Recurrent hypoglycaemia in HIV-positive narcotic addicts

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Summary

Questions under study: We describe two narcotic addict women with recurrent hypoglycaemic episodes. In both patients, hyperinsulinaemic hypoglycaemia occurring in the fasting state was documented and computed tomography of the pancreas was normal.

Methods and Results: In patient 1, selective arterial calcium stimulation with hepatic venous sampling (ASVS) revealed pronounced insulin hypersecretion predominantly in the tail and, to a lesser extent, in the corpus and the head of the pancreas. On laparoscopic exploration, tumours could not be detected be it grossly or by intraoperative ultrasound. Distal pancreatectomy was performed laparoscopically, and histological examination of the resected tissue revealed nesidioblastosis. ASVS was also performed in patient 2 revealing less marked increases in insulin secretion, ie up to 2.3-fold in response to calcium stimulation of the superior mesenteric artery, consistent with the presence of pathological β-cells located predominantly in the head of the pancreas. Surgical exploration was not performed in this patient.

Conclusion: HIV infection had been known in both women for around ten years and both patients were not on antiretroviral therapy. Because symptomatic nesidioblastosis in adult patients is a very rare disorder, we speculate that nesidioblastosis may develop in the context of HIV infection and/or abuse of narcotic drugs. Our observations illustrate that neurocognitive impairment in HIV-positive patients is not always due to toxic compounds or a cerebral disorder but may be caused by an apparently rare pancreatic disorder, nesidioblastosis. Thus, the patients should be checked for the presence of hyperinsulinaemic hypoglycaemia.

Key words: nesidioblastosis; hypoglycaemia; insulin; HIV; drug addict

Introduction

Loss of consciousness may occur due to intoxication with various drugs and often requires admittance to an intensive care unit. Detailed history of the patient is often missing and, therefore, careful physical examinations as well as monitoring of vital functions and crucial laboratory parameters are indispensable. Description of the circumstances under which the patient was found may be helpful and additional information regarding the patient's history can occasionally be obtained from friends or relatives. If the patient is an addict, administration of an overdose of narcotics is a probable cause of unconsciousness. Nevertheless, it is crucial to look for hints, signs, and symptoms indicating further disorders underlying unconsciousness such as head injury, cerebral bleeding, infectious disease, or endocrine disorders. Hypoglycaemia, for instance, may be life threatening if not detected early and treated appropriately.

Material and methods

Laboratory investigations

For the determination of plasma glucose, venous blood samples were drawn into sodium-fluoride containing tubes. Plasma glucose was determined by the glucose oxidase technique (Beckman Analyzer; Beckman, Fullerton, CA). Immunoreactive insulin was measured by solid-phase radioimmunoassay (intra-assay coefficient of variation (CV) 5%, inter-assay CV 4.9%, lower limit of detection, 14 pmol/l) (Coat-A-Count Insulin; DPC, Los Angeles, CA). Measurement of C-peptide was performed with a solid-phase, chemoluminescent enzyme immunoassay (intra-assay CV 6.3%, inter-assay CV 6.3%, lower limit of detection, 12 pmol/l) (Immulite C-peptide; DPC, Los Angeles, CA; [1,2]).

First and second generation sulfonylureas were measured in plasma by gas chromatographic mass spectroscopy and liquid chromatographic mass spectroscopy, respectively. β-hydroxybutyrate, cortisol, and ACTH were determined at the Institute of Clinical Chemistry of the University Hospital of Zürich by standard methods.

