Virchows Arch (2000) 436:481–486

ORIGINAL ARTICLE

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Adult hyperinsulinemic hypoglycemia not caused by an insulinoma: a report of two cases

Received: 5 July 1999 / Accepted: 19 January 2000

Abstract Nesidioblastosis is rare in adults and accounts for 0.5–5% of cases of organic hyperinsulinemia. The diagnosis of nesidioblastosis should be considered when peroperative imaging modalities fail to localize a lesion in patients with hyperinsulinism. Two female patients, aged 55 and 16 years, with hyperinsulinemic hypoglycemia are reported. Somatostatin receptor scintigraphy showed slight focal activity in both patients. The first patient underwent a Whipple procedure and became diabetic. The second patient underwent a distal hemi-pancreatectomy and suffered from recurrent hypoglycemic episodes 3 months after surgery, for which she is presently being treated with octreotide. Histological examination of the resected pancreata revealed focally increased islet tissue and a number of slightly hypertrophic beta cells. Such histological abnormalities have been related to functional changes of β-cells. In infantile nesidioblastosis, a proportion of cases has been associated with mutations in one of several genes. Whether such mutations, leading to hyperinsulinism, also play a role in adult nesidioblastosis is presently unknown.

Key words Adults · Hyperinsulinemia · Hypoglycemia · Nesidioblastosis

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Introduction

Hyperinsulinism, although rare, is the most common cause of persistent neonatal hypoglycemia. Neonates with hyperinsulinism may have either focal or diffuse abnormalities of the pancreatic beta cells [5, 14]. In adults, insulinoma is the most common cause of persistent hyperinsulinemic hypoglycemia (PHH), while diffuse beta cell abnormalities are the exception.

Laidlaw coined the term nesidioblastosis in 1938 to characterize the neogenesis of islet cells from pancreatic duct epithelium [11], but the term is now usually used as a diagnostic term in patients with hyperinsulinemia without localized pancreatic lesions such as insulinomas.

Nesidioblastosis in adults has been described in hyperinsulinemic conditions and in association with other disorders: chronic pancreatitis, pancreatic duct obstruction, cystic fibrosis, gastrinoma, multiple endocrine neoplasia (MEN I) and sulfonylurea therapy. In adults with hyperinsulinemic hypoglycemia there are so few cases of nesidioblastosis that their relationship is still a matter of controversy [25]. The diagnosis of nesidioblastosis should be considered when imaging modalities fail to localize a lesion. The use of somatostatin receptor scintigraphy (SRS) in patients with nesidioblastosis has never been described in the literature. There is also little experience in the use of octreotide in adult-onset PHH.

In this report we describe the clinical and histological characteristics of two patients with PHH in the absence of an insulin-producing tumor and discuss the diagnostic (e.g. SRS, venous sampling) and therapeutic options.

Case histories

Case 1

A 55-year-old woman was admitted after she had been found unconscious by her husband. For 1 year before admission she had had episodes of profound weakness associated with sweating,

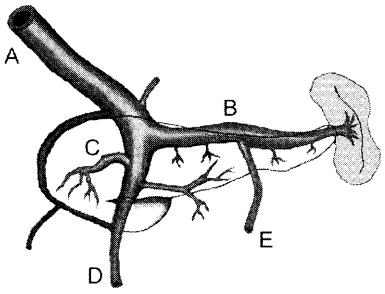


Fig. 1 Measurement of insulin levels by venous sampling

	portal vein (A)	Splenic vein(B)	uncinate vein (C)	inf.mes.vein(D)	sup.mes. vein(E)
case 1	280[a]	70	480	NM[b]	370
case 2	51	496	NM	NM	16

