insulin antibodies should be measured to distinguish insulin autoimmune hypoglycemia from other causes of hyperinsulinism.

●In patients with endogenous hyperinsulinemic hypoglycemia (and negative screens for sulfonylurea/meglitinide and insulin antibodies), localization studies are necessary to distinguish between the presence of an insulinoma versus a diffuse process (islet cell hyperplasia/nesidioblastosis).

- An octreotide scan mostly positive but some report case did not show focal abnormality to suggest insulinoma but the SACST was positive [19] ,

Localization studies — After diagnosis of endogenous hyperinsulinemic hypoglycemia. Several noninvasive procedures are available (computed tomography [CT], magnetic resonance imaging [MRI], transabdominal ultrasonography, 18F-DOPA PET]). The choice of procedure depends upon which tests are available and local radiologic skill. Transabdominal ultrasonography is initial test for the identification of an insulinoma.

Radiological localization studies are negative in patients with NIPHS. In the Mayo series, as an example, all radiologic studies were negative for insulinoma. The sensitivity of each of these preoperative studies is only about 50 to 60 percent, but their combined sensitivity is significantly higher.

EUS has the best diagnostic performance in detection and localization of insulinoma. EUS could detect insulinoma with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 93%, 80%, 93% and 80%, respectively. The corresponding performances for CT were 78%, 100%, 100%, 50% and MRI were 71%, 33%, 71%, 33%, respectively. EUS was able to detect insulinoma in 50% of patients with negative CT. EUS detect insulinoma in 67% of patients with negative MRI. EUS, CT and MRI correctly localized insulinoma in 87%, 67% and 57%, respectively. The most common incorrect localization was between pancreatic body and tail[10]. EUS has a limited role in diagnosing diffuse nesidioblastosis[11]

In patients with complex cases of endogenous hyperinsulinemic hypoglycemia and negative radiologic localization studies, a selective arterial calcium stimulation test (SACST) with hepatic venous sampling should be performed to establish that the hyperinsulinemia has a pancreatic origin and in addition its regionality within the pancreas. Focal versus diffuse positivity does not provide incontrovertible evidence for or against insulinoma/nesidioblastosis, since insulinoma may be multiple and nesidioblastosis may be concentrated in one portion of the pancreas. A SACST involves injections of calcium gluconate, an insulin secretagogue, into arteries supplying the pancreas with subsequent sampling of the hepatic venous effluent for insulin . A positive result is defined as a doubling or tripling of the basal hepatic venous serum insulin concentration.

Histopathology — Histopathology descriptions of excised pancreatic tissue include islet cell hypertrophy and were more irregular in shape and size [5] with enlarged and hyperchromatic nuclei, sometimes islet cell hyperplasia, and increased periductular islets . Islet-like cells budding off exocrine ducts have been noted and were most evident on

immunohistochemical staining for chromogranin A . The hypertrophic islet cells also stained positively for insulin, glucagon, somatostatin, and pancreatic polypeptide [1]. The distribution of the hormones within the islets was normal, with between 60 to 80 percent of the islet cells staining for insulin. Many of the cells budding off ducts also contained insulin.

However, in an analysis of pancreatic tissue from 36 cases (27 post-gastric bypass) of nesidioblastosis, increased insulin-like growth factor 2, insulin-like growth factor 1 receptor alpha, and transforming growth factor receptor beta 3 expression were noted in the islets of patients compared with controls who had benign exocrine pancreatic tumors [6]. These findings suggest a role for growth factors in the pathogenesis of nesidioblastosis in adults.

DIFFERENTIAL DIAGNOSIS — In adults, hypoglycemia due to endogenous hyperinsulinism, with negative screens for sulfonylurea/meglitinide and insulin antibodies, can be caused by:

●A beta cell tumor (insulinoma) A negative 72-hour fast is suggestive of noninsulinoma pancreatogenous hypoglycemia; a positive test is more consistent with insulinoma. However, the hypoglycemic response to a 72-hour fast cannot definitively distinguish NIPHS from insulinoma.

●A functional beta cell disorder (eg, nesidioblastosis) due to either noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) or post-gastric bypass hypoglycemia.Post–gastric bypass hypoglycemia is rare, reported to occur in 0.2% of operated patients[7]. NIPHS is much less common than post-gastric bypass hypoglycemia

The etiology of islet cell hyperplasia following RYGB surgery: hormonal changes (possibly involving insulin-stimulating glucagon-like peptide-1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP], or ghrelin), unidentified factors from the proximal intestine, or disruption in the presurgery homeostasis of insulin resistance and hyperinsulinemia with rapid weight loss [8,9].

