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# Nesidioblastosis in adults

*Minireview*

I. DRAVECKA*, I. LAZUROVA

*Internal Medicine, Pavol Jozef Safarik University Hospital, Kosice, Slovakia*

**Correspondence: ingrid.dravecka@upjs.sk*

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The persistent hyperinsulinemic hypoglycemia may be caused either by a solitary tumor of the pancreas secreting excessive amount of insulin, known as insulinoma or, rarely, by nesidioblastosis. Nesidioblastosis is a rare cause of persistent hyperinsulinemic hypoglycemia in adults. The incidence of nesidioblastosis in adults is unknown, but it is generally thought to be very low. The β cell changes in adult nesidioblastosis suggest a dysregulation of the function of the cell. The cause of the functional dysregulation in adults is unknown. The pathogenesis of adult nesidioblastosis may be different from infantile congenital hyperinsulinism caused by a genetic effect. Histologically nesidioblastosis is almost always characterized by a proliferation of abnormal β cells throughout the entire pancreas. Clinically and biochemically , it is not possible to distinguish between diffuse nesidioblastosis and insulinoma. If all highly selective noninvasive imaging techniques fail to identify a tumor, selective arterial calcium stimulation testing should be performed. The final diagnosis relies on the histopathologic evaluation. The treatment of adult nesidioblastosis is surgical resection of the pancreas.

*Key words: hyperinsulinemic hypoglycemia, nesidioblastosis, insulinoma, pancreatectomy*

Maintainng the plasma glucose level within the narrow physiological range is a basic condition of health. Extended hypoglycemia is extremly dangerous because glucose is the most crucial energy substrate for the brain. Hyperinsulinism represents the most important cause of hypoglycemia following excesive consumption of glucose. It is most frequently found in the course of insulinoma and nesidioblastosis, less frequently in myelomas, lymphomas, or leukemias, and relatively rarely in tumors generating insulin-like growth factor-2 (IGF-2) [1]. Organic persistent hyperinsulinemic hypoglycemia (PHH) is a disorder of the endocrine pancreas that occurs in newborns and adults [2]. In adults, PHH may be caused either by a solitary insulinoma or, rarely, by nesidioblastosis [3]. The term "nesidioblastosis" was coined by Laidlaw in 1938 to emphasize that in this condition cells differentiate and bud from the pancreatic ductal epithelium to form new islet tissue, but it also encompasses broad „pathological overgrowth" of pancreatic islet cells [2,4]. Since then a variety of names, including islet cells hyperplasia, ductuloinsular proliferation, islet cell adenomatosis, endocrine cell dysplasia, and nesidioplasia, have been applied to describe these pancreatic islet changes leading to a clinical symptoms of insulinoma [5]. Our knowledge of the pathogenesis of this disease has grown in recent years. A number of genetic abnormalities underlie the disease. Postgastric bypass patients with nesidioblastosis represent a new and growing number of cases in adults.

## Incidence

β cells nesidioblastosis and hyperplasia are rare and cause neonatal hyperinsulinemic hypoglycemia as well as adult noninsulinoma pancreatogenous hypoglycemia syndrome [4]. The incidence of nesidioblastosis in adults is unknown, but it is generally thought to be very low. Since the first reported case of nesidioblastosis in 1975 fewer than 100 patients have been described [2,3,6]. Other authors estimate a relative frequency

of 0,5-7 % of PHH with a slowly rising tendency suggesting that diffuse nesidioblastosis is not as infrequent as thought [1,2,3,7,8]. Recently several cases of adult patients with PHH have been increasingly observed in whom no insulinoma could be detected and whose PHH improved after partial resection of the pancreas [6]. The low number of patients suggests that the relative frequency of PHH in adults who are not suffering from insulinoma is very low, but precise figures do not exist.