[a]Insulin levels in mU/l

[b]NM = not measured

tremors and confusion. The attacks resolved after eating, and she had gained 10 kg in weight in 1 year. There was a family history of diabetes in her mother and grandmother. Her medical history revealed: urolithiasis, Guillain-Barré syndrome, hypertension, primary hypothyroidism. Her medication list included: omeprazol, felodipine and levo thyroxine. She had never used sulfonylureas. She smoked 40–50 cigarettes a day. Her serum glucose in the emergency room was 2.6 mmol/l. Following an intravenous injection of hypertonic glucose she promptly regained consciousness. During a 24-h fast she developed tonic-clonic movements of her extremities with a serum glucose of 1.1 mmol/l and serum insulin 89.6 mu/ml. The C-peptide level measured excluded an exogenous source of insulin. A few days later she was transferred to the University Hospital Rotterdam, with a putative diagnosis of insulinoma. Parenteral glucose infusion was started, and the patient remained euglycemic. Physical examination revealed no other abnormalities than obesity. Baseline biochemistry and hematology laboratory values were unremarkable, as were TSH and AM cortisol levels. An ACTH stimulation test was normal. Ultrasound examination and a dynamic CT scan did not show any nodules in the pancreas. SRS revealed slightly higher activity in the pancreatic head. To determine a localized lesion a laparoscopy with intraoperative ultrasound was performed, but no tumor was found. Subsequently an exploratory laparotomy was performed, with intraoperative ultrasound and manual palpation of the pancreas. Again no tumor was found. Venous sampling showed elevated insulin concentrations in the pancreatic head, especially in the uncinate process (Fig. 1). Because of the elevated insulin concentrations in the pancreatic head, 2 days later a pancreaticoduodenectomy was performed, removing 80% of the pancreas. On palpation there was a possible nodule in the pancreatic head. Frozen section examination of the suspected lesion revealed no insulinoma. Macroscopic examination of the pancreas showed mild chronic pancreatitis. The patient had an uneventful recovery. Three and half weeks after surgery the patient had a normal diet and was euglycemic. However, 4 months after discharge she developed insulin-dependent diabetes with blood sugars >10 mmol/l, for which she is being treated with insulin.

Case 2

In April 1995, a 16-year-old girl was admitted because of a sudden loss of consciousness. Three months before she had had an episode of weakness, dizziness and heavy sweating, which relieved spontaneously. Otherwise she was in good health with no relevant past medical history and was not taking any medication. Her father suffered from type II diabetes mellitus. An EEG showed epileptic activity. She underwent a brain CT, which revealed no abnormalities. Meningitis was excluded. Baseline biochemistry and hematology, including blood glucose (3.0 mmol/l), TSH and AM cortisol levels were normal. An ACTH stimulation test was normal. Subsequently she had several seizures accompanied by low blood glucose levels (0.8–1.5 mmol/l) and a serum insulin of 298 mu/l. The C-peptide level measured excluded an exogenous source of insulin. A glucose infusion was started. Abdominal ultrasound, CT, MRI scans and pancreatic arteriogram revealed no abnormalities. The patient was then transferred to the University Hospital Rotterdam with a diagnosis of hyperinsulinemic hypoglycemia with no detectable insulinoma. A SRS revealed slightly higher activity in the pancreatic tail (Fig. 2). An exploratory laparotomy was performed, and intraoperative ultrasound was normal. The pancreas was also palpated but no tumor was found. Venous sampling showed an elevated insulin concentration in the region of the pancreatic tail (Fig. 1). The next day a hemi-pancreatectomy was performed with resection of the tail and a part of the body of the pancreas, amounting to 50% of the parenchyma. Macroscopic examination of the resected pancreas revealed no focal abnormalities. She had an uneventful recovery, and during a 24-h fast her lowest blood glucose level was 2.6 mmol/l.

Six months later she was admitted again with symptoms of hypoglycemia. Her blood glucose level was 2.2 mmol/l and the insulin level, 182.7 mu/l. Diazoxide therapy was initiated (1 daily dose 100 mg), and the girl became euglycemic (blood glucose levels remained in the range of 5.3–7.5 mmol/l). After 3 months' diazoxide therapy she had gained 18 kg in weight. Therefore this therapy was stopped and octreotide treatment (50–50–100 µg s.c.) was started. At present, the patient's weight is stable, her blood glucose levels are within the normal range, and she has no symptoms of hypoglycemia.

