*Rev Port Endocrinol Diabetes Metab. 2022;***17(3-4)**

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Caso Clínico

Insulinoma Misdiagnosed as Factitious Hypoglycemia

Nádia Mourinho Bala [a,*], José Maria Aragüés [a], Sílvia Guerra [a], Mónica Peixe [a], Cristina Valadas [a]

[a] *Serviço de Endocrinologia, Hospital Beatriz Ângelo, Loures, Portugal*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2021-12-12
Accepted/Aceite: 2022-07-14
Publicado / Published: 2023-01-18

Keywords:
Insulinoma;
Factitious Disorders;
Hypoglycemia.

Palavras-chave:
Hipoglicemia;
Insulinoma;
Perturbações Autoinduzidas.

A B S T R A C T

Hypoglycemia is an important cause of referral to endocrinologists. We report a case of 34-year-old female presenting with Whipple's triad. The blood test documented hyperinsulinemic hypoglycemia and the presence of glibenclamide. Blood tests were repeated, confirming the results. Considering these laboratory findings, factitious hypoglycemia was suspected and the patient was referred to a psychiatry clinic. However, following further investigation, a pancreatic neuroendocrine tumor was diagnosed and submitted to surgical resection. At this point two highly unlikely scenarios remained: either the patient had a simultaneous diagnosis of a neuroendocrine tumor and factitious hypoglycemia or the glibenclamide result was a false positive due to a serum interference. In order to clarify the situation further investigation was performed and the interference hypothesis was confirmed. This case shows that a diagnosis of factitious hypoglycemia should not be categorically assumed, even when in the presence of a positive measurement of secretagogues in blood tests.

Insulinoma Diagnosticado como Hipoglicemia Factícia

R E S U M O

A hipoglicemia é uma das causas de referenciação à consulta de Endocrinologia. Apresentamos o caso de uma doente de 34 anos encaminhada por sintomatologia compatível com tríade de Whipple. A avaliação analítica documentou hipoglicemia hiperinsulinémica e, na mesma amostra, doseamento positivo de glibenclamida. Foi realizada uma nova colheita e confirmados os resultados. Tendo em conta a avaliação analítica, foi assumido o diagnóstico de hipoglicemia factícia e a doente foi encaminhada à consulta de Psiquiatria. Contudo, após investigação adicional, foi diagnosticado um tumor neuroendócrino pancreático. Nesta fase, colocaram-se duas hipóteses: tratar-se de um tumor neuroendócrino não funcionante e apresentar, concomitantemente, hipoglicemia facticia, ou tratar-se de um insulinoma e o doseamento de glibenclamida ter sido um falso positivo. Foi realizada investigação adicional e confirmou-se a segunda hipótese. Com este caso, salientamos a importância de considerar a presença interferentes, independentemente do método laboratorial, e não assumir categoricamente o diagnóstico de hipoglicemia factícia.

* Autor Correspondente / Corresponding Author.
E-Mail: nadia.mourinho@gmail.com (Nádia Mourinho Bala)
Hospital Beatriz Ângelo, Serviço de Endocrinologia
Avenida Carlos Teixeira 3, 2674-514 Loures, Portugal

https://doi.org/10.26497/cc210046

Introduction

Hypoglycemia is an uncommon clinical issue in patients not undergoing treatment for diabetes mellitus.[1] The symptoms of hypoglycemia include autonomic symptoms, such as tremor, diaphoresis, hunger, and palpitations, and neuroglycopenic symptoms, such as dizziness, weakness, drowsiness, confusion and altered mental status. The evaluation and management of hypoglycemia is only recommended in patients in whom Whipple's triad is documented.[2] Whipple's triad consists of symptoms and/or signs of hypoglycemia, low plasma glucose concentration and relief of symptoms following the administration of glucose. In these patients a detailed clinical history, physical examination and laboratory evaluation are fundamental. When the cause of the hypoglycemic disorder is not obvious, the laboratorial evaluation should include the measurement of plasma glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate concentrations and screening for oral hypoglycemic agents (sulfonylureas and meglitinides). The blood samples should be collected during an episode of spontaneous hypoglycemia. Insulin antibodies should also be measured, since autoimmune hypoglycemia is a differential diagnosis of hyperinsulinemic hypoglycemia.[3] When a spontaneous hypoglycemic episode cannot be observed, a provocative test of 72-hour fast should be performed. If the hypoglycemia typically occurs in the postprandial period, a mixed-meal test might be the preferred provocative procedure.[1] By observing the presence of symptoms and signs of hypoglycemia and performing the above laboratory evaluation, it is usually possible to distinguish between the several causes of hypoglycemia.

