

## Case Report

# Corticotrophin deficiency in end-stage renal failure led to recurrent hypoglycemia

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Reactive hypoglycemia caused by an insulinoma, pre-diabetic metabolic state, fluctuations in diabetic metabolic situation and antidiabetic medication is commonly known. We report on the case of an unusual multi-factorial occurrence of a woman with recurrent hypoglycemia, which cannot be explained adequately by a single commonly known cause. We refer to a cachectic non-diabetic 52-year-old German woman, admitted to our clinic for clarification of an insulinoma. The possibility of an insulinoma could be excluded as well as co-morbidities linked to non-diabetic hypoglycemia like sepsis, alcohol dependence liver disease, cancer or self-harm with hypoglycaemic agents. However, our diagnostics revealed a corticotrophic insufficiency as a result of longtime cortisol medication. Still, further causes have additionally to be considered, including dysfunctional elimination of glucose, renal and hepatic gluconeogenesis and glucose regulation on dialysis. These reasons are assumed as the pathological factors. Although insulinoma is a possible cause of hypoglycemia, it is not the only pathogenesis. Here, various alternative factors are defined, examined and in part treated specifically. As therapy, besides nutritional counselling, the patient received cortisol. After a 20 month follow-up symptoms of symptomatic hypoglycemia were absent.

**Key words:** Case report, hypoglycemia, chronic kidney disease, corticotrophic insufficiency, epileptic seizure.

## INTRODUCTION

Recurrent hypoglycemia can lead to a life-threatening event with severe health complications, including autonomic symptoms like addephagia, nausea, emesis, bleeding, tachycardia, hypertension, tremor, agitation and neuroglycopenic symptoms like dizziness, disorientation, slurred speech, convulsion, headache until coma and death. A positive diagnosis of hypoglycemia is defined with venous blood glucose level  $< 0.55$  g/L (or  $< 3$

mmol/L) during the symptoms. The presence of the so-called Whipple's triad is considered positive, if biochemical hypoglycemia (blood glucose level  $< 0.55$  g/L) is accompanied by hypoglycemic symptoms, which resolved after correcting the hypoglycemia. Each hypoglycemia should be investigated. For many years it is known that hypoglycemia in non-diabetics is very likely a result of several mechanisms (Rutsky et al., 1978). It is

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absolutely necessary to clarify the specific etiology for each patient.

## CASE PRESENTATION

A 52-year-old German woman was referred by an emergency physician to a neurological clinic nearby, with hypoglycemia and symptomatic epileptic seizure. By venous blood glucose from 35 mg/dl, in a setting with recurrent hypoglycemia, the clinic remarked suspicion of an insulinoma. The last tonic-clonic cramp attack took place one month earlier. The epileptic seizures began one year before. We admitted the cachectic woman to clarify the suspicion. The woman was free of symptoms at admission, except of pruritis on her entire body and pain in the right knee as a result from a fall six month earlier. The physical examination was otherwise unremarkable. She took prednisolone (20 mg daily) after renal transplantation and furthermore she engaged immunoglobulin (Sandimmun 250 mg daily) and mycophenolatmofetil (Cell Cept 2500 mg daily), all deposited about five years before admission. Her medical history includes hypertension, which she is taking Lercanidipin (Carmen 5 mg) for, on dialysis free days.

She must have hemodialysis three times a week and this is the second period of time she gets regular dialysis, concerning recurrent terminal chronic renal insufficiency. The patient has a body mass index (BMI) of 15.9, by 170 cm height and 46 kg weight. There was no weight gain over the last months. She is living consolidated with her husband and their only daughter. She smoked about 15 pack a year of cigarettes in her life. No family history of any metabolic or endocrine disorder is known. Neither abdominal sonography nor abdominal computer tomography did demonstrate any pathology.