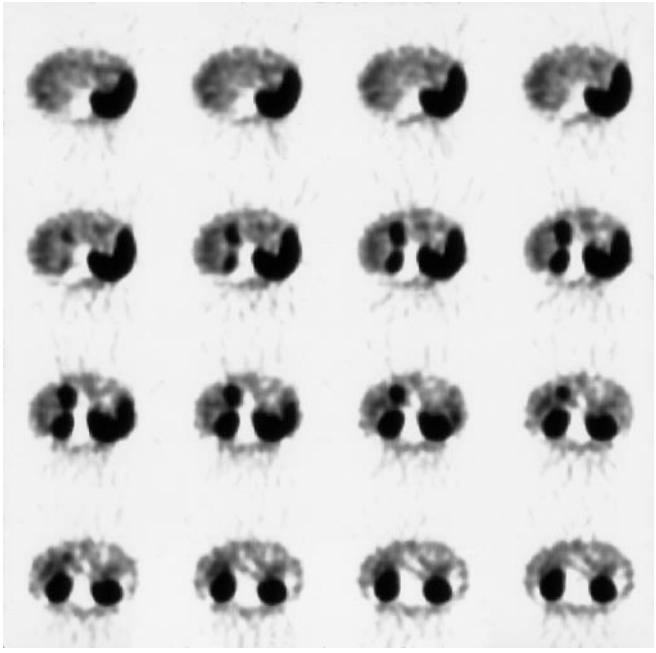


Fig. 2 SPECT images from SRS in patient 2. Images run from cranial (*top left*) to caudal (*bottom right*). *Right side* of image is left side of patient. Normal uptake in the liver and spleen (*top row*), gallbladder (*second row*), and kidneys (*lower three rows*). In *images 2–4* in the *second row*, slightly increased uptake is seen ventral to the left kidney

Materials and methods

Both histological and immunohistochemical methods were used. Pancreatic resection specimens were sliced completely in slices 2–4 mm thick. Multiple blocks were taken from all regions of the pancreatic resection specimens. All blocks were step-sectioned. Sections 5 µm thick were deparaffinized and stained with hematoxylin and eosin according to standard methods. For immunohistochemistry, sections were incubated for 30 min at room temperature with antibodies to insulin (1:500, Dako, Glostrup, Denmark), glucagon, somatostatin, chromogranin-A and pancreatic polypeptide (1:40, 1:2000, 1:150, and 1:10.000 respectively, Dako). Then sections were washed and a biotinylated goat-anti-multilink (1:50, Klinipath Biogenex, Uden, The Netherlands) with 2% normal human serum and 2% normal goat serum (Dako) was added for 30 min, followed by the avidin–biotin complex (1:50, Klinipath Biogenex) for 30 min. Sections were developed with diamino-benzidine tetrahydrochlorate (Fluka, Neu-Ulm, Germany) with 0.3% H_2O_2 for 7 min, counterstained, dehydrated, and mounted. Negative controls included replacement of primary antisera by phosphate-buffered saline.