Case Report

Female patient, 34-year-old, with no relevant personal history. The patient reported only an aunt with type 2 diabetes mellitus and one cousin with type 1 diabetes mellitus, with no other relevant familial history. The patient was referred to our endocrinology clinic due to recurrent episodes of diaphoresis, tremor, weakness, hunger, and blurred vision associated with hypoglycemia resolving after eating and achieving normal blood glucose levels, configuring Whipple's triad. The patient's weight remained stable, and no other symptoms were reported. These symptoms began eight months before and were becoming more frequent and incapacitating. At first, hypoglycemic episodes occurred predominantly during the night period, after long fasting periods. However, in the previous five months these symptoms started to occur in the postprandial period as well. The patient was evaluated by a general practitioner and was medicated with metformin, which the patient stopped taking after two weeks due to worsening symptoms. Three months later the patient was evaluated in our endocrinology clinic for the first time. A laboratorial evaluation of hypoglycemia was requested. The blood tests were collected after a fasting night period, revealing glycemia of 31 mg/dL, insulin 14.0 uUI/mL (reference range 3.0-25.0), pro-insulin 13.3 pmol/L (reference range 0.7-4.3), C peptide 2.9 ng/mL (reference range 0.8-3.9), insulin antibodies of 6.0% (negative < 8.2). In the same blood sample, the measurement of circulating oral hypoglycemic agents revealed detectable levels of glibenclamide of 0.15 ug/mL (reference range 0.03-0.20). However, the patient denied taking any herbal supplements or medication, except for metformin, which she had stopped taking 4 months prior. Due to these findings, we decided to repeat the blood tests that revealed, once again, detectable levels of glibenclamide (0.04 ug/mL, reference range 0.03-0.20), glycemia 46 mg/dL and high levels of insulin, pro-insulin and C peptide. At this point the diagnosis of factitious hypoglycemia induced by oral hypoglycemic agents was considered the most likely hypothesis, and the patient was referred to the psychiatry department. The psychiatric evaluation excluded Munchausen syndrome, personality disorders and any other psychiatric disorder that could justify a case of factitious hypoglycemia. Since the symptoms persisted, the patient asked for a second evaluation at a different medical clinic. An abdominal magnetic resonance was performed, showing a pancreatic lesion in the body/tail transition, with a larger axis of 16 mm. Cytology by echo-endoscopy was performed and the results were suggestive of a neuroendocrine tumor. The patient was submitted to distal pancreatectomy and splenectomy, with no intercurrences. The histological examination confirmed the diagnosis of a well differentiated G2 neuroendocrine tumor, with 20 mm of larger axis, 3 mitoses per 50 high power fields, Ki67 10%, with no lymph nodes metastasis detected in the 22 nodes that were excised. There was a complete resolution of symptoms after the surgery. The C peptide, plasma insulin, proinsulin and serum glucose levels returned to normal. Plasmatic glibenclamide, however, remained detectable (0.70 ug/mL). In order to confirm the presence of an interfering substance, we opted to collect a blood sample at morning for measurement of serum glibenclamide concentration, followed by an urine sample 8 hours later in order to test for glibenclamide metabolites. The blood test was positive for glibenclamide (0.59 ug/mL) but no metabolites were identified in the urine sample. Thus, the diagnosis of an insulinoma was assumed. In this case, there was no familial history of endocrine tumors and at this point patient does not present any evidence of other tumors associated to MEN1 syndrome.

Discussion

An hypoglycemic disorder is established by the presence of Whipple's triad, characterized by the presence of symptoms and signs consistent with hypoglycemia, a documented low plasma glucose concentration and resolution of symptoms after glucose administration and correction of hypoglycemia.[2,4] Once the presence of a hypoglycemic disorder is confirmed, it is important to establish the etiology. In this case, the initial laboratory evaluation was performed after an overnight fast period, documenting a case of hyperinsulinemic hypoglycemia. Adult-age onset hyperinsulinemic hypoglycemia may be caused by an insulinoma, autoimmune hypoglycemia syndrome, factitious hypoglycemia due to exogenous administration of insulin or secretagogues, pancreatogenous hypoglycemia syndrome, related to bariatric surgery, or by a paraneoplastic syndrome due to tumors of mesenchymal or epithelial origin.[5,6] Factitious hypoglycemia resulting from exogenous insulin administration is promptly distinguished from hypoglycemia resulting from endogenous hyperinsulinism by an inappropriately high insulin level in presence of suppressed C-peptide and proinsulin levels.[7] On the other hand, insulinomas and insulin secretagogues, like sulfonylureas and meglitinides, present with increased levels of plasma insulin, C peptide and proinsulin.[4] The only way to differentiate between insulinoma and secretagogues induced hypoglycemia is by detecting the drug in the blood or urine tests.[4] In presence of detectable levels of an oral hypoglycemic agent, accordingly with literature, no further investigation is needed. In the reported case, glibenclamide was detected in two different blood samples, using high performance liquid chromatography (HPLC). Thus, facing these results we suspected of factitious hypoglycemia and requested observation by psychiatry

