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Bilateral, incidentally found adrenal tumours — results of observation of 1790 patients registered at a single endocrinological centre

Obustronne przypadkowo wykryte guzy nadnerczy — wyniki obserwacji 1790 pacjentów zarejestrowanych w pojedynczym ośrodku endokrynologicznym

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Abstract

Introduction: During the last 22 years we registered 1790 patients with incidentally found adrenal tumours (AI, adrenal incidentalomas). In 351 of them, bilateral tumours were detected. The aim of our study was to analyze the character of bilateral tumours and summarize the methods of their management.

Material and methods: In the whole group of 1790 patients, there were 1311 women and 479 men, aged 11-87 years. The group of patients with bilateral adrenal tumours included 258 women and 93 men, 25-83 years old. Hormonal investigations and imaging examinations were performed to search for subclinical adrenal hyperfunction and to define the malignant potential of the tumours.

Results: Sixty-nine patients were treated by surgery for oncological or endocrinological purposes (mainly pre-Cushing's syndrome). Histological findings included malignant tumours: metastases — 9, adrenal cancer — 7, and lymphomas — 5; and non-malignant tumours: adenomas — 24, nodular hyperplasia — 14, myelolipomas — 4, and pheochromocytomas — 4. Subclinical Cushing's syndrome was relatively more frequent in nodular hyperplasia (40%) than in adenomas (30%).

Conclusions: Indications for surgery were recommended in 20% of patients with bilateral AI, most frequently for adenomas, nodular hyperplasia, and oncological pathologies, with a good prognosis in the non-malignant group.

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Key words: *adrenal tumour, adrenal cancer, adrenal incidentaloma, subclinical Cushing's syndrome, pheochromocytoma, cortisol, aldosterone, metanephrines, androgens*

Streszczenie

Wstęp: W okresie ostatnich 22 lat 1790 pacjentów z przypadkowo wykrytymi guzami nadnerczy (AI, *adrenal incidentalomas*) zostało zarejestrowanych w klinice. U 351 spośród nich rozpoznano obustronne guzy nadnerczy. Nasze badania miały na celu analizę charakteru obustronnych guzów i podsumowanie metod postępowania w tych przypadkach.

Materiał i metody: W całej grupie 1790 pacjentów było 1311 kobiet i 479 mężczyzn, w wieku 11–87 lat. Grupa pacjentów z obustronnymi guzami nadnerczy obejmowała 258 kobiet i 93 mężczyzn, w wieku 25–83 lat. Przeprowadzono badania hormonalne i obrazowe, w celu poszukiwania podklinicznej nadczynności nadnerczy i określenia potencjału złośliwości guzów.

Wyniki: Chirurgicznie leczono 69 pacjentów, ze wskazań onkologicznych albo endokrynologicznych (głównie podkliniczny zespół Cushinga). Wyniki badań histologicznych wykazały istnienie złośliwych zmian nowotworowych: przerzuty — 9, rak nadnercza — 7, chłoniaki — 5 i niezłośliwych zmian: gruczolaki — 24, rozrost guzkowy — 14, myelolipoma — 4, pheochromocytoma — 4 przypadki. Podkliniczny zespół Cushinga występował względnie częściej w rozroście guzkowym (40%) niż w przypadkach gruczolaka (30%).

Wnioski: Wskazania do leczenia chirurgicznego ustalono u 20% pacjentów z obustronnymi guzami nadnerczy, najczęściej z powodu gruczolaków, rozrostu guzkowego i złośliwych zmian nowotworowych; rokowanie było dobre w przypadkach nieonkologicznych.

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Słowa kluczowe: *guz nadnercza, rak nadnercza, incydentaloma nadnercza, podkliniczny zespół Cushinga, pheochromocytoma, kortyzol, aldosteron, metanefryny, androgeny*

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Introduction

During the last 22 years we observed 1790 patients with incidentally found adrenal tumours, so-called adrenal incidentalomas (AI). Our first publication on AI, in 1992, was based on an analysis of 64 patients observed at our department [1]. Since that time our group of patients with AI has grown and is worthy of evaluation. The number of the incidentally discovered adrenal tumours increased rapidly in the last 15–20 years. The greatest cohort of patients with AI, in the literature, was described by Mantero et al. [2], including 1096 patients from 26 Italian endocrinological centres.

