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Bilateral adrenal tumors with subclinical hypercortisolemia. To operate or observe?

Obustronne guzy nadnerczy z podkliniczną hiperkortyzolemią. Operować czy obserwować?

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Key words

adrenal incidentaloma, hypercortisolemia, AIMAH, adrenalectomy

Słowa kluczowe

incydentaloma nadnerczy, hiperkortyzolemia, AIMAH, adrenalektomia

Summary

According to various sources, subclinical hypercortisolemia caused by benign adrenal tumors shows unquestionable indication to adrenalectomy. However, some works assessing effects of such surgery revealed no clinical benefits due to operation in some patients. We have also noted this fact in big series of patients treated in our clinic.

We present three cases of women from the group observed by us with bilateral benign adrenal tumors with subclinical hypercortisolemia. Despite similar results of hormonal examinations, the course of disease was different in the described cases. Only in one of two operated women regression of hypercortisolemia led to clinical improvement. In the non-operated one the development of overt Cushing syndrome has not been observed. Hypertension, diabetes and obesity not always are caused by hypercortisolemia – thus regression of hormonal disturbances after a successful adrenalectomy doesn't lead to a clinical improvement in all the patients. The approval of patients for surgery must not be based only on results of hormonal testing.

Streszczenie

Subkliniczna hiperkortyzolemia powodowana przez łagodne guzy nadnerczy według wielu źródeł stanowi automatyczne wskazanie do adrenalektomii. Jednakże niektóre prace oceniające wyniki leczenia operacyjnego zwracają uwagę na brak u wielu chorych jakiejkolwiek korzyści klinicznej z przebytego zabiegu. Również obserwowaliśmy to zjawisko w dużej serii chorych leczonych w naszej klinice.

Prezentujemy trzy przypadki kobiet pochodzące z obserwowanej przez nas grupy z obustronnymi łagodnymi guzami nadnerczy przebiegającymi z podkliniczną hiperkortyzolemią. Mimo podobnych wyników badań hormonalnych przebieg choroby był inny w każdym z opisanych przypadków. Jedynie u jednej z dwóch operowanych kobiet ustąpienie hiperkortyzolemii doprowadziło do poprawy stanu klinicznego. U nieoperowanej chorej nie obserwowano rozwoju jawnego klinicznie zespołu Cushinga. Nadciśnienie tętnicze, cukrzyca i otyłość nie muszą wynikać z hiperkortyzolemii i stąd ustąpienie zaburzeń hormonalnych po skutecznej adrenalektomii nie powoduje poprawy klinicznej u każdego pacjenta. Decyzja o leczeniu operacyjnym nie może opierać się jedynie na wynikach badań hormonalnych.

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INTRODUCTION

The problem of incidentally detected bilateral adrenal tumors (incidentaloma) can be examined in several different ways. First of all, if such lesions are found, an "oncological vigilance" is obligatory as they might be bilateral neoplastic metastases (1). A quick differential diagnosis of metastatic lesions is possible by means of CT examinations during which the so-called imaging phenotype of tumors is assessed. Malignant lesions are characterized by a high coefficient of X-ray attenuation (density) prior to the administration of contrast medium and a low absolute and relative coefficients of contrast washout (which indicates a slow washout of the contrast medium in practice). Lipids are not found in such lesions on MRI (the assessment consists in comparing in-phase and antiphase signals produced by the tumor) (2, 3). A lack of lipids in the tumors might also give rise to suspicion of bilateral phaeochromocytomas – the presence of such lesions can be expected in patients with multiple endocrine neoplasia syndro-

me, whereas they are almost never present in other patients (4). Thus, it can be summarized that a detection of tumors containing no lipids in both adrenal glands is a definite indication for surgery after carrying out extended diagnostics (imaging examinations for detection of primary lesion in case of metastasis, a determination of 24-hour urinary catecholamines/metoxycatecholamines excretion, a MIBG scintigraphy and examinations for detection of other endocrinopathies in case of suspected phaeochromocytomas).

