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Adrenal Crisis in a Female with Undiagnosed Secondary Adrenal Insufficiency and Norovirus Infection: A Case Report

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Abstract

Introduction: Adrenal crisis is a life threating condition that occurs under physical or mental stress on a basis of chronic adrenal insufficiency, commonly in primary adrenal insufficiency but may even occur in secondary or tertiary adrenal insufficiency. The aim of this study is to present a case with adrenal crisis caused by infection with Norovirus on the basis of secondary adrenal insufficiency; and how to manage it.

Case presentation: A 51 year old woman, with a known hypothyroidism and tiredness, is presented with hypovolemic shock because of diarrhea and emesis after a travel abroad. Final diagnosis during the care time was secondary adrenal insufficiency.

Discussion: The anamnesis of hypothyroidism and unexplained tiredness led us to suspect an adrenal insufficiency that could be diagnosed with cortisol at 8 o'clock. Despite the fact that the patient was in a hypovolemic shock with a high stress level the cortisol was immeasurable; and the diagnosis, adrenal insufficiency, could be made. Other tests including ACTH and Imaging are usually needed to discover the subtype of insufficiency. The follow up after 1 month showed no signs or symptoms left and much better condition.

Conclusion: Adrenal insufficiency should be kept in mind when treating patients with unexplained tiredness especially with other endocrinal diseases. The replacement therapy is essential and supporting the patient with information about treatment in special situations is always important.

Keywords: Adrenal insufficiency; Adrenal crisis; Steroid hormones

Introduction

Adrenal insufficiency is a severe condition in which the adrenal glands do not produce adequate and/or enough amounts of steroid hormones, mainly cortisol but may also include impaired production of aldosterone if the insufficiency is primary. It can occur in all age groups and the incidence in Sweden is nearly 1 per 100000 inhabitants. In Europe the main reason is primary, first of all autoimmunity, whereas it is tuberculosis in many developing countries (also primary). The adrenal glands consist of cortex that produces cortisol, aldosterone and androgens; and a medulla that produces adrenalin. Cortisol is a steroid hormone with many functions as stress hormone, protein metabolism, regulation of immune response, stimulating gluconeogenesis and glycogenolysis and a mild effect in sodium retention and water diuresis, whereas aldosterone is a mineralocorticoid hormone that helps in regulation of blood pressure and balance of electrolytes. Cortisol secretion is controlled by the pituitary by ACTH hormone, while aldosterone is controlled by Renin-Angiotensin axis [1-3].

Addison disease (Primary adrenal insufficiency) was described first in the 1800´s. Fatigue, dehydration and weight loss are common symptoms. Craving for salt or salty foods due to the urinary losses of sodium is also common. The patient can seek medical care because of abdominal pain, muscle pains or even depression. In the primary adrenal insufficiency the patient can come because of darkening of the skin (hyperpigmentation). Secondary adrenal insufficiency has the same symptoms except hyperpigmentation (which happens because of higher production of ACTH, which is secreted first as precursor ´POMC´ and then derived to ACTH and MSH ´melanocyte stimulating hormone´) [4,5]. If not treated, adrenal insufficiency may result in severe abdominal pain, vomiting, profound muscle weakness, extremely low blood pressure, weight loss, kidney failure, changes in mood and personality, and in the end shock (adrenal crisis). An adrenal crisis often occurs if the body is subjected to stress, such as an accident, injury, surgery, or severe infection in which death may quickly follow. Adrenal insufficiency can also occur when the hypothalamus or the pituitary gland does not produce adequate amounts of CRH and ACTH relatively. It is more likely that the primary adrenal insufficiency is responsible for adrenal crisis, but sometimes even secondary or tertiary insufficiency can cause it especially if not diagnosed early [6].

Case Presentation

A 51 year old woman presented to our hospital complaining of vomiting, diarrhea and dehydration. Her problem started the same day with syncope in the bathroom, as the husband called the ambulance. In the emergency room the patient had a hypovolemic shock, low blood pressure 60/34, somnolence and Glasgow coma scale 13. The patient stated that the problem began in the early morning of the same day with nausea and diarrhea, and that her husband had also diarrhea nearly one week ago. The clinical diagnosis was a hypovolemic shock secondary to gastroenteritis. Intravenous crystalloids were

administered and the patient received 3 liters Ringer Acetate the first 6 h. Better blood pressure was initially attached with small doses of phenylephrine 0, 1 mg/ml. Metabolic acidosis in an arterial blood gas sampling with the results are shown below (Table 1).