Results

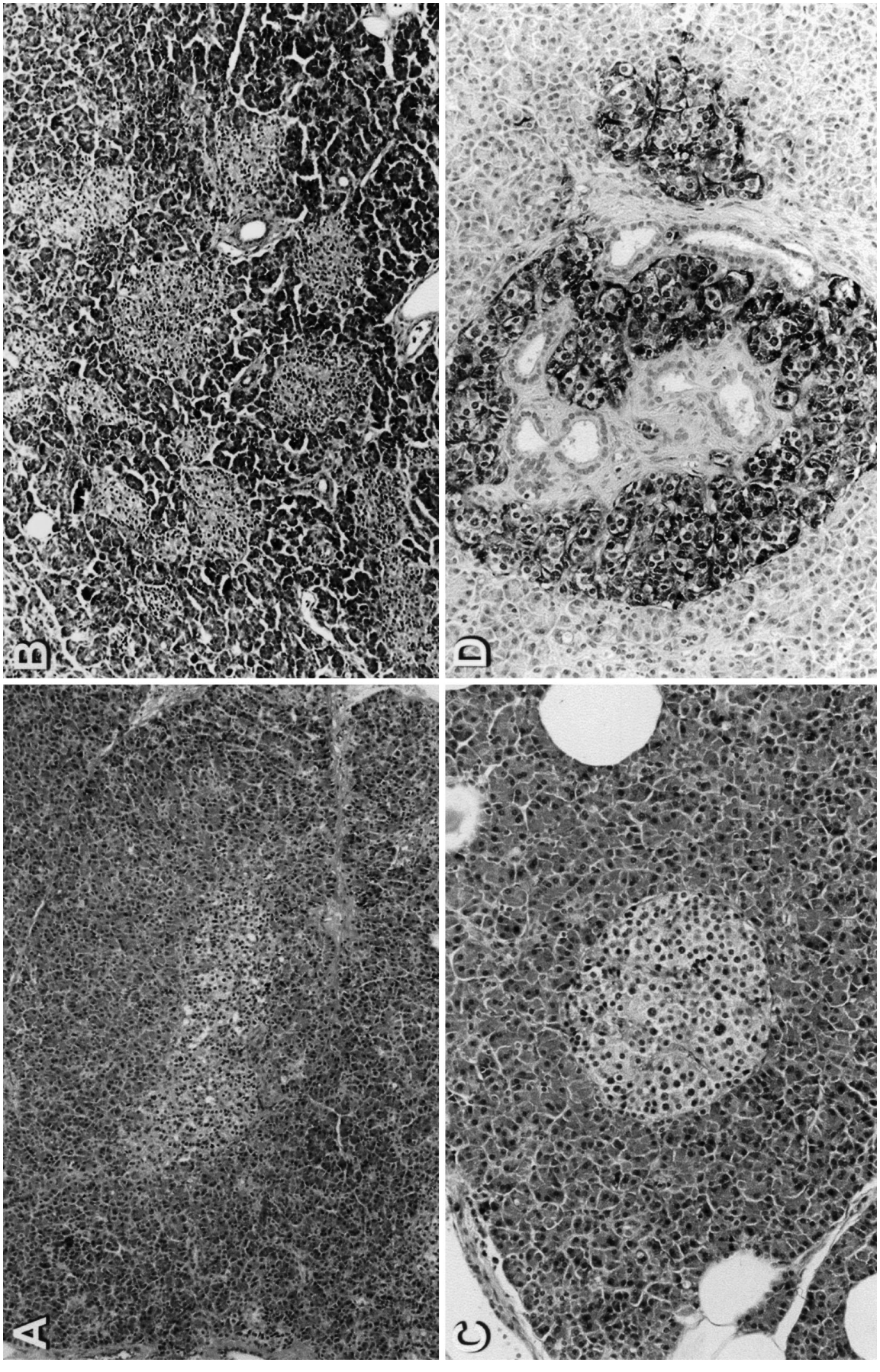
Histopathology of the pancreatic resection specimens showed similar findings in all samples from both cases. There were many islets of Langerhans, some of which appeared to be irregular in outline and increased in size (Fig. 3A). Also, the total amount of endocrine tissue (islets of all sizes and smaller endocrine cell clusters) appeared to be increased (Fig. 3B). In some islets, nuclei of a proportion of the insulin-producing ß-cells were enlarged (Fig. 3C). In the immunohistochemical analysis, insulin showed strong immunoreactivity in all slides, indicating that the majority of the histologically identified islets of Langerhans and endocrine cell groups were composed of insulin-producing β-cells. Many single insulin-reactive cells were identified, even in the walls of ducts, as were so-called ductulo-insular complexes (Fig. 3D). The numbers and distribution of glucagon, somatostatin-reactive and pancreatic polypeptide cells were normal.