Selective arterial calcium stimulation with hepatic venous sampling (ASVS)

The procedure was performed as previously described with some modifications according to the variant arterial pancreatic anatomy [3–5]. A sampling catheter (Cobra, 6 French) was placed transfemorally in the right hepatic vein close to its junction with the inferior vena cava. Selective arterial angiography and stimulation was performed via a percutaneous femoral access with a 5 French visceral catheter and a coaxial 3 French catheter (for the PDA and PTA). Each artery was stimulated with calcium gluconate (0.025 milliequivalents Ca++ per kg body weight). Blood was collected from the left hepatic vein before (= 0), 30, 60 and 120 seconds after the intra-arterial injection of calcium. At least 5 minutes lapsed between each calcium injection. The SA supplies primarily the body and tail of the pancreas, the GDA supplies the head and secondarily the uncinate, the SMA supplies the uncinate and secondarily the pancreatic head. The PDA artery in patient 1 supplied the whole pancreas after contrast administration. A more than 2-fold increase in insulin levels as assessed by RIA [2] within 30–120 seconds after the injection of calcium indicates the localisation of an insulin secreting tumour in the vascular territory of the stimulated artery (in contrast to no response from normal β-cells; [2-5]).

Pathology

The resected pancreatic tissue from patient 1 was systematically sectioned into 1 mm slices, fixed in buffered formalin, and embedded in paraffin. 4 mm thick paraffin sections were immunostained using the avidin-biotin-peroxidase technique with diaminobenzidine as peroxidase substrate (Vectastain ABC-kit, Vector Laboratories, Burlingame, CA, U.S.A.) with nickel cobalt amplification as previously described [6]. The primary antibodies were directed against chromogranin A (1:1000, Boehringer Mannheim, Mannheim, Germany), glucagon (1:250, DAKO, Glostrup, Denmark), insulin (Bio-Genex, San Ramon, CA, U.S.A), alpha-HCG (1:50, Seralab, Crawley Down, Sussex, GB), somatostatin (1:300, DAKO), pancreatic polypeptide (1:60000, Chance, Indianapolis, U.S.A.), gastrin (1:200, DAKO), and substance P (1:3000, Seralab).

Results

Case 1

A 35-year old woman was admitted because of intoxication in a suicidal attempt with 4 g methadone, 0.5 g sertraline, and an unknown amount of oxazepame. She was known as a narcotic addict and had witnessed the suicide of her partner a few hours before. She had a history of drug abuse for several years and, participating in a program, received 130 mg methadone daily. Occasionally, she consumed additional drugs such as benzodiazepines, heroin and cocaine. She was known to be HIV-positive (CDC A2) but had refused to take antiretroviral medications. She had medroxyprogesterone injections every three months for contraception.

On admission, the patient had impaired consciousness (Glasgow Coma Scale 13) and became unconscious a few minutes after admittance. Blood pressure was 90/60 mm Hg, pulse rate 76 beats/min, and respiration rate 12/min. Consciousness of the patient could not be improved by repetitive administration of naloxone and flumazenile. Initial laboratory evaluations were normal except for a venous plasma glucose concentration of 1.7 mmol/L. Glucose was infused but had no effect on her mental state. Drug screening was positive for methadone, opiates, and benzodiazepines. Screening for alcohol, cocaine, and barbiturates was negative. β-hydroxybutyrate concentration was as low as 1 µmol/L.

When glucose infusion was stopped after two days for 4 hours plasma glucose concentration dropped to 2.3 mmol/L. Plasma insulin concentration was 137 pmol/L and the C-peptide level was 950 pmol/L at that time. Plasma sulfonylurea screen was negative for first and second generation sulfonylureas, insulin antibodies were not detectable. These results suggested endogenous hyperinsulinaemic hypoglycaemia. A plasma cortisol level of 47 nmol/L and a repeated plasma cortisol level of 43 nmol/L the next morning (at 8.00 a.m., reference 280–690 nmol/L) indicated glucocorticoid deficiency. ACTH concentration was <10 ng/L (normal <46) and plasma cortisol increased to 615 nmol/L following injection of 250 µg corticotropin. A diagnosis of acute secondary adrenocortical insufficiency was made. Seven days after admission, plasma cortisol level at 7.30 a.m. was 420 nmol/L and increased to 630 nmol/L following intravenous injection of 250 µg corticotropin, suggesting that the hypothalamic-pituitary-adrenocortical (HPA)-axis returned towards normal.