Her initial laboratory assessment revealed hyperkalemia at 8.0 mmol/L, low hemoglobin A1c at 4.3%, hypoproteinemia at 55 g/L, increased kreatinine at 6.56 mg/dl, low estimated GFR (MDRD-formula) at < 15 ml/min, increased urea at 68 mg/dl, low erythrocyte count at 3.1 T/L, low hemoglobin level at 94 g/L, low hematocrit level at 0.30 l/L, increased platelet level at 442 G/L, increased C-reactive protein at 9 mg/L, high TSH at 38 mU/L, low fT3 at 2.7 pmol/L, increased C-peptide at 7.52 µg/L and low insulin level at 8.15 mU/L. Glucose has a normal value with 88 mg/dl. By routine laboratory value examination, we detected pathological high values for alanine aminotransferases at 58 U/L and blood coagulation (INR 1.2 Ratio, PTT 48 s).

The patient shows a long history of hospital stays, beginning with an ureter plastic and an uterus exstirpation about thirty years ago. Eighteen years before admission, dialysis was initiated, because of persistently poor kidney function in chronic pyelonephritis. Allogenic

kidney transplantation ensued nine years before admission. At that time cachexia was mentioned for the first time in the documentations. Phases of infections and phases of hypokaliemia are described. Six years before admission succeeded a gall bladder excision by recurrent trouble with gall stones and chronic inflammation. Recurrent anemia occurred most likely from renal insufficiency. Five years before admission, a second episode of dialysis followed (clearance of 2.5 ml/min and creatinine above 5 mg/dl). One year before admission and over five years of secondary hyperparathyroidism with PTH levels above 1600 ng/L, a complete parathyroidectomy and a complete thyroidectomy by nodular goiter was realized. In that year, the first epileptic seizure occurred. The grand-mal seizures resulted in the medication of valproate 1000 to 1500 mg daily, but continued nevertheless. Because of low blood levels of valproate in several controls, malcompliance was assumed to be the reason for ongoing seizures. Also one year before admission, the European Transplantation Centre defeated a second kidney transplantation. They justified the refusal because of the following facts:

1. Depressive psychological situation.
2. Cachectical malnutrition with BMI values about 14 to 15.
3. Non-compliance with the daily intake of her medicine because of a recurrent valproate level lower than 10 mg/L, inspite of stationary adjustment.
4. Recurrent hypokaliemia.
5. Actually intermittent tonic-clonic cramp attacks.

## Consent

Written informed consent was obtained from the patient for publication of this case report.

## RESULTS

Initially we arranged an oral glucose tolerance test (Table 1) and a 72-h fasting test (Table 2), but stopped after 36 h, concerning a blood glucose level from 33 mg/dl. The fasting test indicates low levels of pro-insulin, insulin and a slightly increased level of c-peptide, which was explained by a renal lack of elimination. The combination demonstrated a normal insulin/glucose-ratio and no consideration for insulinoma or diabetes. Toxicological testing for antidiabetic medication showed no serum detection for gliquidon, nateglinid, repaglinid, chlorpropamid, glibenclamid, glibornurid, tolazamid, tolbutamid or glimepirid and eliminated the diagnosis of hypoglycemia factitia. As we detected low cortisol levels in spite of hypoglycemia, we continued with a pituitary

**Table 1.** Patients' data of the OGTT (oral glucose tolerance test).

Time (min)	c-peptide (µg/L)	glucose (mg/dl)	insulin (mU/L)	Pro-insulin(pmol/L)
0	4.26	61	3.82	3.0
30	6.80	67	18.8	3.5
60	6.41	64	11.3	3.2
120	8.44	90	15.9	4.8
240	9.82	69	16.8	4.9

**Table 2.** Patients' data of the fasting test\*

Day	Time	Glucose (mg/dl)	insulin (mU/L)	c-peptide (µg/L)	Pro-insulin (pmol/L)
Day 1	8:00	63	< 2.00	2.20	2.5
	12:00	55	< 2.00	2.02	2.6
	16:00	52	< 2.00	1.67	3.4
Day 2	8:00	46	2.97	2.80	3.4
	12:00	43	< 2.00	2.09	2.8
	16:00	33	< 2.00	1.76	2.7

\*Only three values per day are pictured, but in reality was measured much tighter