Test	Patient value	Reference Range
PH	7,16	7,32-7,43
Pco2	6,6 kPa	5,3-6,6 kPa
Po2	2,0 kPa	>10 kPa
BE	-11 mmol/l	-3-3 mmol/l
Bicarbonate	15 mmol/l	22-27 mmol/l
So2	81 %	>95 %
Fo2Hb	80 %	>93 %
CoHb	1,0 %	<2 %
MethHb	0,3%	<1,5 %
Sodium	138 mmol/l	137-145 mmol/l
Potassium	4,5 mmol/l	3,6-4,6 mmol/l
Chloride	110 mmol/l	98-107 mmol/l
Calcium, free	1,44 mmol/l	1,08-1,32 mmol/l
Lactate	3,4 mmol/l	0,5-2,3 mmol/l
Hb	144 g/l	117-153 g/l
Glucose	3,9 mmol/l	4,0-6,0 g/l
osmolality	279,7 mmol/kg	275-295 mmol/kg
Anion Gap	6,3 mmol/l	8-16 mmol/l

Table1: Blood sampling in the emergency room.

The patient was transferred to the intensive care unit for monitoring and optimal treatment of the shock. Change from Phenylephrine to Noradrenalin with better effect and arterial needle inserted for blood pressure control.

In the intensive care unit the patient declared that she was in Greece nearly one week earlier. She stated that she was awfully tired over the last year. Furthermore she was not able to work as usual as a teacher for children with special needs. She was forced to report sickness twice in the last 6 months, 4 weeks for each one.

It was approximately the same period when she quitted smoking after 17 years of smoking (17 pack-year). She had problems with tiredness, muscle weakness and lower appetite. She suffered even from migraine with aura and is treated with Zolmitriptan. The patient had even unexplained low vitamin B12 levels and was treated with B12 tablets. Patient started to lose weight gradually and ended up to 14 kilo lower than the previous year. Patient has hypothyroidism that is followed via family doctor, who reduced the thyroxin dose one month ago. Her mother had hypothyroidism as well. Due to the weakness and rash examination for Systemic lupus was done one year ago with negative results (Table 2).

Test	Patient value	Reference range
CRP	8 mg/l	<3 mg/l
INR	1,3 INR	<1,2 INR
aPTT	30 s	20-30 s
TSH	0,02 mE/L	0,3-4,2 mE/L
T4 free	18 pmol/L	12-22 pmol/L

T4 (thyroxin)	108 nmol/L	69-141 nmol/L
T3 free	6,3 pmol/L	3,1-6,8 pmol/L
T3 (Triiodothyronine)	2,0 nmol/l	1,3-2,5 nmol/L
Albumin	32 g/l	36-45 g/l
Creatinine	71 micromole/l	<90 micromole/L
Bilirubin	11 micromole/l	<26 micromole/l
AST	0,57 microcat/L	<0,61 microcat/L
ALT	0,25 microcat/L	<0,76 microcat/L
GGT	0,35 microcat/L	<1,3 microcat/L
leucocytes	11,9 × 10^9 /L	3,5-8,8 × 10^9 /L
Erythrocytes	5,1 × 10^{12}/L	3,9-5,2 × 10^{12} (12)/L
MCV	81 FL	82-98 FL
MCH	27 pg.	27-33 pg.
Thrombocytes	274 × 10^9/L	165-387 × 10^9 /L
Amylase	0,26 microcat/L	0,15-1,10 microcat/L

Table2: In the intensive care unit Day 1.

Clinical examination showed a reduced general condition, pallor, tiredness, tachycardia, tachypnea and weak pulse. No lymph nodes could be detected with palpation and also general fatigue and abdominal pain with no focus and no skin symptoms detected.