Discussion

Since the clinical and biochemical presentation of nesidioblastosis in adults mimics insulinoma, the diagnosis is usually made postoperatively by histology [13]. Fasting hypoglycemia is present in most patients with organic hyperinsulinism. When it is absent, a prolonged fast (between 14 and 72 h) will reveal hypoglycemia in nearly 100% of cases [25]. With a putative diagnosis of insulinoma, localization studies, such as dynamic CT scanning, celiac angiography, endoscopic ultrasonography and transhepatic portal venous sampling, are undertaken. However, none of these methods is completely adequate, and each may result in diagnostic errors [8]. In fact, preoperatively, it may be impossible to distinguish nesidioblastosis from insulinoma in adults. Percutaneous transhepatic selective intravenous sampling and direct intraoperative pancreatic venous sampling have both been used to differentiate hyperinsulinism caused by an insulinoma from that caused by nesidioblastosis [16]. Portal transhepatic venous sampling did detect two of five reported cases with nesidioblastosis, but sometimes nesidioblastosis presents an insulinoma-like gradient [13]. The present cases both presented with an insulinoma gradient. SRS is a technique that has been shown to localize both primary islet cell tumors and metastases with high sensitivity (80%) [2]. The detection rate for insulinomas is about 50% and is related to the low incidence of somatostatin receptor subtype 2A on insulinoma cells. Positive scan results predict a suppressant effect of octreotide on hormone secretion from endocrine-active tumors [10]. In both cases presented in this paper there was a slightly higher activity on SRS in the pancreatic head or tail, with subsequent higher insulin levels on venous sampling. The role of SRS in diagnosing adult nesidioblastosis should be evaluated further.

Frozen section examination has been reported not to be useful in most instances of nesidioblastosis in adults [16], in contrast to infants [14, 19]. In infants, partial pancreatectomy with excision of the diseased focus is the treatment of choice for patients with focal nesidioblastosis [5, 15, 18], whereas neonates with diffuse lesions require near-total pancreatectomy [5, 14].

In adults a lesser (~70%) pancreatectomy has been recommended, utilizing diazoxide if postoperative hypoglycemia recurs, and reserving extensive resection when the limited operation and medication fails [22]. Our first


B
D
A
C

patient underwent a pancreatoduodenectomy and became diabetic, indicating a too-extensive resection. However, there have been many reports of recurrent hypoglycemia even after 95% resection of the pancreas [22]. Since there was a family history of type II diabetes and the patient remained obese, it is possible that the partial pancreatectomy not only cured the patient of hyperinsulinism, but also precipitated diabetes. Our second patient underwent a distal hemi-pancreatectomy and was suffering from hypoglycemic episodes again 3 months after surgery. She is now euglycemic with octreotide therapy. There is little experience with the use of octreotide in adult-onset nesidioblastosis. In insulinoma, Lamberts et al. [12] have reported that its use is associated with exacerbations of hypoglycemia.

While the initial morphometric evaluations seemed to reveal an increase in islet tissue and insulin cells [6, 9, 23], more recent studies have demonstrated that in the majority of patients the volume density of endocrine tissue or insulin-producing β-cells is not significantly increased [7, 20, 27]. Although histological examination of the resected specimen appeared to show an increase in the amount of endocrine tissue in our cases, this cannot be concluded without morphometrical analysis. Because somatostatin normally exerts a negative paracrine effect on islet cell function, it has been suggested that islet proliferation may result from reduced somatostatin secretion by pancreatic D-cells [3]. In our cases no abnormalities of islet non-beta-cells were noted.