**Table 3.** Patients' data of the combined pituitary stimulation test.

Parameter	Dosage
Human growth hormone	Basal 11.8 ng/ml, peak with 19.9 ng/ml after 30 min
Luteinising hormone	Basal 5.0 U/L, peak with 33 U/L after 30 min
Follicle stimulating hormone	Basal 68 U/L, peak with 100 U/L after 60 min
Estradiol	Basal 23 ng/L
Progesterone	Basal 0.34 µg/L
Prolactin	Basal 34.1 µg/L, peak with 85.9 µg/L after 60 min
Adrenocorticotrophin	Basal 14.3 pg/L, peak with 23.6 pg/L after 30 min
Cortisol	Basal 127 µg/L, peak with 157 µg/L after 60 min
Thyrotrophin	Basal 4.8 mU/L, peak with 41 mU/L after 30 min
free tri-iodothyronine	Basal 2.8 pmol/L
free thyroxine	Basal 12 pmol/L
Glucose	Basal 45 mg/dl

stimulating test (Table 3).

Basically the corticotrophic, gonadotrophic, somatotrophic and thyretrophic axis was stimulated by using a standardized stimulation test. A pituitary stimulation test is done with corticotrophin releasing hormone 100 µg (CRH), growth hormone releasing hormone 100 µg (GHRH), arginine 0.5 g/kg body weight, maximal 30 g, gonadotrophin releasing hormone 0.1 mg (GnRH) and thyrotrophin releasing hormone 200 µg (TRH) (Uitz et al., 2013). Concentrations of adrenocorticotrophin (ACTH), cortisol, growth hormone

(GH), insulin- like growth factor- I (IGF-I), luteinising hormone (LH), follicle- stimulating hormone (FSH), oestradiol and progesterone, sexual hormone binding globulin (SHBG), thyrotrophin (TSH), free tri-iodothyronine (fT3), free thyroxine (fT4), and prolactin (PRL) were measured.

The stimulation test allows a normal interpretation of the somatotrophic axis in a postmenopausal situation, with a rather low luteinising hormone concentration, but over all normal gonadotrophic axis. The basal prolactin shows an already increased value, in the context of renal

insufficiency according to reduced elimination. We find an insufficient stimuable cortisol at baseline glucose from 45 mg/dl. But physiologically, you can expect much higher cortisol stimulation in that moment. Further more, there was a latent hypothyroidism. The result demonstrated a partial hypopituitarism (Uitz et al., 2013).

## DISCUSSION

In adult non-diabetic patients, the diagnosis of hypoglycemia usually involves classical causes, especially insulinoma. But hypoglycemia can also be related to drugs, alcohol, critical illness, cortisol or glucagon insufficiency, non-islet cell tumour or severe liver disease. A complete physical assessment is necessary to make the diagnosis. Our case shows an unusual combination of recurrent hypoglycemia, which according to the authors' knowledge cannot be explained by one reason, but only by the combination of various etiologies. We report a case of this unusual condition and summarize data published in the literature. The following knowledge exists about the pathogenesis of hypoglycemia:

1. Current studies lead to the conclusion that human kidney plays an important role in the regulation of glucose homeostasis, by making more gluconeogenesis than ever presumed, taking up glucose from the blood circulation and by reabsorbing glucose from the glomerular filtrate (Mitrakou, 2011). A retrospective study in the USA presents a higher incidence of hypoglycemia in patients with chronic kidney disease (CKD) versus without CKD. They find in analysis of 243,222 patients a rate from 3.46 versus 2.23 per 100 patient-months for CKD versus no CKD. The mortality is increased (Moen et al., 2009).
2. In cases of hemodialysis, the malnutrition derives from following dietary arrangements to prevent uremia and harmful waste products between treatments. Therefore it is not remarkable that dialysis predisposes to hypoglycemia because of the chronic state of malnutrition (Desai et al., 2005). Adverse effects at the time of end stage renal failure are more frequently than previously assumed (Haviv et al., 2000), without identifying detailed pathology until today.
3. Physicians should consider that studies reveal significant changes in glucose concentration during and after hemodialysis, including an influence by the dialysate itself, which can lead to a life-threatening event by glucose disturbance (Sobngwi et al., 2010; Takahashi et al., 2004).
4. Malnutrition in cases of renal failure can cause hypoglycemia, probably by an impaired renal gluconeogenesis (Peitzman and Agarwal, 1977), but maybe an increased glucose utilization also plays a role

in this pathogenesis (Bansal et al., 1979).