## Etiology and pathogenesis

The β cell changes in adult nesidioblastosis suggest a dysregulation of the function of the cell, as there is no evidence of a neoplastic process. Unfortunately the cause of the functional dysregulation is unknown. Some authors suggest a genetic effect, like in neonates with congenital hyperinsulinism, or a reactive process that occurs in response to the metabolic and hormonal changes due to the substantial weight loss after gastric bypass surgery for morbid obesity [3,4,9]. Geoffrey et al described six patients with postprandial symptoms of neuroglycopenia owing to endogenous hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass surgery. There was no radiologic evidence of insulinoma. After partial pancreatectomy nesidioblastosis was identified in resected specimens from each patient, and multiple insulinomas were identified in one of them. Authors speculate that hyperfunction of pancreatic islets did not lead to obesity, however beta-cell trophic factors may have increased as a result of gastric bypass [10]. The risk of recurrent symptomatic hyperinsulinism after limited pancreatectomy in patients with post-gastric bypass nesidioblastosis is significant and relative euglycemia may be achieved with subtotal or total pancreatectomy [11]. Rumilla et al analyzed 36 cases of nesidioblastosis including 27 cases of postgastric bypass nesidioblastosis and 9 cases of idiopathic nesidioblastosis in adults. There was found an increase in IGF2 (insulin-like growth factor2), insulin-like growth factor receptor1 receptor-α and transforming growth factor-β receptor 3 expression in islets from nesidioblastosis patients compared to controls. Increased expression of IGF2 has been identified in the idiopathic nesidioblastosis group compared to postgastric bypass group. Authors concluded that an increased production of growth factors and an increased amount of growth factor receptors may contribute to the development of nesidioblastosis in adults [9]. In patients with PHH after gastric bypass surgery because of morbid obesity, elevated glucagon-like peptide 1 release was found in response to meal. Interestingly, in rodents, glucagon-like peptide 1 seems to have an effect on islet cells neogenesis and β-cell apoptosis, thereby producing islet hyperplasia. Therefore, it has been suggested that in some patients the special hormonal situation caused by weight loss after gastric bypass operations might unmask a β-cell defect that promotes hyperinsulinism and islet hyperplasia [3]. However, some of genes including *ABCC8* (formerly *SUR1), KCNJ11 (*formerly *Kir6.2), GCK, GLUD1*, and short-chain 3-hydroxyacyl CoA dehydrogenase that are commonly affected in congenital hyperinsulinism has been reported in adult nesidioblastosis too. These abnormalities result in a loss of gene function leading to a permanent stimulation of insulin secretion [2,3,6,9]. The lack of recognised mutations in most adult cases suggest that the pathogenesis of adult nesidioblastosis may be different from infantile nesidioblastosis [9]. The pathohistologic appearance and genetic background of nesidioblastosis in adults is not as well defined as in children. Patients have been shown to lack *SUR1/Kir6.2* gene mutations, and further genetic studies are needed. Occassionaly, nesidioblastosis has been observed in patients after gastric bypass surgesy.

## Histology

Despite these facts the histopathologic criteria are still unclear or even questionable [2]. Grossly the pancreatic tissue of patients with adult nesidioblastosis looks normal. On histopathologic evaluation the lobular architecture of the exocrine parenchyma is usually preserved and the alterations in the endocrine pancreas may vary from patient to patient [3]. Nesidioblastosis is almost always characterized by a proliferation of abnormal β cells throughout the entire pancreas [7]. Histologic features of nesidioblastosis include enlarged islet size and number, increased periductular islets, enlarged beta-cell nuclei and abundant clear cytoplasm [3,6,9], respectively. In patients with severe PHH after gastric bypass surgery for morbid obesity, changes of the endocrine pancreas are similar to those seen in adults with PHH but without gastric bypass surgery [3,9]. Pancreatic endogenous lesions have been referred to as diffuse or focal nesidioblastosis [5,6], which is found in about 40% of newborns with congenital hyperinsulinism, however it has rarely been described in adults [3]. Histological examination is a useful feature that can assist in the diagnosis. Table 1 shows major histopathological criteria for nesidioblastosis.