Test	Patient value	Reference range
Cortisol 8 am	<15 nmol/L	>100 nmol/L
CRP	80 mg/L	<3 mg/L
ESR	18mm	<20 mm
CRP	80 mg/l	<3 mg/l
INR	1,4 INR	<1,2 INR
aPTT	30s	20-30s
Albumin	25 g/l	36-45 g/l
Creatinine	49 micromole/L	<90 micromole/L
Urea	2,9 mmol/L	3,1-7,9 mmol/L
Bilirubin	17 micromole/L	<26 micromole/L
AST	0,36 microcat/L	<0,61 microcat/L
ALT	0,18 microcat/L	<0,67 microcat/L
Leucocytes	6,7 × 109/L	3,5-8,8 × 109 /L
Thrombocytes	231 × 109 /L	165-387 × 109 /L
Magnesium	0,69 mmol/L	0,70-0,95 mmol /L
Potassium	4,1 mmol/L	3,6-4,6 mmol/L
Calcium ,free	1,25 mmol/L	1,02-1,31 mmol/L

Table 3: Intensive care unit Day 2.

Blood and urine culture were negative, but the faeces culture was positive for Norovirus RNA which can explain the diarrhea that even her husband had. Followings of the blood gas sampling showed better results after treatment with crystalloids (6L Ringer Acetate), glucose and inotropes.

As the patient had Norovirus she was isolated and got hydrated intravenously. Because of the hypothyroidism, earlier tiredness and weight loss and lately slow improvement of blood pressure, adrenal insufficiency was suspected, and a cortisol test along with other tests were taken the day after with results below (Table 3).

The diagnosis (adrenal insufficiency) was made. Adrenal crisis happened because of gastroenteritis. For making a more specific diagnosis ACTH and adrenal antibodies were taken; and even repeating of cortisol sampling.

It showed secondary adrenal insufficiency with low ACTH and no antibodies (No Addison disease and no primary insufficiency) (Table 4). Therefore pituitary hormones were analyzed to see if it was a total insufficiency. Even an MRI for the pituitary gland was implemented (Figure 1).

It showed flat pituitary gland without signs on micro or macro adenoma, with ordinary signal with/without contrast. The results for hormones are shown in Table 5.

Test	Patient value	Reference range
ACTH	<0,50 pmol/L	1,6-14 pmol/L
Adrenal cortex antibodies IgG	neg	neg
21-hydroxylase (21-OH) antibodies	<0,4 kE/L	<0,4 kE/L
Cortisol	<15 nmol/L	>100nmol/L

Table 4: Intensive care unit-Day 3.

Test	Patient value	Reference Range
Prolactin	31 mIE/L	102-496 mIE/L
FSH	42 E/L	3,5-13 E/L follicle phase, 4,7-22 E/L ovulation phase, 1,7-7,7E/L Luteal phase,26-135E/L postmenopausal phase
LH	35 E/L	2,4-13 E/L follicle phase14-96 E/L ovulation phase, 1,0-11E/L Luteal phase,7,7-59E/L postmenopausal phase
Cortisol 8 am	<15 nmol/L	>100 nmol/L
IGF	94 microg/L	53-191 microg/L
Estradiol	<80 pmol/L	<600 pmol/L follicle phase,300-2000 pmol/L middle cycle phase, 300-1000 pmol/L luteal phase

Table 5: Internal medicine unit Day 4.

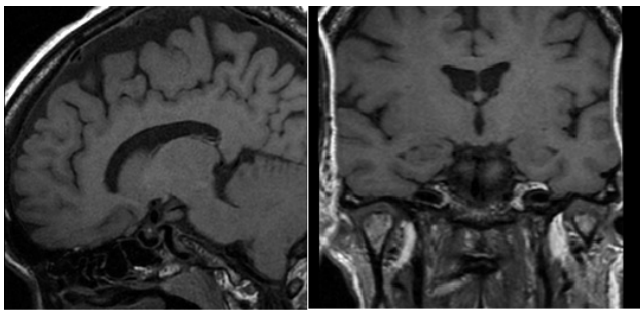

Figure 1: MRI for the pituitary gland.

No abnormalities were detected in pituitary hormones. The low ACTH level was the only pituitary hormone with low levels in the patient who was in postmenopausal period.

