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Identification of Predictive Criteria for the Primary Bilateral Macronodular Adrenal Hyperplasia Gene ARMC5: A European Series of 352 Unselected Patients.

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Objective: Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) is a heterogeneous disease characterized by adrenal macronodules and variable levels of cortisol excess, with not clearly established clinical diagnostic criteria. PBMAH can be caused by germline inactivating variants of the tumor suppressor gene ARMC5. We aimed to better characterize ARMC5-mutated and wild-type patients and to identify predictive criteria for ARMC5 variants.

Methods: We included 352 consecutive index patients from 12 European centers, sequenced for germline ARMC5alteration because of PBMAH suspicion, regardless their clinical presentation. Clinical, biological and imaging data were collected retrospectively. Sensitivity, specificity, negative and positive predictive values for the prediction of ARMC5variant were calculated for various parameters.

Results: 53 patients (15.1%) carried 40 different ARMC5 germline pathogenic variants and showed a more distinct phenotype than non-mutated patients for cortisol excess (24-hour urinary free cortisol 2.32 vs. 1.11-fold ULN, respectively, $p<0.001$; plasma cortisol after 1 mg dexamethasone suppression test 337.5 vs. 142.4 nmol/L, respectively, $p<0.001$) and adrenal morphology (maximal adrenal diameter 104 vs. 83 mm, respectively, $p<0.001$; 9.8 vs. 3.2 adrenal nodules, respectively, $p<0.001$), with more frequent metabolic complications such as diabetes (51.0 vs. 35.4%, respectively, $p=0.038$) and hypertension (88.0 vs. 70.6%, respectively, $p=0.014$). Thus, ARMC5-mutated patients were more often surgically or medically treated in order to control cortisol excess (67.9 vs. 36.8%, respectively, $p<0.001$). Among operated patients, a bilateral adrenalectomy was more often performed in those carrying an ARMC5 pathogenic variant than in wild-type patients (56.7 vs. 32.3%, respectively, $p=0.019$). Even if all patients were more often primarily investigated in front of adrenal incidentaloma than clinical evidence for Cushing's syndrome (73 vs. 27%, respectively), ARMC5 patients were more often referred for Cushing's syndrome than wild-type patients (44 vs. 24%, respectively, $p=0.004$). To improve the ARMC5 mutation rate, the association of a clear bilateral adrenal involvement with evidence for autonomous cortisol secretion (defined at least by a plasma cortisol after 1 mg dexamethasone suppression test above 50 nmol/L) holds the better yield with a 27% specificity and a 20% positive predictive value, and a 100% sensitivity and negative predictive value, meaning that a useless genotyping could have been avoided for more than 20% of negative patients, without missing any mutated patient.

Conclusion: We report the largest series of index case patients investigated for ARMC5 with clinical characterization and confirm that ARMC5 pathogenic variants are associated with a more severe phenotype. In order to minimize negative ARMC5 screening, genotyping could be limited to clear bilateral adrenal involvement on imaging and autonomous cortisol secretion, with an optimum yield for routine clinical practice. These findings will also help better define PBMAH diagnostic criteria.

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