## Diagnosis

It is very difficult to diagnose diffuse nesidioblastosis in adults on the basis of clinical features [3]. Clinically and biochemically , it is not possible to distinguish between diffuse nesidioblastosis and insulinoma [6,12]. Hypoglycemic

**Table 1. Major histopathologic criteria for the diagnosis of diffuse nesidioblastosis in adults [2]**

| Major criteria |
|---|
| • Macroscopic, microscopic, and immunohistochemical exclusion of an insulinoma |
| • Multiple β-cells with enlarged and hyperchromatic nucleus and abundant clear cytoplasm in the majority of the islets |
| • Islets with normal spatial distribution and regular hormone expresion patterns of the various cell types |
| • No proliferative activity of the Ki-67 antigen (Mib-1) of endocrine cells |

symptoms commonly develop not during fasting but rather postprandially, that is, a few hours after consuption of a meal. When insulinoma or factitious hypoglycemia is excluded, and selective arterial calcium stimulation test demonstrates an abnormal insulin response from all parts of the pancreas, PHH due to adult nesidioblastosis is the most likely cause. The final diagnosis relies on the histopathologic evaluation [3]. The intraarterial calcium stimulation test with hepatic venous sampling facilitates diagnosis and guide surgical intervention, and the subsequent resection specimen confirmed the diagnosis of nesidioblastosis. In this procedure, arteries supplying the pancreas are cannulated with the subsequent injection of intra-arterial calcium gluconate, a pancreatic secretagogue which stimulates insulin release [2,5,13]. To date, it is very difficult to diagnose diffuse nesidioblastosis in adults on the basis of clinical features. An indication of adult nesidioblastosis is the development of hypoglycemic symptoms not during fasting but rather postprandial. The final diagnosis, however, relies on the pathologic analysis of the pancreatic tissue. The differences between nesidioblastosis of neonates and adults are described in table 2.

## Clinical presentation

The clinical presentation of organic hyperinsulinism ranges from mental retardation and life-threatening hypoglycemic attacks in neonates to adult patients presenting hypoglycemia symptoms during fasting, similarly to the patients with insulinoma-dependent hypoglycemia. This makes clinical differention of adult nesidioblastosis from an insulinoma markedly difficult. However, in contrast to patients with insulinomas, such symptoms may also occur postprandially [8]. Patients are usually presented with severe neuroglycopenic symptoms (loss of consciousness, seizures, vertigo and cofusion) and symptoms caused by hypoglycemia-induced catecholamine response (sweating, tremor and hunger) [14]. Nesidioblastosis cannot be reliably differentiated from insulinoma by clinical signs and symptoms, and it can be quite difficult to diagnose prior to surgery.

**Table 2. Nesidioblastosis: differences between neonates and adults [8]**

| Parameter | Neonates | Adults |
|---|---|---|
| Causes | Autosomal recesive and dominant forms affecting *SUR1* gene, *Kir6.2* gene, *GCK* gene, GLUD1 gene, H19-IGF2, P257KIP2 | Genetic causes widely unknown, MEN-1 syndrome, *SUR1* and *Kir6.2* gene not affected |
| Frequency | Sporadic: 1/50 000 births<br>Familial: up to 1/2500 births | Unknown, up to 10% of organic hyperinsulinism (0,09/100 000) |
| Histologic findings | Hypertrophic beta cells and islets, Beta cell with pleomorphic nuclei, ductuloinsular complexes, neoformation of islets from ducts | Hypertrophic beta cells and islets, beta cells with pleomorphic nuclei, ductuloinsular complexes, neoformation of islets from ducts |
| Diagnosis | Glycemic response to glucagons<br>Absence of ketonuria,<br>Blood ammonia concentration | Serum glucose <2,2 mmol/l<br>Insulin >6 uU/ml<br>Positive 72 hour fasting test |
| Preoperative localization | Percutaneous transhepatic pancreatic venous sampling<br>Selective arterial calcium test | Endosonography, MRI, multislice CT, selective arterial calcium stimulation test |
| Surgical treatmenr | Focal form: partial pancreatectomy<br>Diffuse form: 95% pancreatectomy | Gradient-guided extent of pancreatectomy according to results of selective arterial calcium stimulation test |