Investigations made in patients with AI aim at evaluating criteria for surgery or for clinical observation. The main indications for surgical treatment include malignant tumours, both primary and metastatic. Since some AI may secrete slightly increased amounts of steroid hormones [3], a search for subclinical adrenal hyperfunction is necessary to define the group also recommended for surgery. Similarly, investigation directed towards chromaffin tumour diagnosis is obligatory in patients with suggestive imaging signs, because of the well-known complications of these tumours. The oncological and endocrinological indications for surgery have been discussed in the literature [4–8]; however, in bilateral adrenal tumours, additional difficulties may arise in deciding which tumour should be removed. We would like to present our opinion in this matter because we have observed a significant number of such patients with bilateral AI.

Material and methods

Material — 1790 patients with AI: 1311 women and 479 men (F/M ratio 2.7), aged 11–87 years. In this group, there were 67 patients up to 30 years old (4%) and 644 patients over 60 years old (34%). The size of the tumours ranged from 1.0 to 23.0 cm. In 836 patients the tumour was right-sided (47%), in 603 — left-sided (33%), and in 351 patients bilateral tumours were found (20%).

In the group with bilateral adrenal tumours, there were 258 women and 93 men (F/M ratio 2.8), 25–83 years old. The tumour diameters ranged from 1.0 to 13.0 cm. In the majority of cases, the bilateral tumours were found at the time of first diagnosis, while in 15 patients the second tumour appeared after an interval of 2 to 18 years (most frequently after 2 to 5 years).

The methods of investigation included 1) imaging examinations: ultrasound scans (US), computed tomography (CT) and magnetic resonance imaging (MRI), 2) hormonal studies, and 3) pathomorphological examinations of the patients treated by surgery. US was used as a screening method to search for anatomical abnormalities and to control the tumour's size in a long-term observation of the patients not qualified for surgical treatment. Computed tomography was the main method of evaluation of the tumour's size and for defining their imaging phenotype and malignant potential. The imaging phenotype was characterized by the shape of the tumours, their margins, texture, attenuation (density) on unenhanced CT, rapidity of washout of contrast medium, presence of necrosis, haemorrhage, pseudocysts or calcifications, and growth rate of the tumour in a series of examinations. High density of the tumour in the native phase of CT, with delayed washout of the contrast medium (< 50% after 10 min) and size over 4.0 cm were considered important indications for surgery. MRI was used mainly to differentiate adenomas from non-adenomas, based on the presence or lack of lipids in the tumours.

Hormonal studies included determination in the serum of the blood of cortisol (circadian rhythm), dehydroepiandrostendione sulphate (DHEA-S), androstendione and 17-OH progesterone concentration, plasma ACTH levels and urinary diurnal excretion of free cortisol or 17-hydroxycorticosteroids (17-OHCS), 17-ketosteroids (17-KS), aldosterone, and metanephrines, if necessary. Serum cortisol was measured initially by radioimmunoassay (RIA), and during last 10 years by chemiluminescence assay (LIA) (Immulite 2000). Serum DHEA-S, androstendione, 17-OH progesterone, and aldosterone were measured by RIA. Plasma ACTH was measured by an immunoradiometric method (IRMA). Dynamic hormonal investigations included dexamethasone suppression test, 1 mg at 22:00 hours with cortisol determination the next morning. The classic Liddle's test with use of 0.5 mg of dexamethasone every six hours for two days (with free cortisol or 17-OHCS and/or 17-KS determination on the second day) was also carried out if necessary. In patients with possible diagnosis of a chromaffin tumour, this test was definitely contraindicated to avoid a pheochromocytoma crisis [9].

