0072 - CLINICOPATHOLOGICAL AND MOLECULAR PROFILE OF BRAZILIAN PATIENTS WITH CUSHING SYNDROME DUE TO PRIMARY PIGMENTED MICRONODULAR ADRENAL HYPERPLASIA

Mode: Research Work

Thematic Unit: Adrenals

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Background/Objectives: To describe the clinicopathological and molecular characteristics of Brazilian patients with pigmented nodular adrenocortical disease (PPNAD) with or without Carney complex (CNC), a population yet not reported in the literature.

Methods: Single-center cohort of patients with Cushing syndrome caused by histopathologically confirmed PPNAD. Molecular strategy: PRKAR1A gene sequencing by Sanger followed by whole-exome sequencing (WES). Clinicopathological features were compared using Welch's test and proportions by Fisher' s test.

Results: 85.7% of the 14 patients had CNC, and 28.6% had a family history of PPNAD or CNC. Most were women (64.3%), with a median symptom-onset age of 9.7 years (range: 2-29.8). The median age at diagnosis was 14.9 years (range: 3.3-67.1), and the median symptom duration was 2.8 years (range: 0.3-37.3). Weight gain (50%), lentiginosis (21.4%), and short stature (14.2%) were the most frequent complaints. Following the diagnosis, in CNC patients, lentiginosis was found in 50%, breast nodules in 43%, and cardiac myxomas in 29%. On adrenal imaging (n= 12), 66.7% had hyperplasia or nodules, 50% had both, and 2 patients had normal imaging. Median baseline cortisol was 23.4 µg/dL (7.7–26, n=10). ACTH was suppressed (<5 pg/mL) in 66,7% and between 5-20 pg/mL in 33,3% (n=12). Median 23h salivary cortisol level was 840 ng/dL (220–2480, n=13) and median morning blood cortisol after 1mg overnight dexamethasone was 21 µg/dL (2.1–31.4, n=11). Most patients were treated by bilateral adrenalectomy (78.6%). Of the three patients submitted to unilateral adrenalectomy, one had a later contralateral adrenalectomy, and one developed cyclical Cushing's. Pathogenic PRKAR1A variants were identified in 9 patients (64.3%): in eight by Sanger and in one only by WES. After detailed WES analysis, no variants in the PDE11A or PDE8B genes were found in the remaining six patients. Comparing patients with or without PRKAR1A variants there were no differences in age of onset (MD -8.9 [95%CI: -18.3; 0.4], p= 0.06), baseline cortisol (MD 2.7 µg/dL [95%CI: -6.4; 11.9], p=0.5), post 1mg dexamethasone cortisol (MD 5.3 µg/dL [95%CI: -13.3; 23.9], p=0.51) or ACTH (MD 1.1 pg/mL [95%CI: -8.1; 10.4], p=0.79).

Conclusion: PRKAR1A variants, but not PDE11A or PDE8B variants, were present in 64.3% of Brazilian PPNAD patients, and no clinicopathological features distinguished mutated from wild-type PRKAR1A. Only bilateral adrenalectomy eliminates the hypercortisolism.