TREATMENT

Mild to moderate symptoms —Nutritional modification is a reasonable initial intervention. NIPHS similar nutritional modification may be helpful. If mild to moderate symptoms persist, we prescribe the alpha-glucosidase inhibitor acarbose[12] (initial dose 25 mg three times daily, with each main meal).There are case reports, octreotide, verapamil[12], diazoxide[13], nifedipine[14]. NIPHS and mild to moderate symptoms refractory to a low carbohydrate diet, we believe it is worthwhile to try a course of acarbose, starting at a low dose and advancing to the point of balance between tolerance and benefit. Success with this approach avoids surgery.

Severe symptoms — For patients with NIPHS and severe postprandial hypoglycemia (neuroglycopenia with loss of consciousness) or with symptoms refractory to medical management, surgery is the mainstay of therapy. In case series and reports, partial or subtotal pancreatectomy successfully relieved hypoglycemic symptoms in the majority of patients with NIPHS and post-gastric bypass nesidioblastosis.

The degree of surgery is determined by the results of the selective arterial calcium stimulation test. The pancreas to the left of the superior mesenteric vein is resected when the selective arterial calcium stimulation test is positive only after splenic artery injection, and the resection is extended to the right of the superior mesenteric vein when the test is positive after injection of an additional artery. The pancreas can be debulked in a gradient-guided fashion, even in patients whose disease appears to involve the whole pancreas.

The extent of surgical resection for adult nesidioblastosis is still controversial. Most surgeons perform distal pancreatectomy, while others prefer to perform almost total pancreatectomy (90% to 95% of the gland). The excision of 60% to 80% of the distal pancreas leads to cure for about half the patients, without any need for medication[15]. Another study by Witteles et al. has show that resection of 60-89% of pancreas (i.e., distal or subtotal pancreatectomy) is possibly the most appropriate surgery for nesidioblastosis because the risk of diabetes mellitus is below 10% with 70% success rate in achieving normoglycemia[16]

For post-gastric bypass patients with severe hypoglycemia due to nesidioblastosis, reversal of gastric bypass has been suggested as an alternative to pancreatectomy. After reversal, hypoglycemia persisted in some case reports . Conversion of the Roux-en-Y gastric bypass (RYGB) to sleeve gastrectomy is the current procedure of choice. However, if there is no improvement, partial pancreatectomy may still be necessary.

Recurrent symptoms — Recurrent hypoglycemia after partial pancreatectomy has been observed in both NIPHS and post-gastric bypass hypoglycemia [17]. In a series of 75 patients, 48 of whom responded to a questionnaire, 87 percent reported recurrence of symptoms but to a lesser degree than preoperatively ,median time to recurrent symptoms was 16 months [18]. Despite symptom recurrence, 75 percent reported overall improvement in symptoms and quality of life. The symptoms are usually mild when they recur, lifestyle modification or medical management may suffice. Only rarely has completion pancreatectomy been conducted [6].

In our case : the patient had post prandial hyperglycemia, positive for endogenous insulin production, negative for localized abnormal mass in pancrease, EUS finding :accessory spleen. Preoperative : high glucose infusion rate and hypoglycemia can not improved with diazoxide . Partial pancreatectomy: increase pancreatic size in gross anatomy and pancreatic islet cell hyperplasia with ductuloinsular complex in microscopy. Symptom hypoglycemia improved when clamped artery intraoperative procedure and off glucose infusion in the next day

