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# Rare Cause of Organic Hypoglycaemia: Association of Nesidioblastosis, Focal Nesidiodysplasia and Multiple Pancreatic Micro-Adenomas

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**ABSTRACT**

The etiological diagnosis of hypoglycemia in the non-diabetic patient is complex and includes a variety of diseases, including endogenous hyperinsulinism caused by functional β-cell disorders, the latter also known as nesidioblastosis or non-insulinoma pancreatogenic hypoglycemia syndrome (NIPHS). We report the case of a 62-year-old patient, not known to be diabetic, hypertensive on triple therapy, presenting with hypoglycemic episodes reaching 0.34 g/l for 2 years. Biological tests showed insulinemia at 676 pmol/l (norms 18-173pmol/l), C-peptide at 2980 pmol/l (norms 300-1400pmol/l). An octreoscan revealed a focus of radiotracer fixation in the head of the pancreas. The patient underwent 2 operations with persistent hypoglycemia; the combination of diasoxide 300mg/d and lanreotide 120mg/3 weeks led to the disappearance of hypoglycemia and a favorable outcome.

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**KEYWORDS**

Nesidioblastosis; hyperinsulinism; hypoglycemia; diazoxide; lanreotide.

## INTRODUCTION

Hypoglycemia due to endogenous hyperinsulinism is a rare entity whose two main etiologies in adults are insulinoma and islet hyperplasia (nesidioblastosis). Nesidioblastosis is a rare disease caused by hyperplasia of the pancreatic islets, developing a state of hypoglycemia due to increased insulin production. It is the main cause of hyperinsulinemic hypoglycemia in children, whereas it accounts for only 0.5-5% of cases in adults [1]. Histopathologically, it is divided into a focal and a diffuse type. Diffuse nesidioblastosis is rare in adults, but may account for over 3% of patients with hyperinsulinemic hypoglycemia [2].

The pathophysiology is still unknown, and treatment consists of surgical reduction [3]. We report here the case of a patient with nesidioblastosis, focal nesidiodysplasia and multiple pancreatic microadenomas successfully treated with lanreotide 120mg LP, after persistent hypoglycemia post-surgery.

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## CASE REPORT

62-year-old patient, not known to be diabetic, hypertensive for 3 years on triple therapy (triplixam 10mg/2.5mg/10mg 1cp/d), for 2 years he has been reporting episodes of non-comatogenic deep hypoglycemia reaching 0.24 g/l felt by adrenergic neurovegetative signs consisting of (tremors, sweating, palpitations) at a rate of 3 to 4 episodes per week mainly in the morning (6 am) with no link to meals. Abdominal CT revealed a lesional process of the pancreatic corporo-caudal junction, oval in shape with regular contours and heterogeneous enhancement, measuring 25 mm x 18 mm x 15 mm. Abdominal MRI revealed a nodular formation of the corporo-caudal junction distorting the anterior contour of the pancreas in T2 hyper signal, T1 isosignal in unrestricted diffusion hypersignal measuring 21mmx18mm. Biological tests revealed a Peptide C level of 2980 pmol/l (norms 300-1400pmol/l), and an insulin level of 676 pmol/l (norms 18-173pmol/l). No hepatic or renal insufficiency or adrenal insufficiency was found in this patient.

The patient underwent surgery on 01/04/23 to remove the body and tail of the pancreas. Postoperatively, hypoglycemic episodes worsened, with a comatogenic episode resulting in sequellar neurological deficit. Anatomopathological examination concluded that the pancreatic parenchyma was generally preserved, and contained slightly hyperplastic

Langerhans' islets, possibly related to a nesidioblastoma. Immunohistochemistry was positive, with expression of anti-CK7 antibodies, anti-chromogranin antibodies and anti-synaptophysin antibodies.

As the symptoms of recurrent hypoglycemia persisted, somatostatin scintigraphy (Octreoscan) was performed, revealing a tracer-binding focus in the head of the pancreas measuring 1.3cm ×1.2cm×1.2 cm.

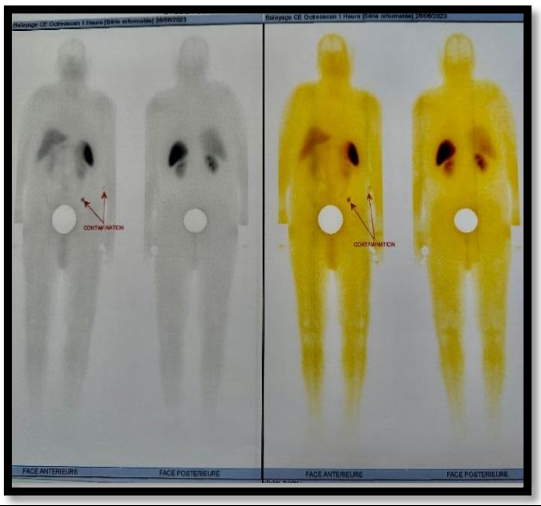

**Figure 1: Whole-body scan after 1 h and 4 h, which revealed the presence of a radiotracer-binding focus in the head of the pancreas.**