Figure 1

A: Selective arterial calcium stimulation test in patient 1. Insulin levels in the left hepatic vein as a multiple of basal, 30, 60 and 120 seconds after the intra-arterial injection of calcium (0.025 mEq Ca++ per kg body weight) into the proper hepatic artery (PHA), superior mesenteric artery (SMA), gastroduodenal artery (GDA), transverse pancreatic artery (PTA), dorsal pancreatic artery (PDA), and splenic artery (SA). A 2-fold and more increase in the insulin level in the hepatic vein indicates pathologic insulin-secreting cells in the arterial distribution of SA and PDA, less pronounced in GDA and PTA. No significant increase in insulin levels is seen after calcium injection into the SMA and PHA. B: Selective arterial calcium stimulation test in patient 2. Insulin levels in the left hepatic vein as a multiple of basal, 30, 60 and 120 seconds after the intra-arterial injection of calcium into the right hepatic artery (RHA), superior mesenteric artery (SMA), gastroduodenal artery (GDA) and splenic artery (SA). A 2.3-fold increase in the insulin level in the hepatic vein indicates pathologic insulin-secreting cells in the arterial distribution of SMA. A 1.9-fold increase of insulin levels is seen after calcium injection into the SA, RHA and a 1.6-fold increase after injection into the GDA.
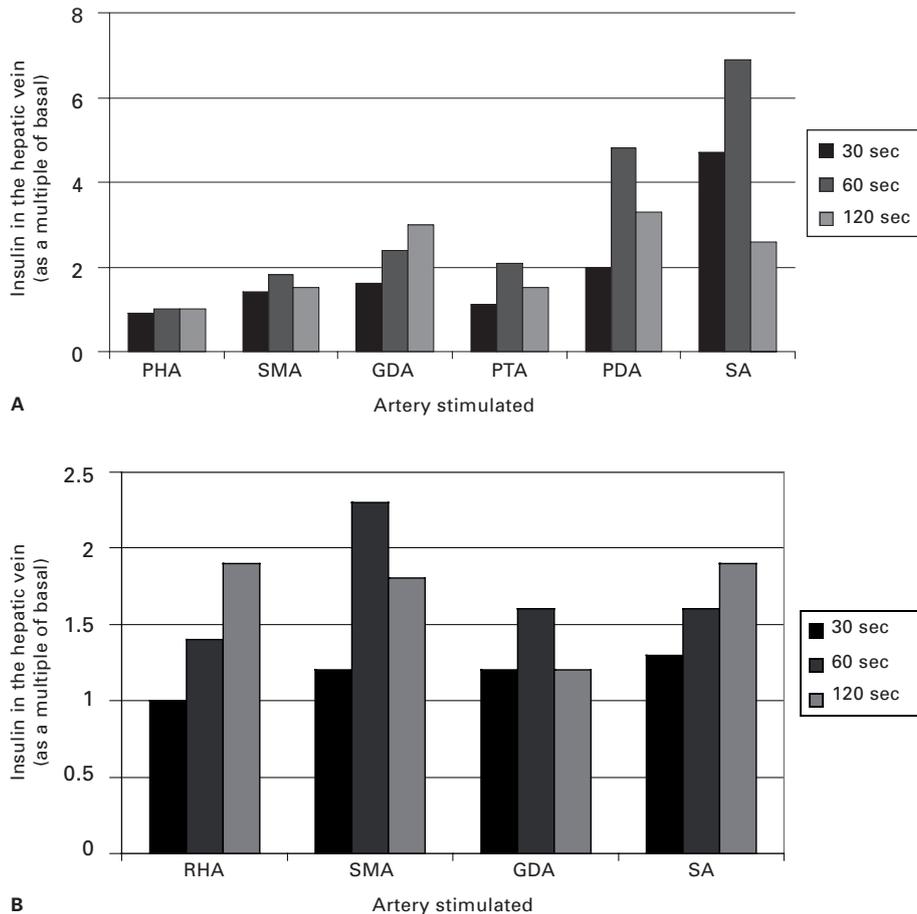
Consciousness of the patient continuously improved over the next three days corresponding to the half-life of the enormous amount of methadone ingested.

