Clinical case of Factitious Hypoglycemia Due to Deliberate Insulin Analog Administration and Spontaneous Hyperglycemia in a Patient with Hypothyroidism.

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Research Article

Keywords: Hypoglycemic syndrome, factitious hypoglycemia, insulin analog administration, Munchausen syndrome

Posted Date: May 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1585614/v1

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Abstract

Background

Hypoglycemic syndrome is a life-threatening condition that can lead to disruption of the brain and internal organs, and in severe stages to irreparable consequences or death due to hypoglycemic coma. Factitious hypoglycemia (FH) is the deliberate use of insulin preparations or oral hypoglycemic drugs to reduce blood glucose level. In addition to the fact of deliberate administration of insulin analogs is difficult to prove: immunoassays targeting different epitopes and thus demonstrating high cross-reactivity are necessary (Abbott ARCHITECT).

Case presentation:

Patient S., 34 years old, was admitted to the Endocrinology Research Centre in September 2021 with a diagnosis of hypothyroidism and DM. On admission she complained of impaired swallowing, sore throat, "twitching" pain in the neck, hoarseness of voice, episodic headaches, periorbital swelling mainly in the morning, high glycemia indexes up to a maximum of 34 mmol/l, numbness and swelling of lower extremities. Only under strict medical supervision was normalization of the free T4 level achieved. Installation of a continuous interstitial glycemic monitoring system made it possible to determine the discrepancy between the blood glucose reading from the finger (up to 18 mmol/L), which may have been intentionally contaminated with a sweet solution, and the system recorded in the interstitium (normoglycemia). An important feature of the case, are the borderline ambiguous results of hormonal parameters against the background of hypoglycemia: there was no suppression C-peptide (more than 0.6 ng/mL), and insulin levels were either greater than 3 µU/mL or less, but both hormones were at borderline levels.

Conclusions

This clinical example illustrates the need for vigilance regarding the intentional taking of medications or, conversely, non-compliance with prescriptions in each patient. Only under strict medical supervision was normalization of free T4 levels achieved. Installation of a continuous interstitial glycemic monitoring system made it possible to determine the discrepancy between the blood glucose reading from the finger (up to 18 mmol/L), which may have been intentionally contaminated with a sweet solution, and the system recorded in the interstitium (normoglycemia).

Background

Factitious hypoglycemia (FH) is the deliberate use of insulin preparations or oral hypoglycemic drugs to reduce blood glucose level [1]. FH is a variant of Munchausen's disease [2].
Hypoglycemia (glucose < 55 mg/dL [3.0 mmol/L]) is rare in people without diabetes mellitus (DM) who do not receive hypoglycemic medications due to the good physiological efficiency of counterregulatory mechanisms [3–5]. In the diagnosis of nondiabetic hypoglycemia (NDH), it is always necessary to consider the possibility of FH [3]. The prevalence of FH among other causes of NDH is approximately 10.8% [1]. This condition is the most common in persons with medical education and/or access to diabetes medications [1, 6–8]. In patients with mental health problems, FH can significantly affect the clinical picture of the disease and the establishment of a correct diagnosis [1, 9].

In the differential diagnosis of the causes of NDH the following are considered: endogenous hyperinsulinism due to insulinoma, autonomous β-cell hypersecretion, autoimmune disorders, as well as in patients after bariatric surgery; hypoinsulinemic hypoglycemia in hypocorticism and tumors producing insulin-like growth factor 2 and pro-insulin-like growth factor 2. In addition, genetically determined disorders of glucose metabolism and insulin secretion can be diagnosed in adult patients in rare cases [1, 3, 10]. FH is one of the most difficult conditions to diagnose [3, 11]. Timely detection of FH avoids costly and time-consuming investigations required to rule out alternative causes of hypoglycemic syndrome [2, 3].

All patients with suspected NDH undergo standard venous blood sampling against the background of manifest hypoglycemia (during fasting test or spontaneous hypoglycemia) to determine glucose, insulin and C-peptide concentrations. Initial results in most cases suggest the cause of hypoglycemia [5].