In agreement with previously published cases of adult and infantile nesidioblastosis, the nuclei of a proportion of the insulin-producing β-cells were enlarged [1]. In addition, there were many islets of Langerhans, some of which appeared to be irregular and increased in size. Such histological abnormalities have been related to functional defects of β-cells. In infantile nesidioblastosis, a proportion of cases have been associated with mutations in genes encoding the sulfonylurea receptor type I (*SUR1*), the inward-rectifying potassium channel ($K_{IR}6.2$), and the glucokinase (*GK*) or glutamate dehydrogenase (*GLUD*) gene [4, 17, 24, 26]. It has been speculated that histological abnormalities such as those described in the present two adult patients may be related to gain-of-function mutations in the *GK* or *GLUD* genes [21]. Whether such mutations indeed lead to hyperinsulinism in adults remains to be analyzed.

Acknowledgements The authors would like to thank Dr. J. Rahier and Prof. Dr. G. Klöppel for their expert consultation of both cases.

◀ **Fig. 3** **A** Pancreatic resection specimen from patient 1, showing a large islet of Langerhans with irregular outline and shape. Hematoxylin and eosin **B** Pancreatic resection specimen of patient 2. The increase in islet tissue is well appreciated in this section. Hematoxylin and eosin **C** Pancreatic resection specimen of patient 1. Frequently, islets had several β-cell nuclei that were enlarged, compared with neighboring cells. Hematoxylin and eosin **D** Pancreas of patient 1, showing an extensive ductulo-insular complex in which several ductal structures are surrounded by an endocrine cell conglomerate. Chromogranin-A, immunohistochemical staining

References

1. Albers N, Lõhr M, Bogner U, Loy V, Klöppel G (1989) Nesidioblastosis of the pancreas in an adult with persistent hyperinsulinemic hypoglycemia. Am J Clin Pathol 91:336–340
2. Eijck CHJ van, Bruining HA, Reubi JC, Bakker WH, Oei HY, Krenning EP, Lamberts SWJ (1993) Use of isotope labelled somatostatin analogs for visualization of islet cell tumors. World J Surg 17:444–447
3. Fong T, Warner NE, Kumar D (1989) Pancreatic nesidioblastosis in adults. Diabetes Care 12:108–113
4. Glaser B, Kesavan P, Heyman M, et al (1998) Familial hyperinsulinism caused by an activated glucokinase mutation. N Engl J Med 338:226–230
5. Goossens A, Gepts W, Saudubray J-M, Bonnefont JP, Nihoul-Fekete, Heitz PU, Klöppel G (1989) Diffuse and focal nesidioblastosis. A clinicopathological study of 24 patients with persistent neonatal hyperinsulinemic hypoglycemia. Am J Surg Pathol 13:766–775
6. Heitz PU, Klöppel G, Hacki WH, Polak JM, Pearse AGE (1977) Nesidioblastosis: the pathologic basis of persistent hyperinsulinemic hypoglycemia in infants. Morphologic and quantitative analysis of seven cases based on specific immunostaining and electron microscopy. Diabetes 26:632–642
7. Jaffe R, Hashida Y, Yunis EJ (1980) Pancreatic pathology in hyperinsulinemic hypoglycemia of infancy. Lab Invest 42: 356–365
8. Kim HK, Shong YK, Han DJ, Cho Y, Lee IC, Kim GS (1996) Nesidioblastosis in an adult with hyperinsulinemic hypoglycemia. Endocr J 43:163–167
9. Klöppel G, Althenar E, Reichel W, Willig R, Freytag G (1974) Morphometric and ultrastructural studies in an infant with leucine-sensitive hypoglycemia, hyperinsulinism and islet hyperplasia. Diabetologica 10:245
10. Krenning EP, Kwekkeboom DJ, Pauwels S, Kvols LK, Reubi JC (1995) Somatostatin receptor scintigraphy. Nuclear medicine annual 1–50
11. Laidlaw G (1938) Nesidioblastoma, the islet tumor of the pancreas. Am J Pathol 14:125–134
12. Lamberts SWJ, van der Lely AJ, de Herder WW, Hofland LJ (1998) Octreotide exacerbated fasting hypoglycemia in a patient with a proinsulinoma: the glucostatic importance of pancreatic glucagon (commentary). Clin Endocrinol 43:120–122
13. Lee WL, Won JGS, Chiang JH, Hwang JI, Lee CH, Tsay SH (1997) Selective intra-arterial calcium injection in the investigation of adult nesidioblastosis: a case report. Diabet Med 14: 985–988
14. de Lonlay-Debeney P, Poggi-Travert F, Fournet JC et al. (1999) Clinical features of 52 neonates with hyperinsulinism. N Engl J Med 340:1169–1175
15. Lyonnet S, Bonnefort JP, Saudubray JM, Nihoul-Féketé C, Brunelle F (1989) Localisation of focal lesion permitting partial pancreatectomy in infants. Lancet II:671
16. McHenry C, Newell K, Chejfec G, Barbato A, et al (1989) Adult nesidioblastosis: an unusual cause of fasting hypoglycemia. Am Surg 55:366–369
17. Nestorowicz A, Inagaki N, Gonoi T, et al (1997) A nonsense mutation in the inward rectifier potassium channel gene, Kir6.2, is associated with familial hyperinsulinism. Diabetes 46:1743–1748
18. Poggi-Travert F, Rahier J, Brunelle F, Féketé C, Saudabray JM (1994) Hyperinsulinismes de l'enfant: à propos d'une serie de 56 cas (1984–1994). (Journées parisiennes de pédiatrie) Flammarion Médecine-Sciences, Paris, pp 29–42
19. Rahier J, Sempoux C, Fournet JC, Poggi F, Brunelle, F Nihoul-Fekette C, Saudubray JM, Jaubert F (1998) Partial or near-total pancreatectomy for persistent neonatal hyperinsulinemic hypoglycemia: the pathologist's role. Histopathology 32:15–19
20. Rahier J, Falkmer S, Falt K, Muntefering H, Becker K, Gepts W (1984) The basic structural lesion of persistent neonatal hypoglycemia with hyperinsulinism: deficiency of islet