A more detailed history could then be obtained. The patient complained that she had experienced several episodes of unconsciousness associated with tremor and sweating during the preceding year. These symptoms were attributed to the drug abuse rather than food ingestion or deprivation. In the five years preceding this hospitalisation seizures occasionally occurred. Benzodiapezine withdrawal was assumed as the underlying reason for the seizures. Reviewing her medical records, a plasma glucose concentration of 2.9 mmol/L was noted ten months prior to admission. This sample was drawn in a sodium fluoride-containing tube at a routine control. Family history was negative for any endocrine disorder. We suspected a hypoglycaemic disorder with relative hyperinsulinaemia during hypoglycaemia and performed a 72-hour fast for further evaluation (table 1). After 48 hours the patient became disorientated and somnolent. Plasma glucose concentration was 1.8 mmol/L, and the neuroglycopenic symptoms resolved immediately when glucose was administrated intravenously. At termination of the fast, plasma insulin concentration was 69 pmol/L and C-peptide level was 230 pmol/L. Sulfonylurea screen was negative and β-hydroxybutyrate concentration was 741 μmol/L (reference for healthy individuals at the end of a prolonged fast: >2500 μmol/L; [1]).

These results were indicative of an insulinoma. However, no tumour in the pancreas could be detected by contrast-enhanced multi-row spiral computed tomography scanning or by contrast-enhanced magnetic resonance imaging. Selective arterial calcium stimulation with hepatic venous sampling (ASVS) was performed. In the digital subtraction angiography no hypervascular lesion in the pancreas was detected. The standard stimulation scheme had to be changed according to the variant arterial supply of the pancreas. The following arteries were stimulated: the gastro-duodenal artery (GDA), the proper hepatic artery (PHA), the splenic artery (SA), the superior mesenteric artery (SMA), the dorsal pancreatic artery (PDA) and the transverse pancreatic artery (PTA). No increase of insulin concentration was measured after stimulation of the PHA and SMA. In contrast, a more than two-fold hepatic venous insulin increase was found after stimulation of the GDA, PTA, PDA, and SA (figure 1A). This indicated that abnormal β-cells were predominantly located in the tail and, to a lesser extent, in the body and head of the pancreas. Such a distribution of abnormal β-cells may be encountered in patients with multiple insulinomas or nesidioblastosis.

The patient underwent laparoscopic exploration of the pancreas. The body and tail of the pancreas were mobilised from their peritoneal end retroperitoneal attachments. However, an insulinoma could not be detected either grossly or by intraoperative ultrasound examination. Considering the results of ASVS, distal pancreatectomy of a