In patients with a probable diagnosis of non-classic congenital adrenal hyperplasia, a $^{1-24}$ACTH test was performed with cortisol and 17-OH progesterone measurement at 0, 60, and 120 mintes of the test.

Pathomorphological studies of the removed tumours were also made, including histological and microscopic evaluation as well as immunocytochemical examinations.

Results

In the whole observed group, on the basis of the previously described methods, we diagnosed tumours that were probably benign in 1590 patients. Malignancy was diagnosed in 200 patients, and tumours of metastatic

origin in 50 patients (2.8%).Primary malignant tumours were found in 150 patients (8.2%), with adrenal cancer in 134 cases (7.5% of the whole group).

Subclinical adrenal hyperfunction was detected in 140 patients (8%), most frequently pre-Cushing's syndrome (6%), while subclinical hyperaldosteronism and hyperandrogenism only in 1%. Chromaffin tumours were found in 58 patients (3% of the whole group).

The results of our investigations allowed us to determine indications for surgery, oncological or endocrinological, in 595 patients (33%). In the case of malignancy, a traditional open surgery was performed. In patients with probable benign tumours less than 7.0 cm in diameter, a laparoscopic method was used.

Among the group of 351 patients with bilateral tumours, 69 patients were treated by surgery (20%), 27 of them — bilaterally. Pathomorphological examinations revealed adrenal carcinoma in 7 patients, metastatic infiltration in 9, lymphoma in 4, adrenal adenoma in 24, adrenal hyperplasia in 15, myelolipoma in 4, and pheochromocytoma in 4 patients. In the remaining 282 patients, benign adrenal tumours were suspected without criteria for surgery. They were qualified for long-term observation. Bilateral adrenal carcinoma was found at the time of diagnosis in 5 patients, while in 2 patients an interval of 2 and 6 years was observed. Bilateral metastatic lesions were discovered at the same time, as in cases of lymphoma. Bilateral pheochromocytomas were found simultaneously in two patients, in one patient an interval of ten years was noticed. In one patient, treated for pheochromocytoma, a contralateral tumour appeared after 18 years, not identified histologically. Additionally, in one patient, a right-sided pheochromocytoma was associated with a left-sided adenoma.

Computed tomogaphy and MRI were our main sources of knowledge on the size, imaging phenotype, and malignant potential of the tumours in the patients under study. Figure 1 presents a typical CT image of an adrenal adenoma. In the patient presented in Figure 2, as well as bilateral adrenal adenomas, an incidentally found liposarcoma was identified by MRI. Figure 3 shows three pheochromocytomas in a male patient with neurofibromatosis.

Rapid growth of adrenal tumours in a series of imaging examinations was considered as an important indication for surgery, suggesting an oncological origin of such a clinical course. However, in a male patient in whom on CT both tumours doubled their size within three months (from 3.0 to 7.0 cm and from 2.0 to 4.5 cm, respectively), microscopic examination revealed bilateral nodular hyperplasia. Similarly, false information was signalled by increased density of the tumour in two cases: a neurofibroma and haemorrhagic necrosis in the "suspected" tumours were diagnosed microscopically.

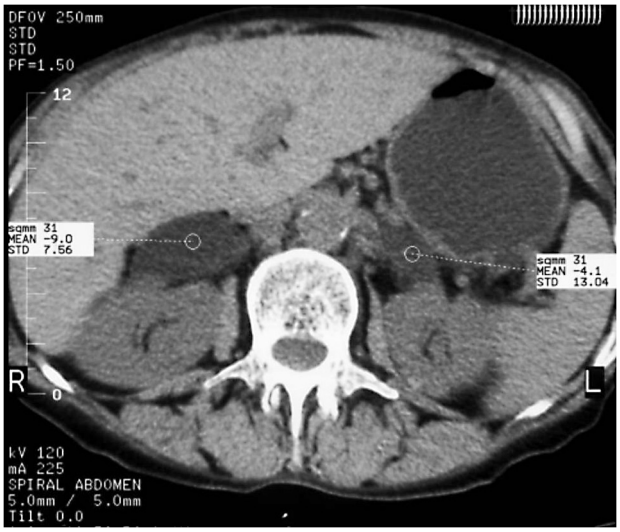

Figure 1. *Bilateral adrenal adenomas on computed tomography (CT). Low density in the ROIs (marked on the masses) is characteristic for adenomas*