5. It has been an assumption for many years that spontaneous uremic hypoglycemia has been attributed to deficiency of precursors of gluconeogenesis, deficient gluconeogenesis, impaired glycogenolysis, diminished renal gluconeogenesis and impaired renal insulin degradation and clearance (Mackowski et al., 1999; Arem, 1989).

6. Another component is the isolated pituitary insufficiency diagnosed in tests as a secondary adrenal insufficiency (SAI). A low cortisol level and symptoms from hypoglycemia to weight loss are following (Andrioli et al., 2006). The glucocorticoid-induced inhibition, which occurs after a long-term cortisol administration, is the most frequent cause of adrenal insufficiency. Almost half of the patients will present corticotrop axis suppression after long-term glucocorticoid treatment. Glucocorticoid dose and duration of treatment might be linked to hypothalamic-pituitary-adrenal suppression. But a progressive cumulative insufficiency can occur at any time as an acute event and can lead to a life-threatening complication. It should be prevented by adapted treatment primarily glucocorticoids and education of the patient.

7. Another insight concerns disturbances of the secretion of pituitary hormones, demonstrated in renal failure (Schaefer et al., 1992).

Glucocorticoids themselves can interact with the regulation of glucose homeostasis and can induce peripheral insulin resistance which can result in reduced glucose disposal and increased endogenous glucose production. The treatment of glucocorticoids can modify pancreatic b-cell function leading to a dysfunctional synthesis of insulin and false registration of blood glucose level. This can lead to hyperglucagonemia, further contributing to glucose homeostasis imbalance and hyperglycaemia (Rafacho et al., 2014).

## Patient perspective

The patient was commenced on hydrocortisone twice daily and had been advised to take stress-dose hydrocortisone in case of intercurrent illness or stressful moments but we cannot reproduce the circadian rhythm of endogenous cortisol production. The patient was contacted for re-evaluation on the phone, twenty months after admission, to find out how she was doing. She said she has never had symptomatic hypoglycemia or seizure attacks again. The lowest measured blood glucose level was 48 mg%.

## Conclusion

The synopsis of all diagnostic findings, after excluding the

opinions of insulinoma, toxicological reasons (hypoglycemia factitia), a positive family history, an extrapancreatic neoplasm, severe liver disease nor radiological signs of malignancy, shows a relevant recurrent hypoglycemia according to a multisystem involvement. We suggest that the secondary adrenal insufficiency derives from a long-term cortisol administration in the setting of a chronic kidney disease. We feel accredited to the assumption that chronic kidney disease and especially hemodialysis play a major part in the glucose homeostasis. The patient took prednisolone over a period of four years, beginning with the kidney transplantation and tapered four years post. We suppose that both the pituitary defect and the terminal chronic kidney disease, play the key role in producing hypoglycemia in this patient. Especially in the case of cachexia, as in our case, the predisposing hemodialysis and therefore the chronic state of malnutrition probably lead to hypoglycemia. Therefore different mechanisms engage and lead to the clinical presentation. We prescribed a substitution of 15 mg hydrocortisone gradable to 45 mg in stressful moments daily. We arranged a nutrition counseling and the recommendation of weight gain. The patient got an emergency certificate and an adaptation of the remaining medicine. The therapy after admission accredited our diagnosis.

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## Conflict of interest

The authors declare that they have no competing interests.

## Abbreviations

**ACTH**, Adrenocorticotrophin hormone; **PTH**, parathyroid hormone; **BMI**, body-mass-index; **TSH**, thyroid stimulating hormone; **ft3**, free tri-iodothyronine; **GFR**, glomerular filtration rate.

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