Both endogenous and exogenous hyperinsulinism can have absolutely identical laboratory signs when taking insulin secretagogues, when the substance of oral sugar-lowering drugs needs to be examined by high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS). When human insulin preparations are administered, unlike endogenous hyperinsulinism, C-peptide levels are suppressed because exogenous insulin does not contain C-peptide (and does not contain proinsulin). However, the determination of exogenous insulin in recombinant form (insulin analogs) can be difficult in most laboratories that use cross-reacting kits exclusively with human insulin. In such cases, we will see in the assay that not only C-peptide but also insulin is suppressed [5, 7]. Often test system manufacturers do not report low cross-reactivity of immunoanalyzes kits with certain insulin analogs, which prevents clinicians and the laboratory service to correctly interpret the results when FH is suspected[12].

Human insulin contains two polypeptide chains that are 21 (A-chain) and 30 (B-chain) amino acid residues in length. All insulin analogs used for the treatment of DM have amino acid sequence modifications in the C-terminal part of the B-chain. Therefore, immunoassays specifically designed to detect endogenous human insulin targeting the carboxy end of the B-chain have low cross-reactivity with Roche Elecsy insulin analogs (RE) whereas others target different epitopes and therefore exhibit high cross-reactivity Abbott ARCHITECT (AA).
AA and RE test systems have these different properties in serum insulin immunoassays. The combination of these kits allows reliable determination of endogenous and exogenous insulin levels [12].

We present the clinical case of Munchausen's syndrome in a patient with multiple endocrine disorders, including proven FH due to insulin analogs administration.

**Case Presentation**

Patient S., 34 years old, was admitted to the Endocrinology Research Centre (ERC) in September 2021 with a diagnosis of hypothyroidism and DM. On admission she complained of impaired swallowing, sore throat, "twitching" pain in the neck, hoarseness of voice, episodic headaches, periorbital swelling mainly in the morning, high glycemia indexes up to a maximum of 34 mmol/l, numbness and swelling of lower extremities.

On examination: the general condition was relatively satisfactory, oriented in space and time, contact was easy; body type was hypersthenic, body weight 95 kg, height 166 cm, body mass index 35.19 kg/sq.m. (II degree obesity); on the back there were areas of vitiligo; on the skin of the front surfaces of both thighs there were rough scars (according to the patient, post-injection abscesses); on other organs and systems without special features; the patient's appearance was unkempt, her clothes and hair were dirty.

In the life history: three childbirths; smoker; DM in a paternal relative. The patient does not work (education: engineer).

According to the medical history of the patient, since the summer of 2020 the patient had been suffering from sore throat, tonsillitis diagnosed, treated with various antibacterial drugs - without positive effect. In October 2020, subacute thyroiditis was diagnosed. She was treated with prednisolone 30 mg/day for about a month with effect. In November 2020, hypothyroidism was diagnosed based on the results of hormonal blood tests, and she was prescribed levothyroxine sodium 50 mcg. Further, due to decompensation of hypothyroidism, the dose of levothyroxine was gradually increased. In February 2021, severe sore throat, reappointed prednisolone at a dose of 60 mg a day, received for 2 months with gradual withdrawal by the end of July 2021. After withdrawal of the drug, she again experienced a worsening of her well-being: complaints of impaired swallowing, hoarseness of the voice. In the blood test of August 14, 2021 (against the background of taking 200 mcg of levothyroxine sodium): TSH 144 mcMU/ml, free T4 was not investigated. Thyroid gland ultrasound investigation of in September 2021: volume 59 ml, thyroiditis pattern. Examination in a specialized medical institution was recommended.