Rycina 1. *Obustronne gruczolaki nadnerczy w tomografii komputerowej (CT). Mała gęstość w obszarach zainteresowania (zaznaczone na masach) jest cechą charakterystyczną dla gruczolaków*

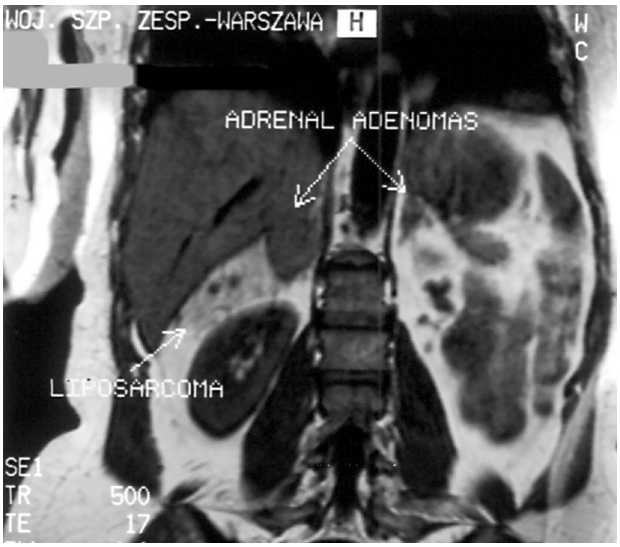

Figure 2. *Bilateral adrenal adenomas (arrows) in a patient with incidentally found well differentiated retroperitoneal liposarcoma on magnetic resonance imaging*

Rycina 2. *Obustronne gruczolaki nadnerczy (strzałki) u pacjenta z przypadkowo wykrytym w rezonansie magnetycznym dobrze zróżnicowanym zaotrzewnowym tłuszczakomięsakiem*

Hormonal investigations and clinical observation revealed subclinical Cushing's syndrome in 14 patients, in two of them presenting only as secondary adrenal insufficiency following removal of the tumour. In summary, pre-Cushing's syndrome was diagnosed in 8 patients with adrenal adenoma (8/25 = 32%) and in 6 pa-

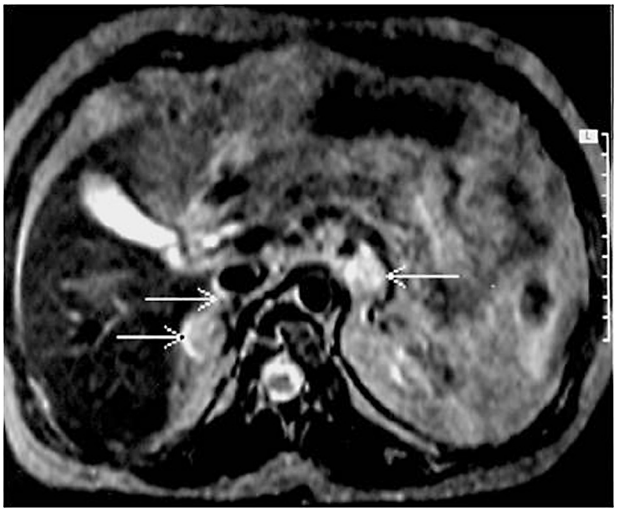

Figure 3. *Multiple, bilateral adrenal pheochromocytomas (3 tumors — arrows) on magnetic resonance imaging (MRI), in patient with neurofibromatosis type 1. On axial T2-weighted image, characteristic for pheochromocytoma, high signal is visible*