As the diagnosis "secondary adrenal insufficiency" was taken, the cortisone treatment began directly after taking the blood samples without waiting for the answer. The Swedish routine for treatment was followed. The patient received injection with hydrocortisone 100 mg intravenously initially, then infusion with 100 mg hydrocortisone in 500 ml saline 9 mg/ml in 4 h. After that a 100 mg hydrocortisone infusion over the rest of the day was administrated. The patient even required crystalloids; ringer acetate 2 L, and 1 L glucose 50 mg/ml. Even addition of electrolytes such as potassium and magnesium needed. The treatment was changed 2 days later to hydrocortisone tablets 10 mg X3. The patient could go home with better condition a week after, with polyclinical following up. The follow up was set one week and one month later, with a doctor and a physiotherapist for rehabilitation.

Discussion

The patient had adrenal insufficiency that probably began more than one year ago, it can even explain the extraordinary tiredness six months ago and the need for sickness reporting twice. The involuntary weight loss and the muscle weakness are well-known symptoms for adrenal insufficiency [7,8]. As the patient had hypothyroidism and Vitamin B12 deficiency she was more expected to have an Addison disease (primary adrenal insufficiency) because of the autoimmunity as a reason for all three; where even Diabetes Mellitus can occur or other autoimmunity diseases. But the patient had low ACTH values talking for a secondary reason and even antibodies for neither 21-hydroxylase nor adrenal cortex suggested. No hyperpigmentation which is often presented in Addison disease. To diagnose more specifically and to see if the reason was an adenoma in pituitary MRI of the pituitary with and without intravenously contrast were ordered. No abnormalities were found. Even the pituitary hormones were measured to define a total pituitary insufficiency. As there were no such problems detected, the diagnosis was an isolated secondary adrenal insufficiency. As the problem was secondary there was no problem in aldosterone as its organization is via the renin-angiotensin axis, consequently; no need for fludrocortisone. The patient received only hydrocortisone 10 mg tab X3, as recommended for adrenal insufficiency with information about increasing the dose to double dose within fever >38, and even three times the normal dose if temperature >39. A revisit to the internal medicine clinic was set both one week and one month after going home. The patient got written information as recommended in Swedish health care national system.

The gastroenteritis with Norovirus after visiting Greece, which even occurred with the patient´s husband, is a stressful event that caused adrenal crisis on a basis of adrenal insufficiency that existed since last year at least. The result of the great fluid loss with both diarrhea and emesis; and on the other side low cortisol levels cooperated to a

hypovolemic shock in the beginning. The story of tiredness the last half year and muscle weakness that could not have been explained with thyroxin-treated hypothyroidism led us to take a cortisol 8 am analysis. As it was very low (<15) despite the infection and high stress level and so adrenal insufficiency was defined. To get a more precise diagnosis there was need for ACTH analyzing, which differs between primary (high ACTH) and both secondary and tertiary insufficiency (low ACTH). As the ACTH was low, and no hyperkalemia or hyponatremia -which can occur because of lower mineralocorticoid levels- were detected, it was defined as a secondary/tertiary adrenal insufficiency; and no autoantibodies for 21-hydroxylase or adrenal cortex talk also for that. The treatment was the same in both cases but it was important to exclude a pituitary tumor and therefore a magnetic resonance imaging with and without intravenously contrast was ordered, and even analyzing of pituitary hormones. As no problem was detected there and patient felt much better after a few days, it was decided to follow up polyclinical. When the patient showed up after a week the situation was remarkably better and eventually could work again with no tiredness by the end.

Conclusion

Adrenal insufficiency should be kept in mind while treating patients with tiredness that cannot be explained with other reasons, especially when weight loss and muscle weakness are found. Even without skin pigmentation that often awake worries and thoughts about Addison's disease, a secondary adrenal insufficiency may exist; and even cause adrenal crisis in high stress levels if it is not diagnosed in good time. Sometimes it can be diagnosed with analyzing cortisol 8 am, but often with Synachten test. Because the patient had adrenal crisis and stress situation and although low cortisol, there was no need for furthermore test for searching for an adrenal insufficiency.

Conflict of Interest

None

Funding

None

Ethnical Approval

The permission for starting this study was obtained from the managing office in the hospital, after getting the patient's allowance.

Consent

Informed consent was obtained from the patient for publication of this case

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