Figure 2

Pathology findings
A. Insulin staining, original magnification 25×: increased number of islets of Langerhans of varying size.
B. Synaptophysin, original magnification 200×: numerous ductuloinsular complexes. Note intimate apposition of ductules (↙) with synaptophysin-positive neuroendocrine cells.
C. H&E staining, original magnification 400×: individual neuroendocrine cells have enlarged nuclei (▲).
D. Insulin staining, original magnification 200×: islets with irregular, ragged border. Note individual cells with enlarged nuclei staining for insulin (▲).
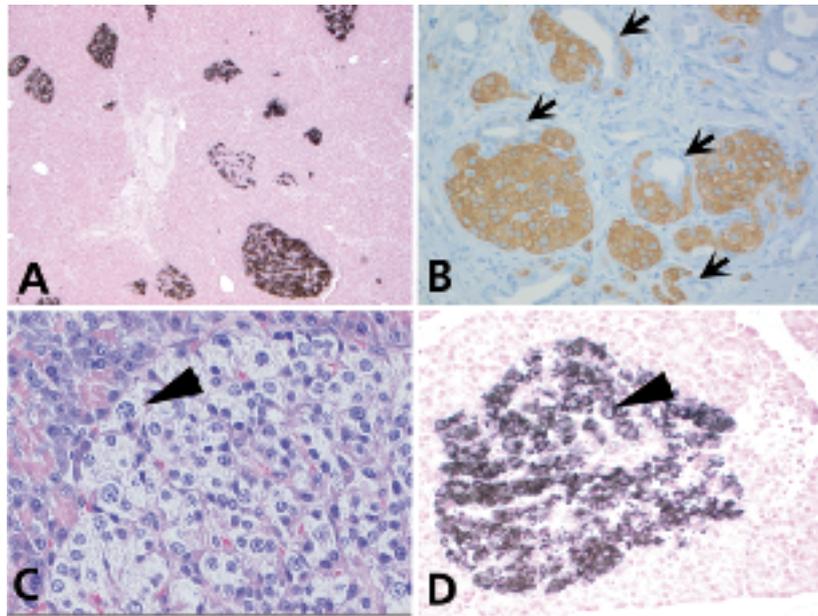
specimen measuring 9 × 5 × 3 cm was performed. The postoperative course was uneventful and glucose levels remained within the normal range.

Histological examination of the pancreatic tissue was characteristic for nesidioblastosis. Most strikingly, the number of islets of Langerhans was increased. Their size and shape was very variable, with individual hypertrophic islets measuring up to 1.5 mm (figure 2A). The islets contained large cells with enlarged pleomorphic nuclei. Focally, islet cells budding from ducts (ductuloinsular complexes) were noted (figure 2B and 2C). Immunohistochemically, the islets contained all major islet cell types staining for insulin, glucagon, somatostatin and pancreatic polypeptide. The distribution of endocrine cell types was normal with the majority of cells staining for insulin and a peripheral ring of glucagon positive cells. Individual cells with hyperchromatic nuclei could be identified as β-cells.

A prolonged fast was repeated three weeks after surgery. No neuroglycopenic symptoms were observed during a 72-hour fast. At the end of the fast, plasma glucose concentration was 3.4 mmol/L in association with an insulin concentration of 101 pmol/L, a C-peptide concentration of 310 pmol/L and a β-hydroxybutyrate concentration of 689 μmol/L. During 4 years follow-up, neither diabetes mellitus nor exocrine pancreatic insufficiency occurred in this patient. No episodes of unconsciousness associated with sweating or seizures were observed any more.

Case 2

A 31-year-old woman was admitted because of osteomyelitis of the right tibia in March 2004. She had several blood glucose readings below 3 mmol/L and she also had a history of narcotic drug and alcohol abuse for several years and, participating in a program, received 400 mg methadone daily. She consumed 1 bottle of vodka and up to three litres of beer a day and occasion-

ally additional drugs such as benzodiazepines, heroin and cocaine. She was known to be HIV-positive (CDC A2), and antiretroviral therapy was not feasible due to malcompliance.

Previous history revealed no loss of consciousness, but massive alcohol consumption. The patient did not consent to a prolonged fast but only to a continuously supervised overnight fast of 5 hours. Fasting plasma glucose concentration was 1.7 mmol/L with a corresponding plasma insulin concentration of 85 pmol/L and C-peptide level of 580 pmol/L, but at that time she suffered from prerenal renal failure (creatinine 226 μmol/l). This fast was suggestive but not diagnostic for hyperinsulinaemic hypoglycaemia. She refused further evaluation of her low blood glucose readings and left the hospital. One year and 3 month later she was admitted again with unconsciousness. Cerebral computed tomography was normal. Initial laboratory evaluations revealed a plasma glucose concentration of 1.5 mol/L, plasma alcohol was 55 mmol/L, renal function was normal (creatinine 76 umol/L). An overnight fast (6 hours) was performed again and morning plasma glucose level was 2 mmol/L, insulin 172 pmol/L and C-peptide 1040 pmol/L. After the overnight fast the patient insisted to leave the hospital again. One month later she was admitted to a psychiatric clinic for an alcohol withdrawal program and was then willing to have a further evaluation of her hypoglycaemic disorder. A fast was started and stopped after 11 hours because plasma glucose concentration fell to 1.9 mmol/L. At this time plasma insulin concentration was 149 pmol/L and C-peptide level was 860 pmol/L. Sulfonylurea screen was negative and β-hydroxybutyrate was 246 μmol/L (table 1). Mental status could not be assessed due to benzodiazepine sedation because of craving.