In case of bilateral adrenal incidentalomas, an assessment of their hormonal function is the second direction of actions. An excessive production of all the three groups of adrenocortical hormones (glucocorticoids, mineralocorticoids, androgens) and its autonomization may occur. In case of unilateral adrenal adenomas that show a subclinical hormonal function, the decision to perform surgery is usually taken. Adenomas can also occur as bilateral tumors with benign imaging phenotype, but they develop more often in the course of ACTH-independent macronodular adrenal hyperplasia (AIMAH) than in the case of unilateral lesions. A suspicion of hyperplasia changes the management method in case of detection of autonomous aldosterone production: a unilateral adenoma that causes a Conn's syndrome is an indication for surgery, but a bilateral hyperplasia should be treated pharmacologically (5, 6). In case of hyperandrogenism with bilateral adrenal enlargement (with or without tumors) one may suspect an undiagnosed so far unclassical form of congenital adrenal cortical hyperplasia or hyperplasia of the reticular zone, which are also not an indication for operative treatment. Subclinical hypercortisolemia was for many years a definite indication for adrenalectomy (7, 8). However, recently arguments for a more cautious approach when making decisions on this operation were provided as it, even with an evident autonomization and increased cortisol secretion, does not always bring about a clinical improvement (9-11). The cases below from a large group of patients with bilateral adrenal tumors treated and observed in our teaching hospital department are illustrative of this problem.

CASE 1

A 66-year-old woman with overweight (BMI 29 kg/m^2), hyperinsulinism diagnosed during OGTT, poorly controlled arterial hypertension (> 140/90 mmHg, 5 antihypertensive drugs) and hyperlipidemia has been admitted to the Teaching Hospital Department of Endocrinology of the Centre of Postgraduate Medical Education because of bilateral adrenal tumors detected during an abdominal cavity ultrasonography. An imaging assessment was carried out and the following lesions were visualized on abdominal CT: a lesion 32 x 30 mm in size in the left adrenal gland and a lesion 21 x 11 mm in size in the right adrenal gland that had a density of +4 Hounsfield units (HU) and from -1 to +1 HU, respectively (fig. 1). A normal renin/aldosteron ratio (RAA), a normal concentration of adrenal androgens, normal both cortisol concentrations and circadian rhythm of cortisol excretion with a low morning ACTH concentration of 5 pg/ml were found in the hormonal evaluation. A lack of cortisol suppression (4.8 μg/dl) was found in the test performed with a dexamethasone (1 mg dose). In order to confirm the diagnosis of secretion autonomization and identify the secreting side, a radio-labelled norcholesterol (NP-59) scintigraphy of the adrenal glands was carried out and a predominant radiotracer uptake in the left adrenal gland was found (fig. 2). In consideration of the diagnosed autonomous hormonal function, the female patient has been approved for a laparoscopic removal of the left adrenal gland. A macronodular adrenocortical hyperplasia was found during a histopathological examination of the tumor. After the operative procedure, the female patient required substitutive doses of hydrocortisone for half a year due to the insufficiency of the other adrenal gland (during the 2nd month after surgery, the morning concentration of cortisol was 6.1 μg/dl, ACTH 2 pg/ml and 17-OHCS 2.1 mg in 24-hour urine collection), which definitely confirmed the preoperative diagnosis of subclinical hypercortisolemia. During the first six months after surgery, a decrease in body mass occured (down to BMI 23 kg/m^2), the control of arterial pressure improved, which enabled a reduction of the doses of hypotensive drugs (at present, she is treated with sartan and a calcium channel blocker). The concentration of triglycerides, cholesterol-LDL fraction decreased.