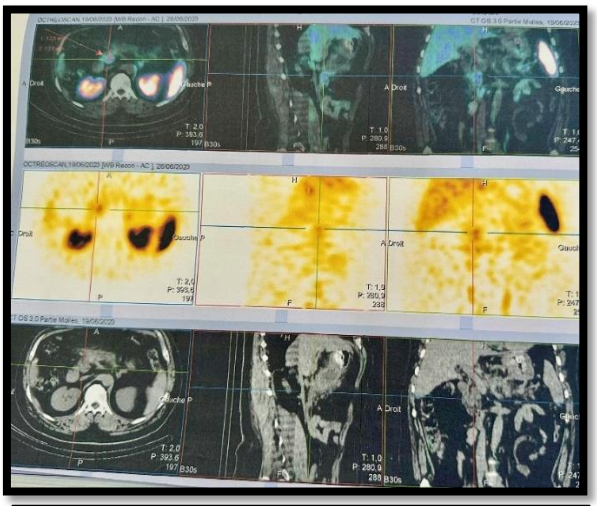

**Figure 2: Transverse, sagittal and coronal sections showing the presence of a focus fixing the radiotracer at the level of the head of the pancreas measuring 1.3cm × 1.2 cm**

The patient underwent repeat surgery on 05/07/23, which involved resection of the nodule at the splenic hilum and removal of peripancreatic fat. Anatomopathological study revealed pancreatic parenchyma with lesions of nesidioblastosis and nesidiodysplasia with multiple endocrine microadenomas not exceeding 5mm. Immunohistochemical study by immunoperoxidase showed cytoplasmic expression of anti-chromagranin antibody (clone LH2H10, Dako) in endocrine cells of irregular and adenomatous islets.

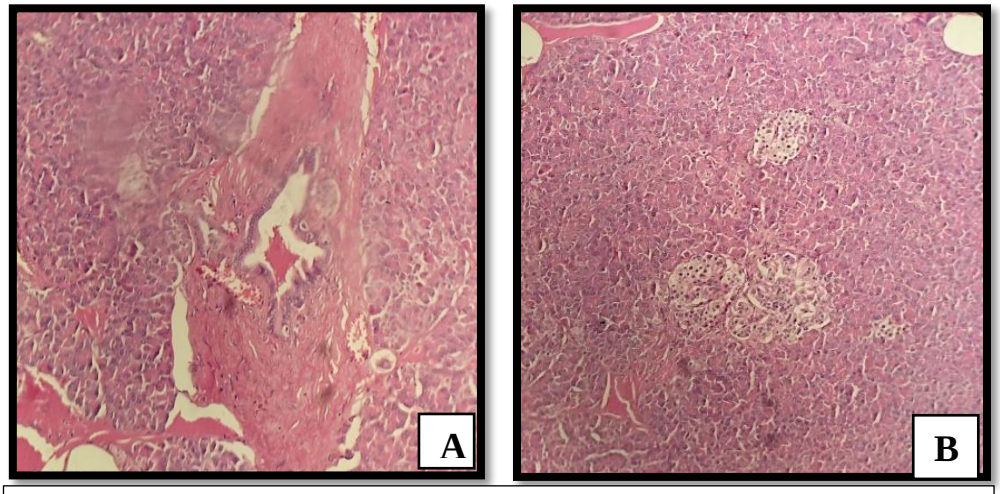


**Figure 3 A and B : enlarged pancreatic islet of irregular size and contour, ducto-insular complex (x40)**

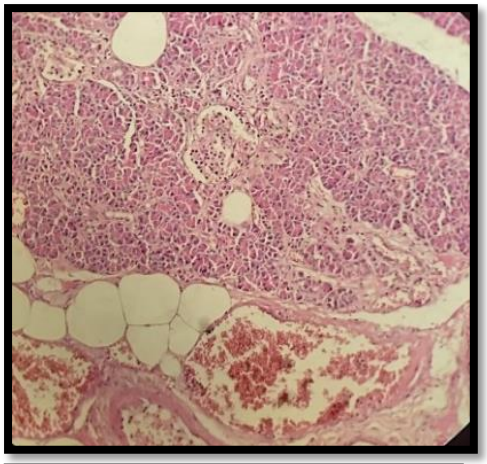

**Figure 4 : Pancreatic beta cells with enlarged nuclei and prominent nucleoli**

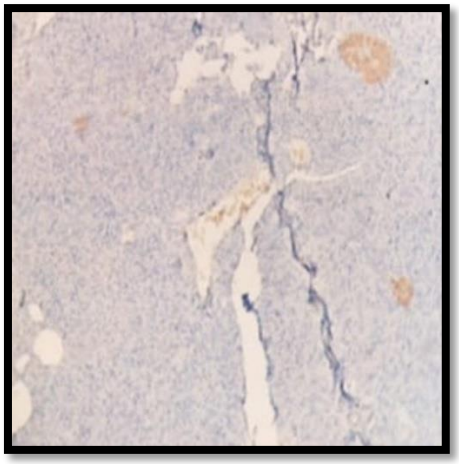

**Figure 5 : Chromagranin immunohistochemical staining of irregular islets**

Postoperatively, the patient continued to have hypoglycemia up to 0.45 g/l, and was started on diazoxide 200 mg/d and hydrocortisone 40 mg/d without improvement. Despite an increase in diazoxide to 600 mg/day, the patient continued to experience hypoglycemia to 0.32 g/l.