These results suggested again endogenous hyperinsulinaemic hypoglycaemia.

Medical records of the past few years revealed that she suffered from several seizures and episodes

Patient	Glucose (mmol/l)	Insulin (pmol/l	C-peptide (pmol/l)	β-hydroxybutyrate (μmol/l)	Mental status
1	1.8	69	230	741	Confusion
2	1.9	149	860	246	not applicable

Table 1

Laboratory values and symptoms after 48 hours (patient 1) and 11 hours (patient 2) at the end of fasting Screening for sulfonylurea in plasma was negative in both patients.

of unconsciousness. These symptoms were attributed to drug withdrawal or intoxication. In retrospect, as in case 1, these results were indicative for insulinoma. However, no tumour in the pancreas could be detected by contrast-enhanced multi-row spiral computed tomography scanning. ASVS was performed. In the digital subtraction angiography no hypervascular lesion was detected in the pancreas. The following arteries were stimulated: the gastro-duodenal artery (GDA), the right hepatic artery (RHA), the splenic artery (SA), and the superior mesenteric artery (SMA). A 2.3-fold hepatic venous insulin increase was found after stimulation of the SMA, and minor increases after stimulation of the GDA, RHA and SA (figure 1B). This suggested that abnormal β-cells were predominantly located in the head and, possibly to a lesser extent, in the body and tail of the pancreas. Taken together, the negative findings by CT and angiography in a patient with hyperinsulinaemic hypoglycaemia and the current pattern in ASVS indicate a distribution of abnormal β-cells which is consistent with nesidioblastosis.

A surgical exploration of the pancreas has not yet been possible in this patient. After alcohol withdrawal and regular carbohydrate supply, her blood glucose concentrations were relatively stable in a low normal range.

Discussion

Neuroglycopenia must be considered in any patient with impaired consciousness, even if there seems to be an obvious explanation for loss of consciousness as it was in the presented cases. As soon as hypoglycaemia is detected, further evaluation is based on the clinical characteristics of the individual patient. Hypoglycaemia in the context of an intoxication of a narcotic and/or alcohol addict HIV-positive patient warrants special considerations. First, changes in mental status [7], a cornerstone in the diagnosis of hypoglycaemia as pointed out by Whipple may be difficult to attribute to hypoglycaemia; second, adherence and consent to standard medical testing and care may not be feasible. An acute intoxication with methadone, sertraline and oxazepame is usually not associated with hypoglycaemia. In contrast, alcohol intoxication associated with hepatic, renal or endocrine disorders may lead to hypoglycaemia. The co-administration of compounds such as insulin or sulfonylureas was excluded by determining insulin, C-peptide and sulfonylurea during hypoglycaemic episodes. Despite the patients being HIV-positive, no HIV-associated illness that could prompt hypoglycaemia was known (including hepatic, renal or endocrine disorders). Drugs with glucose-lowering properties including pentamidine or trimethoprim-sulfamethoxazole had not been prescribed.