Rycina 3. *Liczne, obustronne guzy chromochłonne nadnerczy (3 guzy — strzałki) w rezonansie magnetycznym (MRI) u pacjenta z nerwiakowłókniakowatością typu 1. W osiowym obrazie T2-zależnym widoczny jest sygnał o dużej intensywności charakterystyczny dla guza chromochłonnego*

tients with nodular hyperplasia (6/15 = 40%). In these patients, gradually reducing hydrocortisone dosing was necessary postoperatively. Persistent pre-Cushing syndrome was observed in two patients following unilateral adrenalectomy for nodular hyperplasia. Additionally, in a male patient treated successfully for pre-Cushing's syndrome by unilateral adrenalectomy (microscopically — nodular hyperplasia), subclinical adrenal hyperfunction recurred three years later, presenting as a painful myasthenia. A complete remission followed the second adrenalectomy. In two patients with congenital adrenal hyperplasia, hyperdense tumours were observed in CT, with increased androgen values.

Two patients with recurrent contralateral adrenal carcinoma, treated by surgery and Mitotane, are still alive. In the group of 5 patients with simultaneously diagnosed bilateral carcinoma, four patients died within one to two years, despite surgery and chemotherapy (Cisplatin, Etoposid, Doxorubicin). Only two patients with metastatic infiltrations are still alive, two and four years after bilateral adrenalectomy. The patients with bilateral lymphoma died within one to two years following bilateral tumour removal. In the patients treated surgically for non-malignant tumours, the prognosis has been good. The remaining patients, not qualified for surgery, have been carefully controlled by imaging examinations and by cortisol and DHEA-S determinations.

Discussion

The observation of a numerous group of patients with adrenal incidentalomas, diagnosed and managed in the same manner in a single clinical centre, has allowed some useful conclusions to be reached in this matter. In part, it was our experience from some previous publications [1, 4, 8, 10, 11]. In 2007 WF Young Jr presented a report on 2005 patients collected from 13 studies found in the literature [7]. This article, therefore, could be considered as a true encyclopaedia of adrenal incidentalomas; however, information on bilateral adrenal masses and their management in this report appeared to be very sparse.

The incidence of pre-Cushing's syndrome and subclinical hyperaldosteronism in our material did not differ significantly from the data presented by other endocrinological centres [7, 12]. An original our observation was the presence of a group of patients with subclinical androgens excess, not described in older [2, 6] or in more recent publications [7, 12].

The main aim of imaging and hormonal studies in adrenal incidentalomas is the selection of patients to be treated by surgery. The oncological and endocrinological criteria are well known and generally respected for patients with unilateral adrenal tumours [4–8]. In bilateral tumours presenting subclinical adrenal hyperfunction, however, the decision could sometimes be problematic. In these patients, we decided to remove first the tumour evidently greater in size, more rapidly growing, or presenting higher density in the first phase of CT [8]. Such tactics appeared to be reasonable in the majority of patients treated by surgery, in whom an adenoma was diagnosed microscopically. In the case of bilateral nodular hyperplasia, however, despite transient improvement following unilateral adrenalectomy, in some cases pre-Cushing's syndrome recurred within one to three years. A rapid growth of the adrenal tumours, observed in CT, was also considered an important oncological indication for surgery, with the dilemma of whether it should be at once a bilateral adrenalectomy. Previously described criteria for patients with subclinical Cushing's syndrome could also be useful in this group of patients.

In our study we present an exceptional group of 7 patients with bilateral adrenal carcinomas. Successful treatment was achieved only in two patients, in whom the malignant tumours did not appear simultaneously. A bad prognosis has also been observed in the majority of patients with bilateral metastatic infiltrations and lymphoma. A study on subclinical Addison's disease was possible in these cases. A careful postoperative observation is necessary in all the patients; however, it must be especially intensive in case of malignancy.

Conclusions

1. Criteria for surgery were established in 20% of patients with bilateral adrenal incidentalomas. Malignant tumours were diagnosed in 30% of the surgically treated patients.
2. Adrenal adenomas and nodular hyperplasia were the most frequent benign bilateral tumours.
3. Persistent or recurrent subclinical Cushing's syndrome was observed after unilateral adrenalectomy only in some cases of nodular hyperplasia.

Competing interests

The authors declare that they have no competing interests.

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