

Diagnosis of insulinoma in a patient with hypoglycemia without obvious hyperinsulinemia

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Background. A 41-year-old Maltese woman with a 12-month history of severe, morning episodes of confusion, blurred vision and sweating was referred to a specialist center for evaluation of fasting hypoglycemia. She was not taking medication and did not report any prior personal or familial history of endocrinopathy or other relevant pathology.

Investigations. Measurement of plasma glucose, insulin, C-peptide, and β -hydroxybutyrate concentrations during a prolonged supervised fast; sulfonyleurea screen; CT, MRI scan and endoscopic ultrasonography of the pancreas; calcium stimulation test; surgical exploration and intra-operative ultrasonography of the pancreas.

Diagnosis. Insulin-secreting lesion (insulinoma) in the tail of the pancreas.

Management. The tumor was resected with cure of symptoms.

Coelho, C. *et al. Nat. Rev. Endocrinol.* 5, 628–631 (2009); doi:10.1038/nrendo.2009.198

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe Whipple's triad for the presentation of insulinomas.
- 2 Describe the clinical and demographic characteristics of patients with insulinomas.
- 3 Describe the diagnostic tests for insulinomas.
- 4 Identify potential reasons for missing a diagnosis of insulinoma.

The case

A 41-year-old Maltese woman was referred to a specialist center for evaluation of fasting hypoglycemia. The patient reported a 12-month history of confusion, blurred vision and sweating during the morning, which could always be prevented by the regular consumption

of a mid-morning snack. She had gained 2 kg in weight over this period. The patient decided to exclude these snacks during Lent, 2 months before admission. On the first morning, she became increasingly confused during a meeting and displayed inappropriate behavior; the episode ended after the intake of a high-carbohydrate lunch. The woman reported no prior personal or familial history of endocrinopathy or other relevant pathology and was not taking any medication. Physical examinations at the referring hospital and the specialist center were unremarkable. Investigations from the referring hospital determined normal basal pituitary function and the patient was negative for autoantibodies for celiac disease.

The patient was submitted to a prolonged supervised fast, which was terminated prematurely after 28 h, at which point she showed symptoms and signs consistent with hypoglycemia, including anxiety and confusion, sweating and dizziness. The patient's symptoms completely recovered with oral glucose administration. Blood samples, taken while the symptoms were present, exhibited no visible evidence of hemolysis. Subsequent measurements revealed levels of plasma glucose of 1.7 mmol/l (normal range 3.9–6.9 mmol/l), insulin levels of 2.7 mIU/l (normal range <3.0 mIU/l in the presence of hypoglycemia), C-peptide concentrations of 0.35 nmol/l (normal range <0.2 nmol/l in the presence of hypoglycemia) and β -hydroxybutyrate levels of 530 μ mol/l (normal range >2,700 μ mol/l in the presence of hypoglycemia). A sulfonyleurea screen was negative (Table 1).

The results of these tests showed that the patient had severe fasting hypoglycemia, but without concomitant hyperinsulinemia according to current guidelines.

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Competing interests

The authors, the Journal Editor V. Heath and the CME questions author D. Lie declare no competing interests.

Table 1 | Biochemical results during a 72 h fast

Time (hours from start of fast)	Glucose (mmol/l)	Symptoms	Insulin (mIU/l)	C-peptide (nmol/l)	β -Hydroxybutyrate (μ mol/l)	Sulfonylurea
0	5.5	No	Not hypo	Not hypo	Not hypo	Not hypo
4	2.3	No	Not hypo	Not hypo	Not hypo	Not hypo
22	3.1	No	2.7	0.345	560	Not hypo
28	1.7	Yes	2.7	0.357	530	Negative

Abbreviation: hypo, hypoglycemic.

Despite the absence of clearly elevated insulin levels, the very characteristic clinical history and suggestive features of the available corroborative investigations, such as an elevated C-peptide level and a low β -hydroxybutyrate concentration, prompted further investigation for localization of a possible insulinoma. CT of the pancreas revealed a slight nodularity of the pancreatic tail, but because no differential enhancement was visible after administration of a contrast agent (Figure 1a), a definite mass lesion in the pancreas could not be confirmed. Nevertheless, a single lesion in the tail of the pancreas of 18.3 mm by 9.5 mm was detected by MRI (Figure 1b), while endoscopic ultrasonography revealed a 16 mm lesion in the pancreatic tail. The latter procedure, however, was also suggestive of a second lesion in the head of the pancreas, which had not been visualized by MRI.

To exclude the possibility that lesions in the pancreatic tail were caused by an accessory spleen and to confirm the presence of the second lesion detected by ultrasonography, the patient was submitted to a calcium stimulation test. Following injection of calcium into the splenic artery, a threefold increase in insulin from baseline was measured from the hepatic vein, a result consistent with the MRI findings. The patient was thus referred for surgical exploration of the pancreas.

