CLINICAL, BIOCHEMICAL AND MOLECULAR CHARACTERISTICS OF THE PATIENTS WITH NONCLASSICAL CONGENITAL ADRENAL HYPERPLASIA DUE TO 21-HYDROXYLASE DEFICIENCY IN CROATIA

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OBJECTIVES

BACKGROUND: Nonclassical congenital adrenal hyperplasia (NCAH) due to mild 21-hydroxylase deficiency is caused by mutations of the CYP21A2 gene located on chromosome 6p21.3.

AIMS AND OBJECTIVES: To determine cut-off for basal and stimulated 17-hydroxyprogesterone (17-OHP) levels, to evaluate CYP21A2 gene mutations frequency among Croatian NCAH patients, to determine correlation between 17-OHP levels and genotype and to evaluate correlation between 17-OHP levels, CYP21A2 gene mutations and phenotype.

PATIENTS AND METHODS

A cohort of 40 fully genotyped patients (31 unrelated) with NCAH (29 female/11 male) was studied. Seven female and 9 male patients were discovered through family studies. All subjects were evaluated for signs of hyperandrogenism. Basal levels of 17-OHP were determined in all patients and ACTH-stimulated 17-OHP levels were measured in 34/40 patients.

RESULTS

At diagnosis, 73.47% of patients were symptomatic. The commonest symptoms were precocious pubic hair development and advanced bone age. The 17-OHP cut-off levels of best sensitivity and specificity in our cohort of patients are 8.8 nmol/l for baseline and 39.2 nmol/l for ACTH stimulated 17-OHP levels (Figure 1. and 2.). Only one patient had baseline 17-OHP levels below 6 nmol/l. Among 40 fully genotyped patients, 12 patients carried two “mild” CYP21A2 mutations, 27 were compound heterozygotes for one “mild” and one “moderate/severe” mutation, and 1 patient had one “moderate” and one “severe” mutation (I172N/ I2G). The commonest mutation in our study group is V281L (85.0%).

No correlation was found between phenotype and basal and stimulated 17-OHP levels. There was no statistically significant difference between basal and stimulated 17-OHP levels among symptomatic and asymptomatic patients (p=0.786 for basal and p=0.531 for stimulated 17-OHP levels). Genotype severity did not correlate with phenotype or basal and stimulated 17-OHP levels.

CONCLUSIONS

Patients with basal 17-OHP levels above 8.8 nmol/l should be further evaluated for NCAH. Phenotype and 17-OHP levels do not correlate with severity of genotype suggesting that modifier factors may modulate phenotypic expression. Thus molecular analysis of CYP21A2 gene should be done in all patients, especially due to high frequency of patients with one “moderate/severe” mutation. Considering the high incidence of heterozygotes in the general population, it is important to genotype the partners of the patients with one severe mutation to offer genetic counseling.

References