department. Factitious hypoglycemia may be a potential differential diagnosis in patients who work in the medical field, who are in close contact with diabetic individuals, and those with underlying psychiatric disorders.[4] During psychiatric evaluation, the observation was suggestive of anxiety disorder with no associated signs of psychopathology, including Munchausen syndrome, that could justify a factitious hypoglycemia. The definitive diagnosis by histological examination was a pancreatic neuroendocrine tumor. However, the term "insulinoma" is only applied if the symptoms and laboratory data are consistent with excessive production of endogenous insulin. Thus, in this case we could hypothesize the presence of a non-functioning neuroendocrine tumor associated with factitious hypoglycemia or, in the other hand, that the glibenclamide detection might be a false positive and the neuroendocrine tumor might be an insulinoma. HPLC is a very accurate and precise method that separates and identifies various compounds in a mixture according to their retention time (tR), by comparing each peak's tR with that of injected reference standards. However, like any other laboratory method, HPLC also has its pitfalls. Although rare, it's possible that two molecules present the same tR (molecules with very similar structures, eg). In this case we suspect that the patient's serum had an interferent substance with the same tR as glibenclamide, which was responsible for a false positive result. To confirm this scenario a blood sample was collected for serum measurement of glibenclamide, and a urinary sample 8 hours later, the time required for the metabolization and excretion of glibenclamide and its metabolites. The blood sample was once again positive for glibenclamide by HPLC method but the urine sample was negative for this drug and its metabolites, using the same laboratorial method (HPLC). These results support the serum interference hypothesis.

We could not conclude which substance was causing this result, since the patient denied taking any medication, herbal preparations or other supplements. To our knowledge, there are no common drugs or substances reported in literature with the same tR as glibenclamide, up to this moment. In this particular case, if the first laboratorial result was considered reliable, and no further investigation was ordered, we would have missed a potentially life-threatening diagnosis of insulinoma, in spite of acting in accordance to international guidelines. We are reporting this case of an insulinoma, as a particularly bewildering differential diagnosis of a hyperinsulinemic hypoglycemia. Even in presence of positive measurement of secretagogues in blood tests, we cannot categorically assume factitious hyperinsulinemic hypoglycemia as the definitive diagnosis, since every laboratorial exam may have potential interfering substances.

Contributorship Statement / Declaração de Contribuição:

NMB: Conceptualization, data collection, writing original draft, and final approval.
MP: Conceptualization, data collection, writing original draft, and final approval.
SG, JMA: Conceptualization, methodology, supervision, review and final approval.
CV: Conceptualization, methodology, supervision, review and final approval.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Consentimento: Consentimento do doente para publicação obtido.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship.
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Patient Consent: Consent for publication was obtained.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Service FJ. Hypoglycemic disorders. N Engl J Med. 1995;332:1144-52. doi: 10.1056/NEJM199504273321707.
2. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009;94:709-28. doi: 10.1210/jc.2008-1410.
3. Davi MV, Pia A, Guarnotta V, Pizza G, Colao A, Faggiano A; NIKE Group. The treatment of hyperinsulinemic hypoglycaemia in adults: an update. J Endocrinol Invest. 2017;40:9-20. doi: 10.1007/s40618-016-0536-3.
4. Awad DH, Gokarakonda SB, Ilahi M. Factitious Hypoglycemia. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022.
5. Shah P, Rahman SA, Demirbilek H, Güemes M, Hussain K. Hyperinsulinaemic hypoglycaemia in children and adults. Lancet Diabetes Endocrinol. 2017;5:729-42. doi: 10.1016/S2213-8587(16)30323-0.
6. Kittah NE, Vella A. Management of endocrine disease: Pathogenesisand management of hypoglycemia. Eur J Endocrinol. 2017;177:R37-R47. doi:10.1530/EJE-16-1062.
7. Griffiths MJ, Gama R. Adult spontaneous hypoglycaemia. Hosp Med. 2005;66:277-83. doi: 10.12968/hmed.2005.66.5.
8. Rajendran S, Philip B, Gopinath R, Suresh B. RPHPLC method forthe estimation of glibenclamide in human serum. Indian J Pharm Sci. 2007;69: 796–9. doi: 10.4103/0250-474X.39436.