

Recurrent episodes of hypoglycaemia with increased production of the tissue hormone adiponectin: A case report

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Abstract

Long-term glucocorticoid therapies are known to be associated with recurrent secondary adrenocortical insufficiency. This paper addresses a case of severe hypoglycemia as a rare side effect of the overproduction of the tissue hormone adiponectin.

Anamnesis

A 54-year-old female patient was admitted to the hospital in December 2012 when she lost eight kilos of body weight in four months. She was diagnosed with Type II diabetes mellitus and was treated with metformin. This treatment caused the woman to suffer bouts of symptomatic hypoglycemia. There was a medical history of a mixed connective tissue disease (initial diagnosis 1996) and adnexectomy (September 2012). A Computed Tomography (CT) scan excluded insulinoma, however, a CRH-test (corticotropin releasing hormone) confirmed that the woman was suffering from adrenocortical insufficiency due to long-term prednisolone therapy. A retarded glucocorticoid was prescribed to the patient. Her blood glucose levels and bodyweight returned to normal and she was discharged from hospital.

The woman suffered from persistent hypoglycemic events and was readmitted to hospital four months after returning home in April 2013. Diagnostics were undertaken and the laboratory values, an initial STH-elevation (somatotrophin) and elevated IGF-1 (insulin-like-growth-factor), were difficult to interpret. It was theorized that the patient had a latent adrenocortical insufficiency and a tendency to suffer hypoglycemia in stressful situations and during physical exertion, when the hydrocortisone taken was almost fully eliminated and counter-regulating hormones were insufficiently available. The patient took the drug Lodotra in the evening. It was at its height of effectiveness between 5 am and 8 am and by lunch time, the drug level was no longer sufficient, leading to the theory that the patient was suffering from a shortage of hydrocortisone. The decision was made to prescribe 15 mg of hydrocortisone at noon until the next hospitalization. The patient was advised to monitor hypoglycemic events.

The temporarily increased STH-values could be interpreted as a counter-regulation to the hypoglycemic events and the hypoglycemia caused by glucose-exposure could be interpreted with a significant insulin increase and insufficient counter regulatory hormones in the late phase. Elevated IGF-1 remained the focus of the treatment and

consideration was given to the possibility that a mixed connective tissue disease could lead to an increase in production of IGF-1 and cause hypoglycemic events. The patient was advised to avoid large quantities of carbohydrates to prevent excessive increases in insulin. As part of ongoing treatment, the patient continued to report persistent hypoglycemic episodes. An extensive analysis of scientific literature revealed a similar case which was published by Venugopal and colleagues in 2013 [1].

Clinical appearance

The patient presented with a Body Mass Index (BMI) of 18,8 kg/m² and exertional dyspnea. She did not have cyanosis or edemas on her legs. Other vitals include vesicular breathing, normal heart sounds, blood pressure at 12/60 mm/Hg and a resting heart rate of 62/min.

Laboratory diagnostics

Laboratory values: hemoglobin: 7,5mmol/l [reference range: 7,45-9,31mmol/l]; hematocrit: 0,35 [reference range: 0,33-0,43]; leukocytes: 3,42/μL [reference range: 4,2-10/μL]; thrombocytes: 141/nL [reference range: 150-400/nL]; c-reactive protein: 0,4mg/L [reference range: < 5mg/L]; creatinine: 52μmol/L [reference range: ≤ 80μmol/L]; urea: 2,7mmol/L [reference range: 3-8,3mmol/L]; erythrocyte sedimentation rate: 20mm [reference range: <20mm after 1h], rheumatoid factor: negative, antinuclear antibodies: 1:3200, dsDNA antibodies: 196, U1-RNP detection, insulin: 288, c-peptide: 2,9. Important endocrinological serum parameters are listed in Table 1.