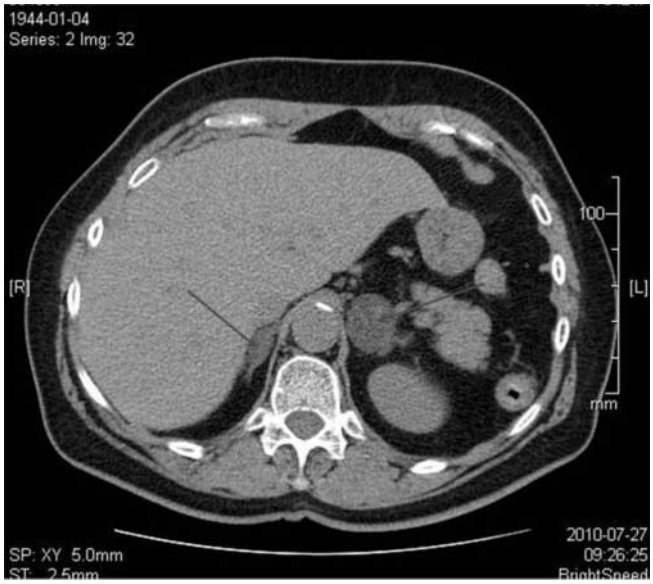

Fig. 1. Abdominal CT in patient No 1: bilateral lesions L > P.

CASE 2

A 59-year-old woman with a normal BMI (22.7 kg/m^2), well controlled arterial hypertension and hyperlipidemia has been referred to the Teaching Hospital Department of Endocrinology of the Centre of Postgrad-

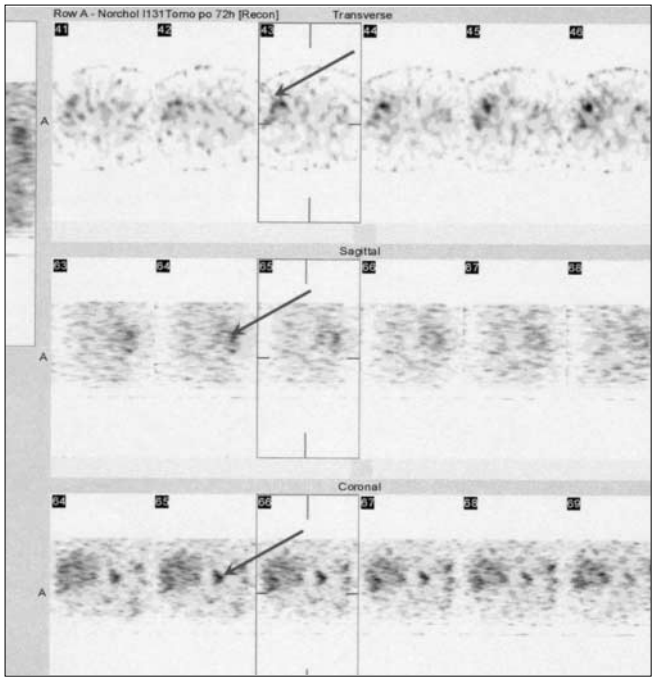

Fig. 2. NP-59 scintigraphy in patient No 1: predominant uptake in left adrenal gland.

uate Medical Education because of tumors in both adrenal glands detected during abdominal cavity ultrasonography. Like in the previous case, tumors with a benign imaging phenotype were found on abdominal cavity CT – a tumor 20 x 24 mm in size with a density of -3 HU in the left adrenal gland and a tumor 9 x 14 mm in size with the same density in the right adrenal gland. A normal RAA, normal concentrations of adrenal androgens, a present circadian rhythm of cortisol secretion with a low morning ACTH concentration (6 pg/ml) and a lack of cortisol suppression during a dexamethasone suppression test (7.7 μg/dl) were found in the hormonal evaluation. A predominant radiotracer uptake on the right side (in the smaller tumor) was demonstrated during a performed NP-59 scintigraphy of the adrenal glands. The female patient was referred for a laparoscopic adrenalectomy on the right side. A macronodular adrenocortical hyperplasia was found during a histopathological examination. An insufficiency of the other adrenal gland occurred after the operation and persisted for 6 months (during the 2nd month after surgery, the morning cortisol concentration was 8.0 μg/dl, ACTH 5 pg/ml). During further observation, a normalization of the ACTH concentration occurred and a complete suppression of cortisolemia was found during a dexamethasone suppression test, however, it was not possible to decrease the doses of hypotensive and hypolipemic drugs. Furthermore, during the second year after surgery, an increment by 10 kg of body mass occurred and a hyperinsulinism, reactive hypoglycaemia were found during a glucose tolerance test. There was a suspicion of a recurrence of subclinical hypercortisolemia, however, the cortisol concentration after a suppression with 1 mg of dexamethasone was 1.6 μg/dl. At present, after starting a diet with low glycaemic index and physical exercise, a gradual decrease in body mass takes place.

