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Bilateral primary pigmented nodular adrenal disease as a component of Carney syndrome — case report

Dwustronny pierwotny pigmentowany rozrost drobnoguzkowy nadnerczy jako składnik zespołu Carney — opis przypadku

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Abstract

We report a case of a 20-year-old patient with Cushing's syndrome as a component of Carney syndrome. Carney syndrome is an autosomal dominant disease with co-existing bilateral pigmented nodular adrenal disease, heart and skin myxoma, skin pigmentation, breast fibroadenoma, testicular and ovarian tumours, thyroid tumours, and pituitary adenomas. **(Endokrynol Pol 2017; 68 (1): 70–72)**

Key words: *Carney syndrome; Cushing's syndrome; primary pigmented nodular adrenal disease; adrenalectomy*

Streszczenie

Przedstawiono opis przypadku 20-letniej pacjentki z zespołem Cushinga, w przebiegu zespołu Carneya. Zespół Carneya jest dziedziczony w sposób autosomalny dominujący i wiąże się z występowaniem: pierwotnego pigmentowanego rozrostu drobnoguzkowego nadnerczy, śluzaków skóry i serca, przebarwień na skórze oraz guzów sutka, jąder, jajników, tarczycy czy przysadki. **(Endokrynol Pol 2017; 68 (1): 70–72)**

Słowa kluczowe: *zespół Carneya; zespół Cushing's; pierwotny pigmentowany rozrost drobnoguzkowy nadnerczy; adrenalektomia*

Introduction

Endogenous Cushing's syndrome in adults is most often caused by ACTH-dependent secondary adrenal gland overactivity; less often it is a result of ACTH-independent primary adrenal gland overactivity. Primary adrenal cortisol hypersecretion is responsible for 15–20% of all cases of Cushing's syndrome. In 10–15% of cases, Cushing's syndrome is due to bilateral adrenal lesions that include micronodular (approx. 1%) and macronodular adrenal hyperplasias and, more rarely, bilateral adenomas or carcinomas [1, 2]. One example of bilateral changes in the adrenal gland is primary pigmented nodular adrenal disease (PPNAD) [3]. The primary pigmented nodular adrenal disease may be isolated, or it may be a component of Carney syndrome with co-existing heart and skin myxoma, skin pigmentation, breast fibroadenoma, testicular and ovarian tumours, thyroid tumours, and pituitary adenomas [4].

Case report

A 20-year-old patient with skin lesions, menstrual disorders, and symptoms of hirsutism was referred to the clinic for further diagnosis and treatment. Physical examination revealed pigmented lesions on the face, redness and rounded face, and hirsutism. Laboratory tests showed abnormal rhythm of cortisol secretion (lack of the evening decrease), normal morning cortisol level, normal results of urine collection, and negative dexamethasone (1 mg and 8 mg) inhibition. MRI excluded pituitary adenoma; however, abdominal CT revealed an oval tumour of 11 × 10 mm (with an average density approx. 30 j.H. and percentage washout about 57%; indicating lipid-poor adenoma) in the right adrenal (Fig. 1). Subsequently, laparoscopic right-sided adrenalectomy was performed. Furthermore, histopathological examination revealed changes typical for primary pigmented nodular adrenocortical disease. After surgery, clinical improvement was achieved.

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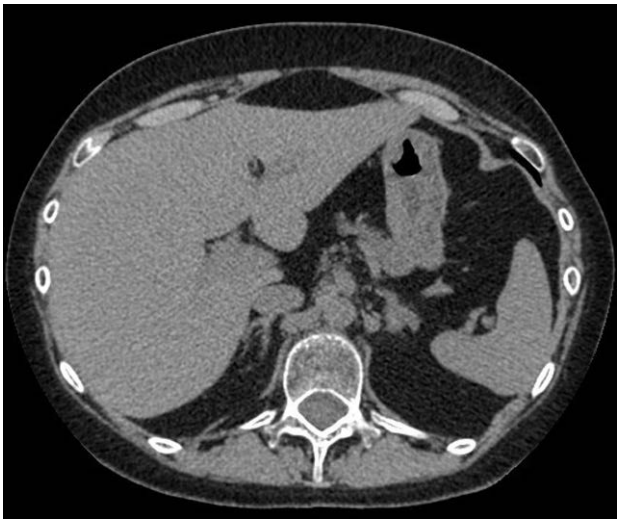

Figure 1. *Adrenal tumour*
Rycina 1. *Guz nadnercza*

Nevertheless, a further follow-up was conducted, as a result of which thyroid nodular goitre was diagnosed. Additional examination demonstrated cardiac myxoma (3 × 3 cm) adjacent to the septal and anterior mitral valve. The tumour showed no clinical symptoms. Thus, cardiac surgery was performed in order to remove the entire tumour. Based on all clinical symptoms and the results of additional tests and examinations, Carney syndrome was suspected. What is more, genetic examination revealed the presence of a genetic mutation in one allele R228X PRKAR1A gene, thus confirming the diagnosis of Carney syndrome. Two years after the right-sided adrenalectomy, the patient developed symptoms of Cushing's syndrome again. Laboratory tests demonstrated low levels of cortisol and low excretion of cortisol metabolites in urine co-occurring with abnormal circadian rhythm of cortisol secretion (lack of the night decrease) and a paradoxical increase in cortisol in the dexamethasone test. It has been shown that patients with PPNAD exhibit a paradoxical increase in cortisol secretion in response to Liddle's test, i.e. administration of dexamethasone at doses of 2 mg/d for two days followed by 8 mg/d for two days [5]. This abnormal cortisol response is now used as a biological criterion for the diagnosis of the disease [1]. The CT scan showed no change in the adrenal gland. Nevertheless, left-sided adrenalectomy and hydrocortisone replacement therapy were recommended. After left-sided adrenalectomy, clinical improvement was achieved. Two years after the left-sided adrenalectomy, the patient developed a breast tumour, diagnosed most likely as a fibroadenoma. In the patient's family, there were no similar cases.