It is important to note that marked secondary adrenal insufficiency (as documented in patient 1 on admission) and alcohol abuse (a problem in patient 2) may cause hypoglycaemia, however, not associated with inappropriately high insulin or C-peptide levels; insulin secretion by healthy b-cells should be suppressed. The occurrence of hyperinsulinaemic hypoglycaemia during the prolonged fast is considered as a clinical hallmark of patients with insulinoma [8]. Small insulinomas may not be localised by pancreatic imaging [9]. Therefore, ASVS is an appropriate investigation to localise an insulinoma [3–5, 9, 10]. A positive response to calcium stimulation in multiple vascular territories of the pancreas is uncommon and points to the presence of multiple insulinomas or nesidioblastosis [4, 11]. Multiple insulinomas are found almost exclusively in patients with MEN-1 syndrome. MEN-1 was unlikely in our patients since family history was negative and calcium serum levels were normal. Moreover, a germline mutation in the exons 2–10 of the *menin*-gene in patient 1 could not be found. Thus, nesidioblastosis of the pancreas was assumed, a diagnosis which can only be confirmed histopathologically [12].

Because of the diffuse nature of the islet-cell disease, the extent of surgical resection in patients with nesidioblastosis is controversial. Most experts recommend distal resection of the pancreas in adult patients with nesidioblastosis [11]. ASVS allows localisation of the distribution of abnormal β-cells and performance of a gradient-guided pancreatectomy. In patient 1 described here, ASVS disclosed abnormal β-cells predominantly in the tail and to a lesser extent in the body and head of the pancreas. Thus, distal pancreatectomy to the right of the mesenteric vein was performed laparoscopically.

In patient 2 the results of the ASVS test disclosed abnormal β-cells predominantly in the head of the pancreas. This finding would be in agreement with an insulinoma in the vascular territory of the mesenteric superior artery. However, because of the marginally pathological increases in insulin after calcium injection into the pancreas-supplying arteries, we believe that nesidioblastosis, predominantly in the head (2.3-fold increase) and to a lesser extent in the tail of the pancreas (1.9-fold increase) should be considered. The normal CT scan and the nega-

tive angiographic findings (no blush) support (but do not prove) this hypothesis.

Symptomatic nesidioblastosis in adult patients has been considered as a very rare disorder. Nesidioblastosis has been well described in infants with persistent severe hypoglycaemia. In some of these patients, mutations of the SUR1 (sulfonylurea receptor) or Kir 6.2 (inwardly rectifying potassium channel) genes have been detected. In adult patients with nesidioblastosis, such mutations were not detected [13]. Only in more recent years case series of (acquired) nesidioblastosis have been reported in adults, either idiopathic [11] or following surgery for super obesity [14]. In these patients, hypoglycaemia occurred predominantly in the late postprandial period; and at least in the latter, β-cells hyperplasia could reflect an adaptation to an increased demand with subsequent loss of β-cell control. Our patients were not obese and had no history of upper gastro-intestinal surgery. Thus, there was no specific reason to suspect that preceding severe insulin resistance or changes in incretins could account for β-cell pathology.

A recent pathological study suggested that islet hyperplasia may be more frequent in adults suffering from hyperinsulinaemic hypoglycaemia than previously thought and could account for about one fifth of the cases. In this series, no information was given as to whether hypoglycaemia occurred in the postprandial or in the fasting state [15].

In our patients, the condition appears to be rather unique in that they suffered from fasting hypoglycaemia. Two additional patients seen at our institution over the past 5 years with histologically confirmed islet hyperplasia (not known for drug abuse and HIV infection) suffered predominantly from postprandial hypoglycaemia. Remarkably, proinsulin levels at the end of the fast (ie in the state of hyperinsulinaemic hypoglycaemia) were in the low normal range of healthy fasting individuals [1], consistent with normal insulin processing by hyperplastic islets of our two patients (as previously reported for one of them; [16]).

Earlier described cases in the U.S. by the Mayo Clinic [12, 14] and by pathologists in Germany [15], revealed no aetiology. It may well be that the occurrence of hyperinsulaemic hyperglycaemia in our two patients with long-lasting narcotic drug abuse and HIV infection occurred by chance and was a coincidence; a link between nesidioblastosis and HIV infection and/or abuse of narcotic drugs is difficult to test for such a rare (apparently acquired) hypoglycaemic disorder.

We suggest that HIV-positive patients with neuroglycopenic symptoms should be checked for the presence of hypoglycaemia.

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