CASE 3

A 54-year-old woman was hospitalized in the Teaching Hospital Department of Endocrinology of the Centre of Postgraduate Medical Education because of bilateral adrenal tumors with a benign imaging phenotype, 42 x 28 mm in size on the right side and 31 x 18 mm on the left side, detected on abdominal cavity CT. Both tumors had a density of -7 HU. Increased values of arterial pressure or an overweight (BMI 24.3 kg/m^2) were not found and diabetes as well hyperlipidemia were excluded on the grounds of laboratory tests. The RAA was normal, just as the concentrations of adrenal androgens. On the other hand, a low ACTH concentration (5 pg/ml) and a lack of cortisol suppression (6.6 μg/dl) during the dexamethasone suppression test were conspicuous. A radiotracer uptake only by the right adrenal gland was visualized on a radio-labelled norcholesterol scintigraphy (fig. 3). The female patient did not consent to the proposed operative treatment. During the fourth year of observation a well controlled with low doses of hypotensive and hypolipemic drugs hyperlipidemia and arterial hypertension were found. An increment of body mass did not occur and we don't observe an enlargement of the tumors. The female patient still does not consent to surgery for which according to the newest recommendations, our experience and studies, in fact, there are no definite indications.

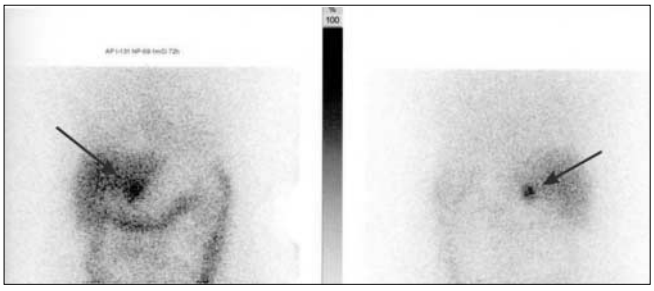

Fig. 3. NP-59 scintigraphy in patient No 3: uptake exclusively in right adrenal gland.

DISCUSSION

Bilateral adrenal tumors with a benign imaging phenotype and a subclinical hypercortisolemia without other hormonal disturbances were found in all these described three female patients. However, the clinical course in these patients varied.

Metabolic syndrome elements, i.e. arterial hypertension and hyperlipidemia which could result from hypercortisolemia, were found in two female patients, but the hypertension did not respond to pharmacological treatment only in the first one. It is