Discussion

Primary pigmented nodular adrenal disease constitutes a histologically benign form of bilateral adrenal hyperplasia. It can occur in isolated form, or as the main component of Carney syndrome [4]. Carney syndrome is an autosomal dominant disease caused by inactivating mutations of the PRKAR1A gene (chromosome 17q22-24) [6]. The PRKAR1A gene encodes the regulatory subunit of kinase-A [7]. However, about 20% of Carney syndrome patients display a different mutation [6]. In fact, Carney syndrome is currently considered to be a multiple neoplasia syndrome [8]. It has a diverse clinical course, typically including: heart and skin myxoma, skin pigmentation, breast fibroadenoma, testicular and ovarian tumours, thyroid tumours, and pituitary adenomas [4]. Only a temporary increase in cortisol secretion, a negative dexamethasone suppression test, as well as a usual lack of changes in adrenal glands in CT are typical for primary pigmented nodular adrenal disease. Given the marked heterogeneity in clinical presentation, the diagnosis of Carney complex is presumptive if two features are present and definite when three or more occur. Rarely are more than five elements of the complex present. Supplemental criteria for the diagnosis of Carney complex are an affected first-degree relative or the presence of causative mutations, as of now only established for PRKAR1A [9]. In the reported case, the patient initially presented merely non-specific symptoms, and only later on detailed diagnosis allowed the identification of other components of Carney syndrome. Early diagnosis appears to be particularly important because bilateral adrenalectomy is crucial in the treatment of the Carney syndrome. Such proceedings prevent the necessity of re-operation and recurrent Cushing's syndrome [10].

Conclusions

Due to the diverse clinical symptoms of Carney syndrome, such as occasional initial subclinical course, only a temporary increase in cortisol secretion, a negative dexamethasone suppression test, and usually no changes in adrenal glands in the CT, diagnosis of the syndrome is difficult. Nevertheless, early diagnosis appears to be particularly important because bilateral adrenalectomy is vital in the treatment of Carney syndrome.

References

1. Louiset E, Gobet F, Libé R, et al. ACTH-independent Cushing's syndrome with bilateral micronodular adrenal hyperplasia and ectopic adrenocortical adenoma. J Clin Endocrinol Metab. 2010; 95(1): 18–24, doi: 10.1210/jc.2009-0881, indexed in Pubmed: 19915020.
2. Bohdanowicz-Pawlak A, Szymczak J, Waszczuk E, Bolanowski M, Bednarek-Tupikowska G. Subclinical Cushing's syndrome in adrenal incidentalomas--possible metabolic consequences. Endokrynol Pol. 2013;64(3):186-91. PubMed PMID: 23873421.
3. Ngow HA, Khairina WM. Primary pigmented nodular adrenocortical disease. Endokrynol Pol. 2011; 62(3): 268–270, indexed in Pubmed: 21717412.
4. Groussin L, Cazabat L, René-Corail F, et al. Adrenal pathophysiology: lessons from the Carney complex. Horm Res. 2005; 64(3): 132–139, doi: 10.1159/000088586, indexed in Pubmed: 16192737.
5. Stratakis CA, Sarlis N, Kirschner LS, et al. Paradoxical response to dexamethasone in the diagnosis of primary pigmented nodular adrenocortical disease. Ann Intern Med. 1999; 131(8): 585–591, indexed in Pubmed: 10523219.
6. Bossis I, Stratakis CA. Minireview: PRKAR1A: normal and abnormal functions. Endocrinology. 2004; 145(12): 5452–5458, doi: 10.1210/en.2004-0900, indexed in Pubmed: 15331577.
7. Groussin L, Kirschner LS, Vincent-Dejean C, et al. Molecular analysis of the cyclic AMP-dependent protein kinase A (PKA) regulatory subunit 1A (PRKAR1A) gene in patients with Carney complex and primary pigmented nodular adrenocortical disease (PPNAD) reveals novel mutations and clues for pathophysiology: augmented PKA signaling is associated with adrenal tumorigenesis in PPNAD. Am J Hum Genet. 2002; 71(6): 1433–1442, doi: 10.1086/344579, indexed in Pubmed: 12424709.
8. Gonçalves FT, Feibelmann TC, Mendes CM, et al. Primary pigmented nodular adrenocortical disease associated with Carney complex: case report and literature review. Sao Paulo Med J. 2006; 124(6): 336–339, indexed in Pubmed: 17322955.
9. J. Larry Jameson, Leslie J. De Groot, A. Grossman, Endocrinology: Adult and Pediatric (Seventh Edition), Elsevier 2016.
10. Stratakis CA, Kirschner LS, Carney JA. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. J Clin Endocrinol Metab. 2001; 86(9): 4041–4046, doi: 10.1210/jcem.86.9.7903, indexed in Pubmed: 11549623.