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Table 1. Patients serum parameters

Serum parameters	Normal range	Patients values
Glucose (mg/dl)	70–110	34,2
Insulin (µU/ml)*	3.0–25.0	112
C-peptide (ng/ml)*	0.9–4.0	7.2
Proinsulin (µU/ml)	1.1–4.4	7.6
Adiponectin (µg/ml)	8.3–13.9	>>30
IGF-1 (ng/ml)	94-252 (51-233)	275
Big-IGF-2 (ng/ml)		
Anti-insulin receptorantibodies	-----	Negative
Anti-insulin antibodies	-----	Negative
Analoguesinsulin	-----	Negative

The results showed a hyperinsulinemia and increased levels of adiponectin at a hypoglycemic serum glucose level. There were anti-insulin receptor antibodies in the patient's serum. There was no evidence of anti-insulin antibodies.

*condition of fasting

Diagnosis

Recurrent hypoglycemia due to an increased adiponectin production.

Relevant secondary diagnoses

- mixed connective tissue disease, initial diagnosis 1996
- partial adrenocortical insufficiency, initial diagnosis 2012 during long-term treatment with prednisolon
- condition after adnexectomy 2012 and hysterectomy 2015 (adenocarcinoma of the uterus)
- coronary heart disease and condition after myocardial infarction 2015

Treatment and progress

The excessive increase of adiponectin was found to be responsible for the patient's hypoglycemic events, after excluding insulinoma and the presence of adiponectin-fragments and treating the latent adrenocortical insufficiency with hydrocortisone. The patient was prescribed Sandostatin. It was taken once a month and the hypoglycemic events could be reduced (minimal blood sugar level before treatment up to 1.2 mmol/l, currently up to 3.8 mmol/l). Elevated HbA1c and IGF-1 values were concurrently focused on and IGF-1 values dropped during the treatment. With 7.2 % (reference range 4–6 %) in 11/17 the HbA1c was in the range of diabetes mellitus, raising questions of the possibility of Big-IGF-2. Blood samples were sent to a specialized laboratory in Utrecht. The results showed a standard value for IGF-2 (13,6 µg/l, reference range 9–27 µg/l) and Big-IGF-2 was excluded. Regarding the HbA1c values consideration must be given to the diabetes mellitus and hypoglycemia. This should be discussed with the patient. Depending on the hypoglycemic events the Somatostatin will be further reduced.

Discussion

Hypoglycemia is known as a differential diagnosis of anti-insulin-receptor-antibody diseases, in patients with manifest autoimmunity [2,3]. Anti-receptor-antibodies can inhibit the insulin bond, which inhibits insulin-clearance and causes a rise in the level of plasma insulin. Because hypoglycemia suppresses the secretion of beta cells, the levels of c-peptide are usually low.

There are rare reports of paradoxical hypo and hyperglycemic states and increased adiponectin levels at the same time [1]. Adiponectin is secreted by the bodies fat cells. Anti-diabetogenic, anti-atherogenic

and anti-inflammatory qualities are attributed to adiponectin. Patients suffering from adipositas or diabetes mellitus type II have low serum levels and are sensitive to insulin compared to people with normal weight [4]. Glucocorticoids and TNF- α inhibit the expression, despite Lodotra 4 mg and hydrocortisone high levels of adiponectin were noticed [5]. Elevated adiponectin levels in women with autoimmune diseases without an effect on the blood sugar levels have been described [6]. What new information is sufficient to modify existing clinical practice? In rheumatological systemic diseases with episodes of hypoglycemia an increased adiponectin production should be considered besides the common causes for hypoglycemia. Especially the role of adiponectin in the glucose metabolism is becoming very obvious. A therapy with a somatostatin receptor blocker could be helpful.

Limitations

- This is a single case, so a misinterpretation of the findings is possible.
- Our results may not be generalizable.
- The individual studied may be atypical of the larger population.

Future directions

In the future, an extended diagnosis of hypoglycaemia should be carried out, in particular an improvement of the therapeutic application possibilities with somatostatin analogues.

Conclusion for clinical practice

Despite the possible incorrect interpretation of the findings, therapy with somatostatin analogues has led to a significant improvement in the clinical situation. The 54-year-old female patient was treated effectively with Somatostatin and further hypoglycemic events were prevented. The actual mechanism needs to be clarified in order to the laboratory values.

This study adds a new perspective regarding clinical diagnostics of hypoglycemia especially in mixed connective tissue diseases and therapeutical approaches with somatostatin analogues.

Conflicts of interest

The corresponding author declares no conflicts of interest for himself and the co-authors.

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