During the operation, inspection and palpation of the pancreas revealed a small nodule at the tip of the gland tail. The rest of the pancreas was normal to inspection, palpation and an intra-operative ultrasonography. A lesion (38 mm \times 18 mm \times 15 mm) in the tail of the pancreas was enucleated, and the patient made a rapid recovery. Histological examination confirmed the complete excision of a benign insulinoma with a Ki-67 labeling index of 1%, which suggests a low risk of malignant behavior. The patient's postoperative fasting glucose levels were normal and she has remained asymptomatic since the operation. She will have a regular endocrine follow-up after 6 months, with a repeat prolonged supervised fast if symptoms recur.

Discussion of diagnosis

Insulinoma is the archetypal cause of hyperinsulinemic hypoglycemia in adults without diabetes.¹ Estimated incidence of this rare, pancreatic β -cell tumor is four in one million people per year.² These pancreatic lesions are often less than 2 cm in size at the time of symptoms

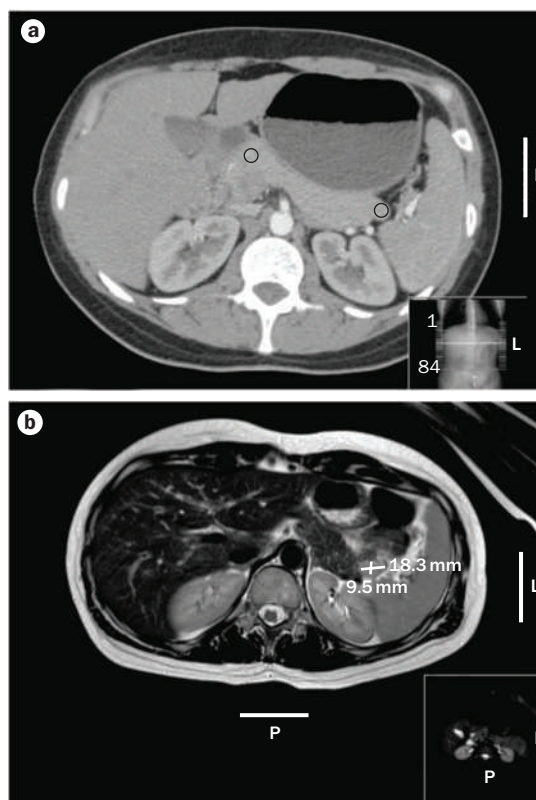


Figure 1 | Localization of a possible insulinoma in the case patient. **a** | CT scan of the abdomen of the patient described showing nodular pancreas but no differential enhancement after contrast. **b** | MRI scan of the abdomen showing a 18.3 mm by 9.5 mm enhancing islet cell tumor within the tail of the pancreas.

manifestation and can therefore be difficult to localize. Although guidelines are available for the biochemical diagnosis of insulinomas, recurrent hypoglycemia can be difficult to diagnose owing to the variability of presenting symptoms.

The 72 h fast is the gold standard test for the diagnosis of insulinomas.³⁻⁵ This test enables the clinical demonstration of Whipple's triad: the occurrence of symptoms consistent with hypoglycemia, low plasma glucose concentration at the time of symptoms and the relief of symptoms upon correction of the hypoglycemia. In addition, the test provides biochemical evidence of nonsuppressed insulin levels associated

with hypoglycemia. In order to interpret the results of a fast, however, the choice of diagnostic threshold for hyperinsulinemia is crucial. Previously suggested diagnostic criteria for insulinoma were an insulin level of ≥ 6 mIU/l in the presence of hypoglycemia.⁵

Measurement of insulin levels is influenced by the type of assay used—commercially available assays employ either polyclonal or monoclonal antibodies. The use of polyclonal antibodies leads to as much as 40–80% crossreactivity with proinsulin.⁶ Monoclonal assays have overcome this issue, and their use has enabled the detection of lower minimum concentrations of insulin.

The crossreactivity of highly specific insulin assays has been evaluated;⁷ as insulin levels measured are 7–63% lower than those assessed with polyclonal assays, a reduction in the diagnostic threshold for hyperinsulinemia has been suggested when monoclonal assays are used in the diagnosis of insulinoma.⁸ A recent consensus set of guidelines for the diagnosis of inappropriate hyperinsulinemia in the presence of documented hypoglycemia has proposed a diagnostic threshold of plasma insulin of ≥ 3.0 mIU/l,⁹ but normative values during prolonged fasting are still needed for newer insulin assays.⁸

The assay used to measure insulin in the described case was a solid-phase two-site immunochemiluminescence assay, which has a lower detection limit of insulin of 2 mIU/l and 8% crossreactivity with proinsulin. Furthermore, no 'hook' effect—the occurrence of falsely low values on an immunoassay, when an overwhelming amount of antigen affects the binding capacity of the added antibody—has been demonstrated up to 70 mIU/ml. The level of crossreactivity was, therefore, intermediate between that of conventional assays and the more novel highly specific assays,¹⁰ which implies that even the former diagnostic threshold for insulin of 6 mIU/l should have been adequate for the detection of biochemical evidence of inappropriate hyperinsulinemia. The patient described exhibited definite biochemical hypoglycemia accompanied by a low level of insulin, but even if the strict threshold of 3 mIU/l used for highly specific assays had been applied, this patient would not have fulfilled the criteria for inappropriate hyperinsulinemia. It appears that insulin levels at or around the new threshold for abnormality, as described in recent guidelines, must be considered in a clear clinical context rather than as absolute levels for decision taking.