The diagnosis of nesidioblastosis, focal nesidiodysplasia and multiple pancreatic micro-adenomas was then made, and treatment with Lanreotide 120mg every 3 weeks was added to diazoxide 400mg/day.

This combination resulted in a regression of hypoglycemic episodes. After 7 months, daily blood glucose monitoring did not reveal any hypoglycemia. Since then, the patient has been treated with Lanreotide 120mg/3 weeks and diazoxide 300mg/d, with a favorable outcome.

## DISCUSSION

Nesidioblastosis is a rare disease characterized by diffuse or focal proliferation of islet cells [4]. In 1938, George Laidlaw described nesidioblastosis as a functional disorder of non-neoplastic beta cells characterized by combined hyperplasia, diffuse proliferation and hypertrophy of islet cells in the exocrine pancreatic ductal epithelium. This clinical entity, also known as non-insulinoma pancreatogenic hypoglycemia syndrome (NIPHS), currently accounts for 0.5-5% of the causes of organic hyperinsulinemia in adults [5].

The pathophysiology of nesidioblastosis is poorly understood; it is generally secondary to genetic abnormalities such as mutations in the SUR1 and Kir6.2 genes, which code for proteins involved in beta-cell function [6]. However, these genetic abnormalities have not been described in adults, although other, as yet unspecified, genetic mutations could be hypothesized.

Les symptômes de la nésidioblastose chez l'adulte peuvent être très divers, allant de manifestations essentiellement cardiologiques à des manifestations neurologiques, voire psychiatriques [7,8]. Les signes autonomes dus à la réaction de contre-régulation adrénergique comprennent les tremblements, les douleurs musculaires, la transpiration, les palpitations, la tachycardie, la faim et la pâleur.

Neuroglycopenic symptoms can mimic many neurological and psychiatric disorders: vertigo, aphasia, visual disturbances, atypical behavior, paresthesia, convulsion, loss of consciousness and coma [9]. In addition, some extraordinary manifestations of nesidioblastosis are described in the literature. Galizia et al [10] reported a case with abdominal pain, vomiting, blurred vision, lethargy and dehydration, bradycardia with intermittent atrioventricular block and ST-segment depression, and hypotension.

Positive diagnosis is based on clinical findings: Whipple's triad, characterized by low blood glucose levels, clinical adrenergic and/or neuroglycopenic symptoms that disappear rapidly after correction of blood glucose levels, followed by a 72-hour fasting test with an inappropriate concentration of insulin and/or C-peptide detected at the time of hypoglycemia, is the first step in defining endogenous hyperinsulinism. Subsequently, imaging studies (CT, MRI) should be performed to exclude an insulinoma [11].

The differential diagnoses of focal or diffuse nesidioblastosis in adults are multiple: the use of insulin-regretatogenic drugs, alcohol, hepatic, renal or cardiac insufficiency, and hormonal deficiencies (pituitary/adrenal insufficiency, glucagon deficiency) must be excluded. Insulin- or IGF-producing tumors (e.g. Doege-Potter syndrome) are another rare cause of hypoglycemia in adults [14, 15].

Management is highly complex, with the main aim of maintaining blood glucose levels within the normal range and establishing age-appropriate fasting tolerance and a normal eating pattern [11]. Treatment can include a dietary approach (a low-carb diet, meal splitting...), medical and surgical, and in the majority of cases, a combination of these approaches.

Pharmacological treatment, consisting of ATP-sensitive potassium channel agonists (diazoxide), calcium channel antagonists (Verapamil, Amlodipine, Nifedipine) [16,17],

and somatostatin analogues (octreotide, lanreotide, pasireotide) [18,19] should be initiated first.

However, with total or partial surgical resection of the pancreas, some patients may achieve clinical cure, particularly those with focal nesidioblastosis, but partial pancreatectomy is beneficial in only 50% of patients with nesidioblastosis and carries a high risk of complications, such as pancreatic fistula, postoperative bleeding, infection and diabetes [20].

## CONCLUSION

Nesidioblastosis is a rare pathology in adults. In the case of patients suffering from nesidioblastosis with hypoglycemia resistant to Diazoxide treatment, or in cases of poor tolerance, the use of Lanreotide 120mg/3 weeks seems to be a therapeutic option to be considered, with increased monitoring of glycemia and digestive disorders.

**Declaration of ties of interest**: The authors declare that they have no ties of interest and have no relevant affiliation or financial involvement with any organization or entity that has a financial interest or financial conflict with the subject discussed in the manuscript.

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