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Addison's disease concomitant with corticotropin deficiency and pituitary CRH resistance — a case report

Współistnienie choroby Addisona z niedoborem kortykotropiny z towarzyszącą przysadkową opornością na CRH — opis przypadku

Krzysztof C. Lewandowski[1, 2], Katarzyna Malicka[1], Katarzyna Dąbrowska[1], Andrzej Lewiński[1, 2]

[1]Department of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital — Research Institute, Lodz, Poland
[2]Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland

Abstract

A 36-year-old woman was found to have a low morning ACTH concentration despite a history of Addison's disease.
Past medical history: At the age of 23 years the subject developed Graves's disease, which was treated with radioiodine. At about the same time, she claimed to have two episodes of pancreatitis treated with cholecystectomy. About seven months later she was euthyroid on L-thyroxine (TSH 1.51 mIU/mL) but was admitted with hypotension, hyponatraemia (sodium 109 mmol/L), and low morning cortisol (119 nmol/L). Further investigations confirmed primary adrenal failure with ACTH concentration of 779 pg/mL (ref. range 0–60) prior to the dose of hydrocortisone. About nine years later she complained about tiredness. Clinically she was normotensive and not pigmented. BMI 22.3 kg/m^2. Periods were regular. ACTH concentration was surprisingly low (ACTH 8.53 pg/mL, ref. range 0–46), despite very low cortisol (3.37 nmol/L). She was admitted for further assessment.
Investigations: Pituitary MRI scan was unremarkable. An insulin tolerance test was performed and showed a clear increase of ACTH (from 15.2 to 165 pg/mL). There was, however, hardly any increase of ACTH after CRH stimulation (from 6.05 pg/mL to 10.2 pg/mL), thus demonstrating central CRH resistance.
In summary, this patient developed secondary adrenal failure in the setting of previous Addison's disease. Interestingly, hypoglycaemia (but not CRH) provided a stimulus for ACTH release, thus demonstrating CRH resistance. The case confirms that besides CRH, other factors are responsible for stimulation of the ACTH-cortisol axis during insulin tolerance test. **(Endokrynol Pol 2017; 68 (4): 468–471)**

Key words: *adrenal failure, Addison's disease, pituitary*

Streszczenie

Prezentujemy przypadek 36-letniej pacjentki z chorobą Addisona, u której stwierdzono niskie poranne stężenie ACTH.
Wywiad chorobowy: w wieku 23 lat pacjentka była poddana radiojodoterapii z powodu choroby Gravesa i Basedowa. Siedem miesięcy później została przyjęta do szpitala z powodu hipotonii z towarzyszącą hiponatremią (sód 109 mmol/l) i niskim porannym stężeniem kortyzolu (119 nmol/l). Dalsze badania potwierdziły rozpoznanie pierwotnej niewydolności kory nadnerczy. Oznaczone wówczas stężenie ACTH było wysokie i wynosiło 779 pg/ml (N: 0–60 pg/ml). Dziewięć lat później pacjentka została przyjęta do kliniki z powodu znacznego osłabienia. W badaniu przedmiotowym nie obserwowano ciemnego zabarwienia skóry, wartości ciśnienia tętniczego były prawidłowe. BMI wynosiło 22,3 kg/m^2. Pacjentka miesiączkowała regularnie. W badaniach laboratoryjnych, pomimo bardzo niskiego stężenia kortyzolu (3,37 nmol/l), stwierdzono zaskakująco niskie stężenie ACTH (8,53 pg/ml, N: 0–46 pg/ml). W badaniu RM przysadki nie stwierdzono nieprawidłowości. W teście z hipoglikemią poinsulinową uzyskano znaczny wzrost stężenia ACTH (z 15,2 do 165 pg/ml). Natomiast w teście stymulacji z CRH wzrost stężenia ACTH był nieznamienny (z 6,05 pg/ml do 10,2 pg/ml). Wyniki te wskazywały na centralną oporność na CRH.
W podsumowaniu, u pacjentki z wcześniej rozpoznaną chorobą Addisona rozwinęła się wtórna niewydolność kory nadnerczy. Brak wzrostu stężeń ACTH w teście stymulacji z CRH u tej chorej, przy zachowanej prawidłowej odpowiedzi przysadki w warunkach hipoglikemii, potwierdza, że poza CRH również inne czynniki są odpowiedzialne za pobudzenie wydzielania ACTH i kortyzolu w teście hipoglikemii poinsulinowej. **(Endokrynol Pol 2017; 68 (4): 468–471)**

Słowa kluczowe: *niewydolność kory nadnerczy, choroba Addisona, przysadka*

Introduction

Addison's disease may appear as an isolated disorder or in concurrency with other autoimmune diseases. We present a case report of a patient with primary adrenal failure, who subsequently developed an isolated corticotrophin deficiency, without evidence of other pituitary dysfunction.