In addition, according to the medical records, in March 2021 there was an episode of unconsciousness, an ambulance team was called, and she was hospitalized with hyperglycemia of 26 mmol/l. Intensive insulin therapy (Insulin lispro 8–35 units 3 times a day, Insulin-isophan 30 units in the morning and in the evening) was initiated at the hospital. After discharge, due to complaints of high glycemia, Metformin was added to therapy (received 1000 mg in the morning and evening) - no effect, glycemia up to 34 mmol/l on self-measurement. Recommendation for examination in a specialized medical institution.
Against the background of taking Prednisolone, she has noted weight gain, since March 2021, of about 40 kg (weight in August 2021 – 100 kg).

On September 21, 2021, she was hospitalized for the first time at the ERC. Decompensation of primary hypothyroidism against the background of autoimmune thyroiditis was confirmed: TSH 108 mE/l, AT to TPO > 1000 ME/ml, AT to TG > 40000 ME/ml, free T4 < 5.15 pmol/l. Thyroid ultrasound: volume 42 ml, signs of autoimmune thyroiditis (according to CT scan, the trachea is not displaced). The dose of levothyroxine sodium was increased to 300 mcg. Under medical supervision, the free T4 level was normalized at 11.29 pmol/l for 5 days.

Discordant glycemia from 33 mmol/l to 2.1 mmol/l according to a glucometer (no hyperglycemia was registered in venous blood), HbA1c 5.2% were noted in the department against the background of insulin therapy. At hyperglycemia, there were no ketones in the urine. Taking into account alternating hyper- and hypoglycemia, presence of autoimmune diseases (thyroiditis, vitiligo) and suspicion of autoimmune diabetes, DM in a relative of the patient, as well as to exclude insulin autoimmune syndrome, antibodies to insulin, glutamate decarboxylase, tyrosine phosphatase were examined - normal. Additional hormonal blood tests were performed: ACTH 13.38 pg/ml, cortisol 499 nmol/l, IGF1 121.3 ng/ml - adrenal insufficiency and tumor producing insulin-like growth factor 2 were unlikely (IGF1 levels were usually suppressed to 100 ng/ml or less in such tumors).

On September 22, 2021 she was transported to the intensive care unit due to an episode of mental confusion, accompanied by nausea, vomiting, headache, with a background glycemia of 3.2 mmol/L. In the intensive care unit, glycemia readings were within 4.5–8.3 mmol/l for 2 days against the background of complete withdrawal of insulin therapy and metformin, with intravenous injection of glucose solution (then the glucose-lowering therapy was not resumed). According to multi-slice computed tomography (MSCT) of the brain: no pathological changes were revealed, heterogeneity of the pituitary gland structure. Presence of type 1 DM, taking into account clinical picture and C-peptide level of 2.05 ng/ml, is unlikely. An oral glucose tolerance test (OGTT) was performed: no evidence of DM was obtained: fasting glucose 4.96 mmol/l, 2 hours later 7.39 mmol/l. Thus, artifical hypo- and hyperglycemia was suspected.

Continuous interstitial glycemia monitoring was performed (Fig. 1). Elevated glucose values (up to 18 mmol/L) were recorded only by glucometer, when no clinically significant hyperglycemia was detected in the interstitial uid at one time (Fig. 2): glucose from 2.4 to 8.1 mmol/L.

Hypoglycemic states were repeatedly noted (Fig. 3), and in one such episode venous blood sampling was performed: glucose 1.86 mmol/l, insulin 2.2 µU/ml, C-peptide 1.18 ng/ml, substance of sugar-lowering drugs by tandem mass spectrometry was not found, proinsulin less than 0.5 pmol/l (Table 1). Taking into account discordant values of insulin and C-peptide (insulin level is typical for hypoinsulinemic variant of hypoglycemia, and C-peptide level for hyperinsulinemic variant), it was decided to perform a fasting test to re-examine these hormones against hypoglycemia.
Figure 2. Glycemic discrepancy between glucometer readings and continuous interstitial glycemic monitoring system readings.

