Nonclassic Congenital Adrenal Hyperplasia (NCCAH) Due to 21-Hydroxylase Deficiency: Clinical Management and Genetic Counseling of Two Portuguese Families

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Introduction: Congenital adrenal hyperplasia (CAH) due to 21-Hydroxylase deficiency occurs in 90-95% of cases, being a common autosomal recessive condition that can present with a wide range of hyperandrogenemic signs in childhood or adulthood. Severity of this disease is correlated with the enzymatic blockade of 21-Hydroxylase which depends of the mutation in gene CYP21A2. Two clinical forms are possible: classic, subdivided in salt-wasting and simple virilizing form (severe) and nonclassic or late onset (less severe).

Aims: We studied two portuguese families with NCCAH due to 21-Hidroxilase deficiency in order to improve clinical management and genetic counseling of their members.

Methods: Clinical presentation and hormonal assays (including test of tetracosactide) were performed in index cases (IC) . Genomic DNA of each family member was sequenced for the 9 most frequent mutations in CYP21A2. Total deletion of CYP21A , conversion in non functioning CYP21A1P or CYP21A1P_ CYP21A2 quimeras were also analyzed by enzymatic restriction.

Results: Family 1- IC: Female, 31 years old with NCCAH diagnosed at age 6 , after investigation of precocious pubarche and with test of tetracosactide positive (17-alpha hydroxyprogesterone levels > 10-15 ng/ml) . Molecular study of CYP21A2 showed a mutation g.1683G> T , homozygous , in CYP21A2 and a non functioning allele of CYP21A2 , heterozygous (non severe 21-Hidroxilase deficiency). Mother was carrying a non functioning allele of CYP21A2 , heterozygous (severe); Father, Brother and Partner were heterozygous for mutation g.1683G> T (non severe).

Family 2- IC: Female, 45 years old presenting hirsutism and oligoamenorrhea at age 35 and with test of tetracosactide positive confirming NCCAH Genetic study identified mutation g.1683G> T (less severe) in a copy and g.655A/C>G in another copy (splicing mutation severe). Familial genetic study identified two sisters (age 36 and age 40), asymptomatic but with pathologic genotype confirming NCCAH.

Discussion: Affected individuals or carriers of severe mutation in CYP21A2 can have descendents with the classic form if their partners are also carriers of severe mutations.

Preconception genetic study of the couple (Family 1) suggests a probability of 50% in which pregnancy, for descendents with 21-Hidroxilase deficiency nonclassic form. In Family 2, genetic studies will be performed in descendents of affected individuals after age 18 or before, if they are symptomatic or considering pregnancy.

Preconception genetic study in the context of a medical genetic consultation is fundamental in programming pregnancy, preventing therapies and unnecessary anxiety.

Nothing to Disclose: MDLD, DA, JG, LL, TK

ENDO 2016: 98th Annual Meeting and Expo of the Endocrine Society April 1-4, 2016 Boston, Massachusetts 02210, United States.