THE CLASSICAL FORM OF CONGENITAL ADRENAL HYPERPLASIA- CLINICAL CHARACTERISTICS AND GENETIC ANALYSIS.

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OBJECTIVES

The classical form of congenital adrenal hyperplasia (CAH) is associated with the impairment of enzyme activity involved in the process of adrenal steroidogenesis. More than 90% of CAH cases are connected with mutations in the 21-hydroxylase gene *CYP21A2* in the HLA class III area on the short arm of chromosome 6p21.3. CAH is characterized by a strong correlation between the genotype and phenotype. Mutations in the *CYP21A2* gene can cause different degrees of loss of 21-hydroxylase enzyme activity which can result in various clinical characteristics. The aim of the study was to determine types of genetic disorders in patients with CAH and to assess correlation between the genotype and phenotype.

METHODS

Fifty patients (31 females and 19 males) with classical form of CAH (CCAH), treated since childhood, were involved in the study: 43 with salt wasting (SW) form and 7 with simple virilization (SV). Patients` anthropometric and metabolic data (height, weight, BMI, concentration of serum fasting glucose, total cholesterol) and in some cases - mineral bone density were assessed. In females history of reconstructive gynecologic surgery and fertility aspects (menarche, pregnancies, miscarriages) were also assessed. In 31 patients genetic analysis using MLPA with use of probemix SALSA MLPA P050 CAH from MRC Holland was performed.

Fig.1. Patients with CCAH

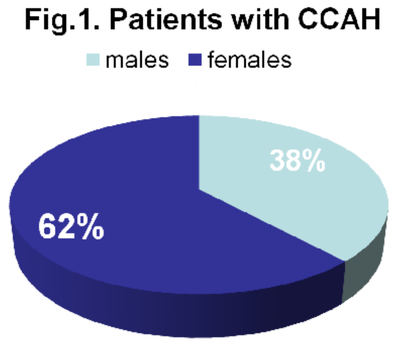
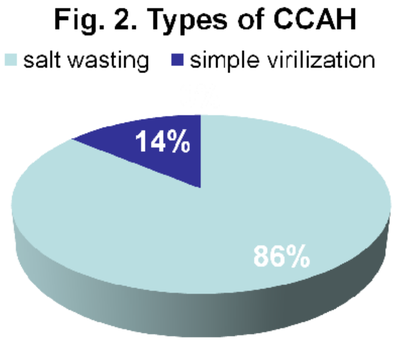


Fig. 2. Types of CCAH



RESULTS

The median height in the group of females was 157 cm (154, 160) and in the group of males 169 cm (166, 174.5). The median women's BMI was 25.4 (21.8, 31.36), while in case of men- 23.7 (21.15, 25). The median concentration of serum fasting glucose was 4.39 mmol/l (4.19, 4.21) and of total cholesterol 4.70 mmol/l (4.41, 5.51). The median age of menarche was 13 years (12, 14.25). Seventeen females reported a history of reconstructive gynecologic surgery. In ten patients mineral bone density was estimated (six of them had osteopenia). Ten different types of genetic changes in both alleles of *CYP21A2* gene were found in thirty one patients, who had genetic testing. One female patient with CCAH presented no changes in both alleles of the *CYP21A2* gene. An extended genetic analysis of this gene should be performed – sequencing together with chimera analysis, as such cases are not captured by MLPA.

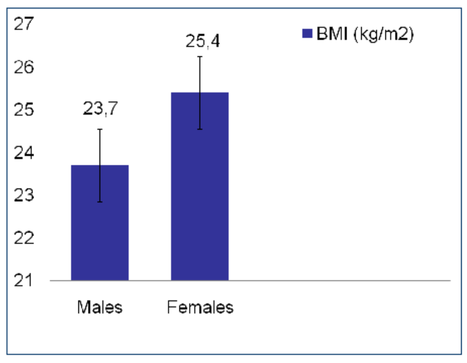


Fig.3. Patients` median BMI

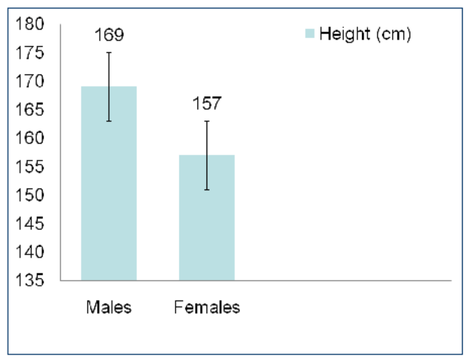


Fig.4. Patients` median height

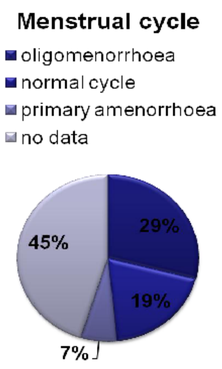


Fig.5. Menstrual cycle

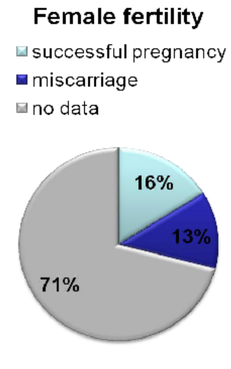


Fig.6. Female fertility

Tab. 1. *CYP21A2* mutations found in 31 patients with CCAH.

CYP21A2 mutations found in 31 patients with CCAH			
Type of mutation	**Enzyme activity (%)**	**No. of alleles with mutation**	**Frequency of mutation in 62 alleles (%)**
I2G *	<1	22	35.48
whole gene copy deletion*	0	17	27.42
I172N*	2-11	6	9.68
3 Kb deletion (exons 4-7 and part of TNXB gene) **	0	3	4.84
whole gene copy deletion and partial deletion of the TNXB gene**	0	1	1.61
Deletion of exons 1-3**	0	1	1.61
Del.8nt(c.332-339del)**	0	1	1.61
F306+T (c.929dupT)**	0	1	1.61
deletion of exons 3-7 of the gene duplication of exons 3-7 in the pseudogene**	0	1	1.61
SNP-113**	undetermined	1	1.61

- **Mutations found in patients with SW and SV types of CCAH**

**** Mutations found only in patients with SW CCAH**

CONCLUSIONS

Genetic defects are well correlated with the phenotypes of classical form of CAH. Further studies are required to search for new genetic disorders which may be responsible for development of CAH.

References

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