## Cases

The majority of cases with nesidioblastosis have been documented in children and only rare cases have been seen in adult patients [5]. Witteles et al described five cases with adult-onset nesidioblastosis. In each of the cases no islet cells tumor was found and multiple sections of the 60% to 80% distal pancreatectomy were succesful in controlling hypoglycemia. All cases showed a diffuse increase in islet tissue, forming islets that varied in size [7]. Kaczirek et al reexamined 66 adult patients operated because of organic hyperinsulinism during a period of 40 years. Five patients fulfilled the histomorphological criteria of nesidioblastosis, including one with a familial form of nesidioblastosis combined with multiple circumscribed insulinomas [14]. Anlauf et al reported 15 adult patients with nesidioblastosis. In all cases, the lobular architecture of the exocrine parenchyma was preserved and the pancreatic ducts were found to be normal [6]. In a case report of Ahn et all a case of nesidioblastosis during pregnancy in a woman receiving medical nutrition therapy for suspected gestational diabetes has been described. However, nesidioblastosis was undiscovered until the development of hypoglycemia after delivery, being previously masked by pregnancy-related changes in insulin sensitivity [15]. Other authors reported a case of a 35-year-old woman presenting both an insulinoma and nesidioblastosis confirmed by histological examination [16] and Rosman et al reported a case of metastatic insulinoma presenting 11 years after enucleation of an isolated insulinoma, and 5 years after distal pancreatectomy for nesidioblastosis [17]. In another interesting case report an adult patient who suffered from insulin-dependent diabetes mellitus subsequently developing PHH caused by diffuse nesidioblastosis has been demonstrated [18].

## Treatment

The treatment of adult nesidioblastosis is surgical resection of pancreas [3]. Majority of patients are treated by 90-95% (near total) pancreatectomy, while others can be treated by small distal resection. According to Witteles et al 40% of

patients after near-total pancreatectomy developed insulin-dependent diabetes mellitus. A distal pancreatectomy of 60 to 80% results in a cure in about half of patients, with no need for medication, an additional 19% of patients were normoglycemic using medication. Insulin-dependent diabetes occured in only 8% of this group [7]. Definitive treatment of postgastric bypass nesidioblastosis includes gradient-guided pancreatectomy to decrease the source of endogenous excess insulin production [9]. If the disease continues to persist, a subtotal pancreatectomy (90%) is very likely to control the disease. A second operation involves less risk than the risk of lifetime diabetes mellitus after functional pancreatectomy [2]. The treatment of adult nesidioblastosis is operative resection. So far it is not possible to predict reccurence of hypoglycemia in adult patients with nesidioblastosis.

Diazoxid is the most frequent medication used in this indication. Other mediacations include somatostatin analogs , glucocorticoids and calcium channel-blocking agents. The administration of 80 mg of verapamil hydrochloride taken 3 times daily and eating 6 small low-carbohydrate meals daily can protect from hypoglycemia [7]. Arao et al describe a patient who postoperatively continued to exhibit hyperinsulinemia and nightime hypoglycemia. Octreotide, voglibose and diet therapies failed. However, treatment with diazoxide resulted in immediate amelioration of nocturnal hypoglycemia [19].

## Conclusion

The preoperative differentiation of adult nesidioblastosis from an insulinoma is markedly difficult. Most patients have hypoglycemia occured with fasting or exercise, just as happens in patients with insulinoma. At the time of hypoglycemia patients have shown inappropriately high insulin and C peptide levels .

Conventional radiologist testing is not reliably helpful in differentiating an insulinoma from nesidioblastosis. The sensitivity of radiologic studies (CT, magnetic resonance imaging, ultrasonography, angiography) is only 50% to 80%. The use of selective arterial calcium stimulation with hepatic venous sampling can be beneficial in demonstrating hyperactive beta-cell activity. Histollogicaly most insulinomas have uniform nuclei, with a fine chromatin pattern and only small nucleoli. Nesidioblastosis in contrast, is histollogicaly characterized by the budding of islet cells from the pancreatic duct epithelium, together with increase in size, shape, and number of the islet cells.

In summary, adults with PHH, in whom no insulinoma is found, show diffuse nesidioblastosis similar to that seen in neonates with PHH. Focal nesidioblastosis, which is also frequently seen in neonates and infants, has not been observed so far in adults . Subtotal (75-90%) pancreatectomy is considered the treatment of choice for nesidioblastosis. Post-surgery, recurrent hypoglycemia or diabetes mellitus are frequent complications .

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