Potential methodological reasons exist for unexpectedly low insulin levels coinciding with hypoglycemia in the context of a prolonged supervised fast. The biological half-life of insulin is very short (approximately 4 min), and thus any delay in the collection of samples may give rise to low results. Hemolysis in the sample may also lead to artifactual changes in insulin levels.¹¹ These two situations were excluded in the current case, as samples were taken under medical supervision and visually checked to exclude hemolysis.

The authors of the new guidelines recognize the importance of interpretation of results in the context of both the clinical picture and corroborating evidence. Their suggestion of concurrent measurement not only of insulin but also of C-peptide, β -hydroxybutyrate and proinsulin is supported by others.^{9,12–17} Indeed, in the case described, values for both C-peptide (0.35 nmol/l) and β -hydroxybutyrate (530 μ mol/l) were compatible with a diagnosis of endogenous hyperinsulinemia. The new guidelines suggest diagnostic thresholds of >0.2 nmol/l for C-peptide and $>2,700$ μ mol/l for β -hydroxybutyrate.⁹

Insulinomas may produce a higher proportion of proinsulin than normal β -cells.^{13,18–22} In patients with insulinomas that secrete predominantly proinsulin, insulin levels below the previous diagnostic threshold,¹⁰ and even below that in the new guidelines,^{6,23} have been measured with highly specific assays. Hypoglycemia in these cases is caused by proinsulin,²² which is known to have a hypoglycemic effect.²⁴ Under such circumstances, measurement of proinsulin as well as C-peptide has proved helpful.^{10,12,25}

Occasional cases of insulinoma have been described that are characterized by persistent low insulin but elevated proinsulin during supervised fasts,^{11,25} the reduction in a rising insulin level after a catecholamine surge in response to hypoglycemia,¹¹ or hypoglycemia provoked only after oral glucose challenge.²⁶ The mechanisms in these cases are unclear.

Only once the diagnosis of inappropriate endogenous hyperinsulinemia in the presence of hypoglycemia is achieved will the next step in investigation usually be taken, namely tests to localize the source of excess insulin. In the described case, cross-sectional imaging and endoscopic ultrasonography did not provide concordant information, but additional data from a calcium stimulation test was compatible with the MRI finding of a lesion in the pancreatic tail as the source of insulin.

Treatment and management

Surgical exploration of the pancreas is not usually performed without biochemical evidence of inappropriate hyperinsulinemia and localization of the source of abnormal insulin secretion. The patient described underwent formal laparotomy and exploration of the pancreas. This procedure is an open, rather than a laparoscopic approach, which allows the surgeon to palpate the pancreas before making a final decision on the location of the tumor. This additional information enables alteration of the planned surgery if required. A tumor was removed from the pancreatic tail in the case described, and this tumor was confirmed to be an insulinoma upon histological examination. Surgical resection resulted in the cure of the patient's symptoms.

Conclusions

We have described a case in which definite biochemical hypoglycemia was accompanied by a low level of insulin,

as determined with a moderately specific insulin assay. If the diagnostic threshold of 3 mIU/l—used when measuring insulin with highly specific assays—had been applied, this patient would not have fulfilled the criteria for inappropriate hyperinsulinemia. When mathematically converted to SI units, the value is borderline, which highlights the importance of the application of judgment rather than the use of a threshold as a definitive cut-off. Owing to a high level of clinical suspicion and suggestive features of the available corroborative investigations, such as an elevated C-peptide level and a

low level of β -hydroxybutyrate, the patient was further investigated for localization of a possible insulinoma. The diagnostic threshold for inappropriately elevated insulin levels in the presence of hypoglycemia has to be considered in the context of the patient's history and other biochemical investigations, such as measurement of concentrations of C-peptide, β -hydroxybutyrate and in some cases proinsulin. The importance of clinical judgment in the investigation and management of cases that do not conform to an expected pattern cannot be overemphasized.

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Acknowledgments

Written consent for publication was obtained from the patient. C.C. was on an elective placement in the Department funded by the Portuguese endocrinology society and the Study Association for Diabetes and Endocrinology of Almada. We thank Mr Satya Bhattacharya for his contribution to the clinical management of the patient. Désirée Lie, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the MedscapeCME-accredited continuing medical education activity associated with this article.