conspicuous that only this female patient did not fulfil the oldest criterion of diagnosis of hypercortisolemia – i.e. the cortisol concentration after a dexamethasone suppression did not exceed 5 μg/dl. An arterial hypertension, diabetes or hyperlipidemia were not present and the body mass was normal in the third female patient with the largest tumors. However, during further observation, an arterial hypertension and hyperlipidemia were found, which is consistent with most clinical observations. Hypercortisolemia even if it is a subclinical one, is recognised by the majority of investigators as being a cause of arterial hypertension, diabetes, lipid disturbances, obesity and worsening of bone mineral density (12-14) (we have put this element aside in the present article). However, a deterioration in clinical state of patients and a transition from subclinical hypercortisolemia to symptomatic Cushing's syndrome were not found in some groups under a long-term observation (15, 16). On the other hand, vascular changes in patients with adrenal tumors without autonomization of secretory function were also described (17). We found the same incidence of diabetes, arterial hypertension, hyperlipidemia and obesity among persons with and without hypercortisolemia in a group of 50 patients with bilateral adrenal incidentalomas (18). Giordano states a similar observation: he did not find any differences in the incidence of diabetes, obesity and hypertension in 128 patients with incidentaloma (including 14% with bilateral incidentalomas), however, only hyperlipidemia was slightly predominant in patients with subclinical hypercortisolemia, compared with persons without hormonal disturbances (16). It has also been demonstrated that the adrenal gland volume and cortisolemia increase in fructose-induced diabetes type 2 in rats (19). Already in 1996, Reinke has postulated that hiperinsulinism may be the cause, not the result of bilateral adrenal lesions (the already known proliferative action of insulin may really explain this phenomen) (20). It may be that hyperinsulinism is one of the factors contributing to the development of ACTH-independent macronodular adrenal hyperplasia (AIMAH) with abnormal receptors in the adrenocortical cells. Focal lesions developed in the adrenal glands in both operated female patients with AIMAH as undelying disease. A hyperinsulinism and reactive hypoglycaemia were already found before the operative procedure in the patient No 1. A hyperinsulinism and increment of body mass were also found during the postoperative course in the patient No 2, however, a tumor enlargement in the nonoperated adrenal gland was not observed.

A period of secondary adrenocortical insufficiency occurred in both operated female patients after the surgery and then a normalization of results of hormonal testing. However, this was associated with a good clinical effect of surgery only in the first patient. In the group of patients after adrenalectomy observed in the teaching hospital department, an improvement in health state was pronounced only in patients in whom a poor control of blood pressure in arterial hypertension (like in the female patient No 1), glycaemia in diabetes or a quick and uncontrolled increment of body mass constituted an additional indication for operative procedure (10). A clinical improvement was achieved in altogether 58% of patients. Other authors described an improvement in the lipidogram, a decrease in body mass, glycaemia and arterial pressure following an effective treatment in 20-67%, however, not in all the operated patients (8, 21). Iacobone states considerably better effects of treatment of bilateral tumors: it was possible to reduce the doses of hypotensive and hypoglycemic drugs in all the operated patients and withdraw these drugs in some patients (22). However, the group consisted of only 7 persons, of whom 6 had arterial hypertension resistant to pharmacological treatment, and of whom 5 had a poorly controlled diabetes, thus these patients had pronounced clinical symptoms of hypercortisolemia. On the other hand, in one paper, none of the patients showed clinical improvement after surgery. Other authors observed an improvement of insulin sensitivity after surgery also in patients without subclinical hypercortisolemia and only large dimensions of tumors were an indication for treatment (23).

As can be seen, a treatment of subclinical hypercortisolemia by removing the hormonally active tumor is not so definitely beneficial – as previously believed. A regression of subclinical hypercortisolemia after a successful effective operative treatment does not automatically bring about an improvement of the course of diabetes and arterial hypertension in each operated patient. Thus, the approval of patients for surgery must not be based automatically on results of hormonal testing and first of all the patient's clinical state should be taken into account. If the glycaemia and arterial pressure are normal or well controlled with drugs and no quick increment of body mass occurs, pharmacological treatment and strict observation of patients might be an allowed alternative to surgery (10). Terzolo, Pia and Reymondo presented an identical opinion in a review study on subclinical hypercortisolemia: they propose that patients between 50 and 70 years of age should be operated only in case of poorly concomitant diseases and recommend only an observation for patients over 70 years of age (11).

CONCLUSIONS

A regression of hormonal disturbances after a successful adrenalectomy did not lead to a clinical improvement in all the patients. Patients with a deteriorated control of diabetes, hypertension or quick increment of body mass before surgery have experienced clear-cut benefits from the surgical treatment.

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