Reference

1. *F John Service, MD, PhD, Noninsulinoma pancreatogenous hypoglycemia syndrome.UPTODATE ,Literature review current through: Dec 2015*
2. *Service FJ, Natt N, Thompson GB, et al. Noninsulinoma pancreatogenous hypoglycemia: a novel syndrome of hyperinsulinemic hypoglycemia in adults independent of mutations in Kir6.2 and SUR1 genes. J Clin Endocrinol Metab 1999; 84:1582.*
3. *Anlauf M, Wieben D, Perren A, et al. Persistent hyperinsulinemic hypoglycemia in 15 adults with diffuse nesidioblastosis: diagnostic criteria, incidence, and characterization of beta-cell changes. Am J Surg Pathol 2005; 29:524.*
4. *Anlauf M, Wieben D, Perren A, et al. Persistent hyperinsulinemic hypoglycemia in 15 adults with diffuse nesidioblastosis: diagnostic criteria, incidence, and characterization of beta-cell changes. Am J Surg Pathol. 2005;29:524-533.*
5. *Kandelaria M Rumilla, Lori A Erickson, F John Service, Adrian Vella, Geoffrey B Thompson, Clive S Grant and Ricardo V Lloyd. Hyperinsulinemic hypoglycemia with nesidioblastosis: histologic features and growth factor expression. Modern Pathology (2009) 22, 239–245*
6. *Rumilla KM, Erickson LA, Service FJ, et al. Hyperinsulinemic hypoglycemia with nesidioblastosis: histologic features and growth factor expression. Mod Pathol 2009; 22:239.*
7. *Marsk R, Jonas E, Rassmussen F, Näslund E. Nationwide cohort study of post-gastric bypass hypoglycaemia including 5,040 patients undergoingsurgery for obesity in 1986-2006 in Sweden. Diabetologia. 2010;53:2307-2311.*
8. *Service GJ, Thompson GB, Service FJ, et al. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. N Engl J Med 2005; 353:249.*
9. *Patti ME, McMahon G, Mun EC, et al. Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. Diabetologia 2005; 48:2236.*
10. *Pongprasobchai S1, Lertwattanarak R, Pausawasdi N, Prachayakul V.Diagnosis and localization of insulinoma in Thai patients: performance of endoscopic ultrasonography compared to computed tomography and magnetic resonance imaging.J Med Assoc Thai. 2013 Feb;96 Suppl 2:S187-93.*
11. *Scott M. Thompson, Adrian Vella, Geoffrey B. Thompson, Kandelaria M. Rumilla,F. John Service, Clive S. Grant, and James C. Andrews. Selective Arterial Calcium Stimulation With HepaticVenous Sampling Differentiates Insulinoma From Nesidioblastosis. J Clin Endocrinol Metab, November 2015, 100(11):4189–4197*
12. *Rodrigo O. Moreira & Rustan B. M. Moreira &Nikolas A. M. Machado & Tatiana B. Gonçalves &Walmir F. Coutinho. Post-prandial Hypoglycemia after Bariatric Surgery:Pharmacological Treatment with Verapamil and Acarbose*
13. *Pongprasobchai S1, Lertwattanarak R, Pausawasdi N, Prachayakul V.Diagnosis and localization of insulinoma in Thai patients: performance of endoscopic ultrasonography compared to computed tomography and magnetic resonance imaging.J Med Assoc Thai. 2013 Feb;96 Suppl 2:S187-93.Pongprasobchai S1, Lertwattanarak R, Pausawasdi N, Prachayakul V.*
14. *Nina Guseva, MD1, David Phillips, MD2, and John P. Mordes, MD1. SUCCESSFUL TREATMENT OF PERSISTENT HYPERINSULINEMIC HYPOGLYCEMIA WITH NIFEDIPINE IN AN ADULT PATIENT. Endocr Pract. 2010 ; 16(1): 107–111. doi:10.4158/EP09110.CRR.*
15. *Alessandra Eifler Guerra Godoy , Rafael Giovanardi , Francine Hehn de Oliveira , Eduardo Pretto Serafini :Adult Nesioblastosis: Case Report .Applied cancer research Vol 28, No 3(2008)*
16. *Witteles RM, Straus II FH, Sugg SL, Koka MR, Costa EA,Kaplan EL. Adult-onset nesidioblastosis causing hypoglycemia: an important clinical entity and continuing treatment dilemma. Arch Surg 2001; 136: 656-663.*
17. *Clancy TE, Moore FD Jr, Zinner MJ. Post-gastric bypass hyperinsulinism with nesidioblastosis: subtotal or total pancreatectomy may be needed to prevent recurrent hypoglycemia. J Gastrointest Surg 2006; 10:1116.*

18. *Vanderveen KA, Grant CS, Thompson GB, et al. Outcomes and quality of life after partial pancreatectomy for noninsulinoma pancreatogenous hypoglycemia from diffuse islet cell disease. Surgery 2010; 148:1237.*

19. *Mohammed Qintar, Firas Sibai,1 and Mohammad Taha1: Hypoglycemia due to an adult-onset nesidioblastosis, a diagnostic and management dilemma :Avicenna J Med. 2012 Apr-Jun; 2(2): 45–47.doi: 10.4103/2231-0770.99164*

20. *A Raffel, M Anlauf, SB Hosch, M Krausch, T Henopp, J Bauersfeld, R Klofat, D Bach, CF Eisenberger, G Klöppel,WT Knoefel . Hyperinsulinemic hypoglycemia due to adult nesidioblastosis in insulin-dependent diabetes. World J Gastroenterol 2006 November 28; 12(44): 7221-7224*

Clinical	Insulinoma	Nesidioblastosis
Sign	Fasting hypoglycemia	Postprandial hypoglycemia
Age	Adult 50 yr	Mostly neonatal
Incident	0.7-4 per million	0.5-7% in hyperinsulinemic hypoglycemis
Insulin ,c-peptide	High Mass	High Islet cell hyperplasia
72hr fasting	Mostly positive	Mostly negative
Gene mutation	MEN1[10%]	SUR1,Kir6.2,GCK, GLUD1,rareMEN1
Treatment	enucleation	Partial panceatectomy Medication

	NIPHS	PGBH
sex	Young male	Female post Sx
symptom	severe postprandial hypoglycemia	severe postprandial hypoglycemia
plasma glucose	Low	Low
insulin	High	High
C-peptide	High	High
X-ray localization	negative	negative
treatment	• Pancreatectomy • Medications response in mild form	• Try treat medication: Octreotide, verapami, diazoxide,acarbose • Reversal of gastric bypass to sleeve gastrectomy • Pancreatectomy (rare)