"COMPLEXITY OF CARNEY COMPLEX": A CASE SERIES FORM A SINGLE EXPERT CENTER FOR RARE ENDOCRINE DISEASES

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Background: Carney complex is a rare, autosomal dominant disorder, caused in most patients by mutations in the PRKAR1A gene. It is characterized by different endocrine tumors, pigmented skin and mucosal lesions, and myxomas. We present a case series of 4 adult patients with proven gene mutations in the PRKAR1A gene.

Table 1 Establishment of the diagnosis - age, presenting symptoms and detected mutations

Patient - sex	Patient 1 - female	Patient 2 - female	Patient 3 - male	Patient 4 - female
***PRKAR1A gene* mutation**	-	c.177+3A>G	c578deITG (17q24.2)	c578deITG (17q24.2)
Age: at diagnosis/current age	3 years / 31 years	13 years / 30 years	16 years / 34 years	37 years / 53 years
Presenting disorder – reason for detecting the mutation	Cardiac myxoma – extirpated, no recidives	ACTH-independent CS– obesitas, striae, hirsutism, left adrenal adenoma	Cardiac myhoma – fatigue, slurred speech, family history, two more operations for recidives – 20, 30 y.	A son with cardiac myxoma; anamnesis fot 2 operations for cardiac myxomas (31, 34 y.), another recidive – 37 y.

Case 1: At the age of 4 years - weight gain and high blood pressure - ACTH-independent CS was diagnosed which had a cyclical course over the years. 2005 – 2014 Active CS. As she refused bilateral adrenalectomy, therapy with Ketoconazole was taken for 6 months and then stopped. The patient was lost of follow-up between the years 2014 and 2020. 2021 (30 yr old) she gave birth to a healthy child. During pregnancy – normal UFC levels.

Case 2: At the age of 13 y. (2006) - ACTH-independent form of CS - left adrenalectomy was performed; lost of follow-up until 2016 when she presented with reccurent ACTH-independent CS. MRI showed right adrenal hyperplasia and right adrenalectomy was performed. 2016 – Microprolactinoma was diagnosed based on galactorrhea/ammenorrhea s-me; moderate hyperprolactinemia and pituitary adenoma (MRI); Cabergoline treatment (1 t. weekly) was initiated

Case 3: 2022 - He was sent to our department because of adrenal incidentaloma and infertility. Paradoxical rise in response to 1 mg DST was detected, however he had no signs and symptoms of hypercortisolism (including normal DXA); monitoring was recommended. Tubular insufficiency was diagnosed.
US of the testes revealed bilateral calcifications. MRI visualized bilateral testicular tumors and the patient was referred for testicular biopsy.

Case 4: Mother of patient #3, as confirmed mutation carrier, was admitted to hospital for evaluation. She was diagnosed with metabolic syndrome (BMI 31.95 kg/m2; insulin resistance, dyslipidemia, hypertension). As her son, she had paradoxical response to 1 mg DST without typical phenotypic features for CS. Metformin treatment was prescribed. Family history: a daughter (sister of p.#3) with a sudden death of brain embolism due to cardiac myxoma at the age of 19 yr.

Table 2. Most recent hormonal results

	Serum Cortisol 24h:	Free urinary cortisol:	Serum cortisol after 1 mg DST	ACTH
Patient 1 - 2014	696.6 nmol/l	1833.2 nmol/24h	630 nmol/l	<0.13 pmol/L
Patient 2 (before BA)	401.7	334.6	526.3	0.5
Patient 3 -2022	145.0	137.5	130.8	6.2
Patient 4 - 2022	138.6	21	237.3	6.2
Normal range	<207	38-275	<50	2.2- 12.2
Pituitary hormones	None of the patients has GH hypersecretion, patient #2 has a microprolactinoma treated with Dostinex, patient #1 has a NFPA.			

Table 3. Imaging and skin manifestations

Images	Patient 1	Patient 2	Patient 3	Patient 4
Abdominal CT	2006 - Left adrenal gland hyperplasia; 2010 – normal adrenal gland	NA	2019 – right adrenal gland adenoma 7 mm	2017 - normal
Pituitary MRI	2005 - microadenoma	2016 – microadenoma; 2017 - normal	normal	NA
Thyroid US	Normal	AITD	Thyroid nodule B3	Thyroid nodules EU-TIRADS 2
Echocardiography	NA		2021 - normal	2021 - normal
Skin manifestations	blue nevi (face, the lips, genital area)	blue nevi (face, the lips, genital area)	blue nevi (face, the lips, genital area)	Myxomas and blue nevi (face, the lips, genital area)

CONCLUSION: Essentially, Carney complex is a multiple endocrine neoplasia syndrome. However, it has many other aspects with the most common causes of death being the complications of heart myxomas. Furthermore, the increased risk for some malignant tumors associated with this rare genetic syndrome requires careful surveillance for improving the long-term outcome of these patients.

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