somatostatin cells or hyperactivity of insulin cells? Diabetologia 26:282–289
21. Reinecke-Lûtghe A, Koschoreck F, Klöppel G (2000) The molecular basis of persistent hyperinsulinemic hypoglycemia of infancy and its pathological substrates. Virchows Arch 436:1–5
22. Rinker RD, Friday K, Aydin F, Jaffe BM, Lambiase L (1998) Adult nesidioblastosis. A case report and review of the literature. Dig Dis Sci 43:1784–1790
23. Sovik O, Vidnes V, Falkmer S (1975) Persistent neonatal hypoglycemia. A clinical and histopathological study of three cases treated with diazoxide and subtotal pancreatectomy. Acta Pathol Microbiol Scand [A] 83:155
24. Stanley CA, Lieu YK, Hsu BLY, et al (1998) Hyperinsulinemia and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. N Engl J Med 338: 1352–1357
25. Tibaldi JM, Lorber D, Lomasky S, Steinberg JJ, Reisman R, Shamoon H (1992) Postprandial hypoglycemia in islet beta cell hyperplasia with adenomatosis of the pancreas. J Surg Oncol 50:53–57
26. Verkarre V, Fournet JC, de Lonlay P, et al (1998) Paternal mutation of the sulfonylurea receptor (SUR1) gene and maternal loss of 11p15 imprinted genes lead to persistent hyperinsulinism in focal adenomatous hyperplasia. J Clin Invest 102: 1286–1291
27. Witte DP, Greider MH, Deschrijver-Kecskemeti K, Kissane JM, White MH (1984) The juvenile human endocrine pancreas: normal versus idiopathic hyperinsulinemic hypoglycemia. Semin Diagn Pathol 1:30