Case report

A 36-year-old Caucasian woman with primary adrenal insufficiency diagnosed at the age of 24 years was admitted to our hospital for metabolic assessment. Prior to the diagnosis of Addison's disease, she had a history of Graves' hyperthyroidism, for which she received radioiodine therapy at the age of 23 years, followed by thyroxine replacement due to post-ablation hypothy-

Prof. Andrzej Lewinski, M.D., Ph.D., Department of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital — Research Institute, Rzgowska St. 281/289, 93–338 Łódź, Poland, tel.: +48 42 271 11 41, fax: +48 42 271 11 40, e-mail: alewin@csk.umed.lodz.pl

roidism. At about the same time she claimed to have two episodes of pancreatitis treated with cholecystectomy. About seven months later, she was euthyroid on L-thyroxine (TSH 1.51 mIU/mL) but was admitted with hypotension and hyponatraemia (sodium 109 mmol/L). Further investigations, performed in an academic unit, confirmed adrenal failure with low morning cortisol (119 nmol/L). On assessment at the age of 26 years (2006) her plasma adrenocorticotropic hormone was clearly elevated at 779.5 pg/mL (reference range 0–60), confirming the diagnosis of primary adrenal insufficiency. However, during hospitalisation at the age of 28 years (2008) and at 34 years (2014) her ACTH levels were low. The available documentation, however, did not include simultaneous cortisol levels; therefore, the results were puzzling and difficult to interpret.

At the age of 36 years she complained about tiredness and had an episode of postural syncope. Physical examination was unremarkable; specifically, orthostatic hypotension was not observed. Her treatment included hydrocortisone 20 mg in the morning and 10 mg at about 3 p.m., fludrocortisone 75 μg, and L-thyroxine 75 μg. Her ECG and echocardiogram were normal. Biochemical analysis revealed normal serum electrolytes and low concentrations of both plasma morning cortisol (0.53 μg/dL [14.7 nmol/L]) and corticotropin (ACTH 8.6 pg/mL, ref. range 0–46), suggestive of secondary rather than primary adrenal insufficiency. Plasma renin concentration was satisfactory on fludrocortisone replacement (31.58 μIU/mL [ref. range: 2.8–39.9 μIU/mL, for supine position]), with aldosterone concentration of 2.69 ng/dL (ref. range: 1.17–23.6 ng/dL), and DHEAS concentration of 15.82 μg/dL (ref. range: 60.9–337 μg/dL). Consequently, the patient underwent MRI scanning, which did not reveal any abnormality in the pituitary region.

In order to evaluate pituitary function, dynamic stimulation tests were performed, including insulin tolerance test (ITT) and CRH stimulation test (100 μg intravenously). Insulin-induced hypoglycaemia revealed excellent GH and ACTH secretion, whereas cortisol concentrations remained low. Interestingly, on performing the CRH stimulation test no significant alteration in ACTH level was observed. During hospitalisation the patient's hydrocortisone replacement dose was reduced to 15 mg in the morning and 10 mg in the afternoon. The patient was discharged for further outpatient follow-up.

Discussion

Our case demonstrates development of an isolated corticotrophin deficiency in a patient with long-standing Addison's disease. Autoimmunity is the main reason for primary adrenal insufficiency (PAI). It is most commonly characterised by the presence of 21-hydroxylase autoantibodies, which can be found in 70% of cases of autoimmune PAI. There have been numerous studies confirming high prevalence of other organ-specific autoantibodies in patients with Addison's disease as well as frequent development of other autoimmune disorders in this population [1, 2]. Some studies also demonstrate an association between autoimmune hypopituitarism and various autoimmune diseases [3, 4]. On that basis the concurrence of primary and secondary autoimmune adrenal insufficiency is probable, but documented reports of such cases are scarce. In contrast to primary adrenal failure, secondary adrenal insufficiency is rarely caused by autoimmune processes. According to some reports, autoimmune hypophysitis accounts for less than 1% of hypopituitarism [5–7]. Furthermore, our patient had no clinical features of other pituitary disease, with regular periods and normal pituitary imaging.

The hormonal diagnostic tests for PAI comprise paired measurement of serum cortisol and plasma ACTH. Low morning cortisol (< 5 μg/dL or < 140 nmol/L) strongly suggests adrenal insufficiency, and it should be accompanied by elevated ACTH — more than two-fold above the upper limit of the reference interval [8]. In equivocal cases ACTH stimulation test is performed using standard (0.25 mg i.m or i.v.) or less often a low dose (0.001 mg — 1 μg) of ACTH synthetic analogue (cosyntropin or tetracosactide) [9, 10]. Standard ACTH-stimulated peak serum cortisol should exceed 18 μg/dL (500 nmol/L).

