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 (NCCAH) 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 NCCAH 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 NCCAH (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.

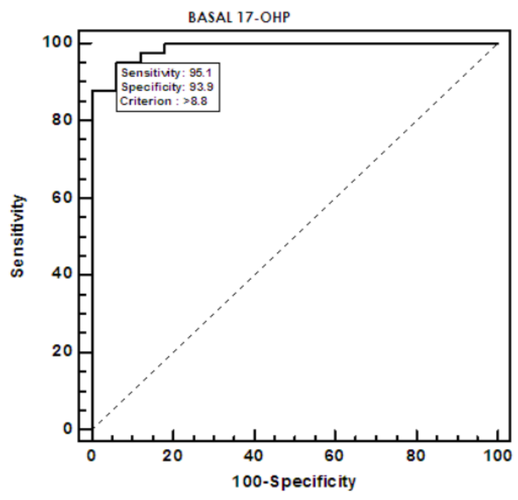

Figure 1. Sensitivity and specificity of basal 17-OHP levels in patients with NCCAH using Receiver Operating Characteristic Curve

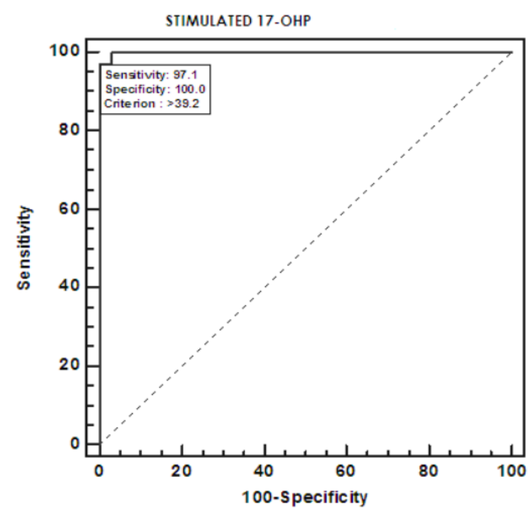

Figure 2. Sensitivity and specificity of stimulated 17-OHP levels in patients with NCCAH using Receiver Operating Characteristic Curve

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 corrrelation was found between phenotype and basal and stimulated 17-OHP levels. There was no statistically significant difference between basal and stimulated 17-OHP leves 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 NCCAH. 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.

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Adrenals and HPA Axis

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