Table 1
The Patient’s Laboratory Data on Spontaneous Hypoglycemic Episode

<table>
<thead>
<tr>
<th>Test</th>
<th>Value (units)</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>1.86 mmol/l</td>
<td>3.1–6.1</td>
</tr>
<tr>
<td>Insulin</td>
<td>2.2 µU/ml</td>
<td>2.6–24.9¹</td>
</tr>
<tr>
<td>Substances of blood glucose-lowering drugs</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>C-peptide</td>
<td>1.18 ng/ml</td>
<td>1.1–4.4¹</td>
</tr>
<tr>
<td>Proinsulin</td>
<td>&lt; 0.5 pmol/l</td>
<td>0.70–4.30¹</td>
</tr>
</tbody>
</table>

¹ - Reference interval for euglycemia

The fasting test was completed 1.5 hours after the meal, venous blood values were consistent with hyperinsulinemic hypoglycemia, and insulin was tested with the kit RE. Since the laboratory data were borderline, this blood sample was tested with the kit AA (Table 2).

Table 2
The Patient’s Laboratory Data at the end of the Fasting Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Value (units)</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>1.64 mmol/l</td>
<td>3.1–6.1</td>
</tr>
<tr>
<td>Insulin (RE)*</td>
<td>3.16 µU/ml</td>
<td>2.6–24.9¹</td>
</tr>
<tr>
<td>Insulin (AA) **</td>
<td>89.9 µU/ml</td>
<td>2.6–24.9¹</td>
</tr>
<tr>
<td>C-peptide</td>
<td>1.41 ng/ml</td>
<td>1.1–4.4¹</td>
</tr>
</tbody>
</table>

* kit Roche
** kit Abbott

¹ - Reference interval for euglycemia

According to the findings, FH was confirmed due to exogenous administration of an insulin analog preparation - Munchausen's syndrome. After discussing the results, the patient calmly denied the administration of insulin preparations. We had a serious conversation about the need to take medications only with doctor’s prescription and the potential danger to life and health of independent use. A psychiatrist consulted the patient and diagnosed the psychogenically induced chronic anxiety-depressive disorder with panic attacks. Found out that when she was 11 years old she suffered from severe criminal
stress, tried to hold herself outwardly, gradually had anxiety attacks, which she relieved by smoking 2–3 packs a day, milder anxiety attacks by several cigarettes; 2017, she suffered a severe loss reaction, after which, in order to calm down, there were repeated alcoholic excesses. The patient was given recommendations for drug treatment and further psychotherapy.

**Discussion**

Presented clinical case has some features:

- Only under strict medical supervision was normalization of free T4 level achieved, which may already indicate a low compliance of the patient as the cause of “uncompensated” hypothyroidism for a long time. In an outpatient setting, an experienced physician can only try to remedy the situation by thoroughly educating the patient about the potential health damage of not following the doctor’s orders.

- When the patient was admitted to the intensive care unit with 24-hour observation and the patient accordingly had no access to personal belongings, euglycemia was observed during this period, and “suddenly” the need for insulin preparations disappeared. Factitious hyper- and hypoglycemia were then suspected. Unfortunately, round-the-clock observation is a costly medical event, but sometimes specialists are forced to use this approach to identify Munchausen's syndrome in order to establish the cause of the patient’s deteriorating condition. Numerous examinations are often performed before an exact diagnosis is made, which also leads to high costs and unnecessary medical interventions for the patient [2].

- The installation of a continuous glycemic monitoring system made it possible to determine a discrepancy between the blood glucose reading from the finger (up to 18 mmol/L), which may have been intentionally contaminated with a sweet solution, and the one recorded by the system in the interstitium (normoglycemia). In such cases, compliance with capillary blood sampling technique is of utmost importance: the patient should wash his hands thoroughly with soap and water, wipe them dry; the nursing staff should supervise this and additionally wipe the puncture site with a dry cotton swab.