We found it intriguing that in our patient low cortisol failed to be an adequate stimulus for ACTH secretion (it is usually very high in Addison's disease), but there was an increase of ACTH in response to hypoglycaemia during ITT. Furthermore, CRH administration also did not result in any substantial ACTH release, thus demonstrating CRH resistance. In the case of our patient, there were previous results showing high ACTH concentrations consistent with Addison's disease, hence development of corticotrophin deficiency and CRH resistance must have been a gradual phenomenon. As a result of this, our patient demonstrated both primary and central adrenal failure due to an isolated corticotropin deficiency, with a hypoglycaemia-induced increase in ACTH, which appeared independently of CRH-related stimulation of ACTH release. Dynamic tests for evaluation of the hypothalamic-pituitary-adrenal axis comprise insulin tolerance test, glucagon stimulation test, CRH stimulation test, and metyrapone stimulation test [11, 12]. Among all provocative tests, insulin-induced hypoglycaemia (ITT) remains the gold standard [13–16]. Plasma glucose concentration of less

Table I. *Results of Insulin Tolerance Test in a 36-year old patient with history of Addison's disease (Insulin Actrapid® 7 units — 0.15 units per kilogram)*

Tabela I. Wyniki testu z insuliną u 36-letniej pacjentki z chorobą Addisona w wywiadzie (Insulin Actrapid® 7 j. — 0,15 j./kg m.c.

Time	0′	15′	30′	45′	60′	90′	120′	minutes
Glucose	4.16	1.61	1.94	2.72	3.33	3.67	3.68	mmol/L
GH	0.28	–	17.8	20.3	21.1	25.0	20.0	ng/mL
Cortisol	4.44	6.10	6.93	5.82	7.48	4.16	4.44	nmol/L
ACTH	15.3	15.2	165.0	112.0	145.0	54.0	31.8	pg/mL

Table II. *Results of CRH test results CRH stimulation test (100 μg i.v) in a 36-year old patient with history of Addison's disease*

Tabela II. Wyniki testu stymulacji z CRH (100 μg i.v.) u 36-letniej pacjentki z chorobą Addisona w wywiadzie

Time	–15′	0′	15′	30′	60′	90′	minutes
ACTH	5.95	6.05	8.71	10.20	7.47	8.68	pg/mL

than 2.2 mmol/L is considered an adequate stimulus for GH and ACTH release from the pituitary, and cortisol levels greater than 500 nmol/L are considered to be consistent with normal ACTH status. The stress of the hypoglycaemia induces the secretion of ACTH and GH, while postulated mechanisms include the release of CRH and vasopressin from the hypothalamus [17], as well as adrenergic stimulation [18]. The clinical utility of the growth hormone-releasing peptide-2 (GHRP-2), as a peptide that stimulates not only GH but also ACTH secretion, has recently been proven [19]; however, the mechanism in which GHRP-2 induces ACTH secretion is poorly defined.

In our case, we have proven that factors other than CRH must have been responsible for stimulation of ACTH secretion. The mechanisms responsible for this phenomenon remain speculative. Potentially, the effects of vasopressin on ACTH release (i.e. independent of CRH) might be confirmed by measurements of copeptin, a peptide secreted in stoichiometric amounts with AVP, which increases concurrently with AVP during ITT [20]. Copeptin assays were, however, not available in our Department.

The reason (or reasons) for the above-described acquired CRH resistance remain speculative, including desensitisation of CRH receptor or other adaptive factors that might influence saturation of central glucocorticoid receptors (GR). For instance, it was demonstrated that efflux transporter P-glycoprotein, encoded by the ATP-binding cassette B1 (ABCB1) gene [21], at the blood-brain barrier, determines penetration of several glucocorticoids, thus regulating their intracellular content and access to GR [22]. There are also data suggestive that polymorphism of P-glycoprotein might determine the amount of intracellular cortisol, thus influencing the susceptibility to develop osteoporosis in some subjects with Addison's disease [23]. Furthermore, there are experimental data showing that in cases of administration of low-dose glucocorticoids there might be a dissociation between peripheral and central saturation of glucocorticoid receptors [24]. It is well-recognised that administration of hydrocortisone in doses still used in Poland (20 mg in the morning, 10 mg in the afternoon), including our patient until her last hospital admission, result in supraphysiological cortisol peaks. Hence, there is a possibility that, if this patient either had a variant of P-glycoprotein associated with its reduced function (e.g. rs1045642 [25]) or gradually developed an acquired P-glycoprotein deficiency, then theoretically an excessive penetration of cortisol into the central nervous system might have led to central suppression of CRH-ACTH secretion. It must be pointed out, however, that such a mechanism remains purely speculative, while the reason for the above described acquired CRH resistance remains unknown.

Conclusions

The hormonal status of the presented patient suggests development of an isolated corticotropin deficiency in an individual with a history of Addison's disease (hypercortisolaemia concomitant with low ACTH level, with documented markedly elevated ACTH in the past). These results show dysfunction of hypothalamic-pituitary-adrenal feedback loop (absence of ACTH response to hypercortisolaemia or CRH stimulation). Nevertheless, the pituitary insufficiency in this case is relative because a different mechanism of stimulation (hypoglycaemia during ITT) proved to be efficient in corticotroph stimulation and resulted in significant ACTH output, as well as intact GH secretion. This case clearly demonstrates that several different mechanisms must

be responsible for ACTH and GH secretion during ITT. From a clinical view-point, it is also known that some patients of the Caucasian race with long-standing Addison's disease remain hyperpigmented, while others have a normal or even pale skin-complexion on standard therapy. It is a puzzling question, whether blunted POMC/ACTH secretion and hence less pronounced melanocyte stimulation might be present in these patients.

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