- An important feature of the case is borderline ambiguous results of hormonal parameters against the background of hypoglycemia. According to Endocrine Society criteria, it is important to clearly define the variant of hypoglycemia (hyper- or hypoinsulinemic), but in our case it was difficult: there was no suppression of C-peptide (more than 0.6 ng/ml) and insulin levels were either more than 3 µU/ml or less, but both hormones were at borderline levels. In our opinion, this is due to a longer half-life of C-peptide compared to insulin [13], and possibly to the presence of insulin resistance in a patient with grade II obesity. Thus, getting borderline results of insulin and C-peptide in the background of hypoglycemia should be interpreted very carefully, diagnostic goals in this situation may be expanded.

**Conclusion**
1. This clinical example illustrates the need for vigilance regarding the intentional taking of medications or, conversely, non-compliance with prescriptions in each patient.

2. When inappropriate use of medications is suspected, the clinician should first conduct an explanatory discussion with the patient about the health benefits of the prescribed therapy and the inappropriateness of off-prescription medications. The discussion should be conducted in a calm, non-accusatory tone and should focus only on presenting the problem as a whole. If psychological disturbances are evident, appropriate help should be recommended for the patient.

3. In patients with nondiabetic hypoglycemia of unclear genesis, careful analysis of the laboratory data obtained and timely initiation of investigations in this direction are necessary. In hyperinsulinemic hypoglycemia and in the absence of visualization of insulinoma by first-line methods, the study of substances of sugar-lowering drugs in a blood sample in the background of hypoglycemia is indicated. In hypoinsulinemic hypoglycemia, after exclusion of hypocorticism and IGF2-producing tumor, insulin testing with a high-sensitivity kit is necessary in this blood sample. The laboratory service must be aware of the specificity of the insulin assay kit used in order to interpret the results correctly.

4. All cases of hypoglycemia with borderline insulin and C-peptide values should be interpreted with extreme caution, and the diagnostic goals in this situation may be broadened: both the search for substance-derived antidiabetic drugs and the determination of exogenous insulin are possible.

5. Timely diagnosis of FH will prevent multiple (including invasive and radiation-loaded) imaging studies to search for tumor pathology.

6. All patients with FH need psychiatric/psychological care.

7. Currently, the search for methods clearly defining exogenous insulin administration is still required, but not based on indirect results, but with detection of a specific molecule of the drug and/or its obligatory component. Such a method could potentially be HPLC-MS/MS with some prior sample preparation.

**Abbreviations**

**Factitious Hypoglycemia (FH)**

Nondiabetic hypoglycemia (NDH)

High performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS).

Diabetes mellitus (DM)

Endocrinology Research Centre (ERC)

Multi-slice computed tomography (MSCT)

Oral glucose tolerance test (OGTT)
ROCHE ELECSYS (RE)
ABBOTT ARCHITECT (AA)

Declarations

Ethics approval and consent to participate

Approved by the ERC Local Ethics Committee.

Consent for publication

The written informed consent to the publication of this article was obtained from the patient.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

Funding

Financial Support: This work was supported by the Ministry of Science and Higher Education of the Russian Federation (agreement No. 075-15-2020-899)

Authors' contributions

MY is the main author, who originally proposed the article, clinically suspected FH in the patient and took part in writing the manuscript. IK made a major contribution to the writing of the manuscript and prepared the figures. MY and IK translated and reviewed the manuscript, making a major contribution to the discussion and the conclusions. MY, IK and NP were the attending physicians of the patient, provided and interpreted the data of the examination, laboratory and clinical studies. ET, GM consulted the patient in a hospital, reviewed the manuscript and made substantial recommendations. All authors have read and agreed to the published version of the manuscript.

Acknowledgements

Not applicable

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References


Figures
Figure 1

Continuous interstitial glycemic monitoring.

Figure 2
Glycemic discrepancy between glucometer readings and continuous interstitial glycemic monitoring system readings.

![Continuous interstitial glycemic monitoring. Arrows indicate episodes of hypoglycemia.](image)

**Figure 3**

Continuous interstitial glycemic monitoring. Arrows indicate episodes of hypoglycemia.