THE NEW ARMENIAN MEDICAL JOURNAL
Vol.7 (2013), No 3, p.52-60

*REVIEW*

# CONGENITAL ADRENAL HYPERPLASIA

**KIRAKOSYAN K.E.**

[1] State-Financed Health Institution "Moscow Regional Research Institute of Obstetrics and Gynecology", Moscow, Russia
[2] "Shengavit" Medical Center, Yerevan, Armenia

*Received 2/15/2013; accepted in final form 5/07/2013*

***ABSTRACT***

*One of the causes of adrenal androgen synthesis disorder is adrenal cortex dysfunction that is denoted by the term "congenital adrenal hyperplasia". In 95% cases this disorder is due to 21-hydroxylase deficiency, i.e. the virial form that depending on the enzyme deficiency level is subdivided into congenital (classic) and non-classical forms.*

*The non-classical form is most common in clinical picture of infertility and requires a detailed differential diagnosis from other diseases associated with hyperandrogenism. The molecular-genetic testing is the gold diagnostic standard for this type pathology. The prevalence of congenital adrenal hyperplasia non-classical form varies in different populations. The highest prevalence among the studied ethnic groups was detected in Ashkenazi Jews (1:27). In structure of hyperandrogenism the percentage of non-classical form is 1-3%, but in certain populations it makes 2.2-10%.*

*In order to detect the prevalence of the non-classical form of congenital adrenal hyperplasia in Armenian women and to identify the incidence of this disorder in hyperandrogenism structure, we conducted genotyping of two polymorphisms of the CYP21A2 gene (Pro31Leu and Val282Leu). The study included 86 infertile women, who applied to the Department of Human Reproduction of "Shengavit" Medical Center (Yerevan), and 30 fertile women. Overall, 116 blood samples were analyzed through mini-sequencing. The prevalence of heterozygous carriage state of congenital adrenal hyperplasia was 5.2% (1:22). The mutations of mentioned 2 polymorphisms were detected at 10.3% rate only in the group of patients with biochemical signs of adrenal hyperandrogenism. The clinical picture of the disease, as well as the adrenal androgens elevation degree did not allow differentiating the latent form of the non-classical 21-hydroxylase deficiency from other forms of endocrine disorders accompanied by hyperandrogenism.*

*Taking into consideration the above-mentioned, molecular-genetic testing should be introduced to the examination scheme of Armenian women with the biochemical signs of adrenal hyperandrogenism. This will allow the selection of a pathogenetically justified tactics of infertility treatment and might prevent the birth of children with life-threatening forms of the disease, as well as the birth of children with false hermaphroditism. Furthermore, newborns screening is required for identification and early treatment of the specified pathology. The screening of adolescent girls will allow to highlight the reproductive disorders risk group and, if necessary, conduct an adequate corrective treatment.*

***Keywords:*** *adrenal hyperplasia, Pro31Leu, Val282Leu, CYP21A2 gene, Armenian women.*

## INTRODUCTION

One of the causes of adrenal androgen synthesis disorder is adrenal cortex dysfunction due to genetic improper functioning of enzyme systems denoted by the term "congenital adrenal hyperplasia" (CAH). Depending on the defective enzyme, there are three forms of the disease.

***ADDRESS FOR CORRESPONDENCE:***
"Shengavit" Medical Center
9 Manandyan Street, Yerevan, 0006, Armenia
Tel.: (374 93) 815 089
E-mail: kirakosyan_karina@yahoo.com

- Virial form is due to deficiency of 21-hydroxylase (*201910, EC 1.14.99.10, 6r21.3, mutations in the genes *CYP21*, *CA2*, *CYP21P, p*) transforming the 17-hydroxyprogesteron (17-OHP) into deoxycortisol.
- Hypertensive form is caused by the lack of 11ß-hydroxylase (*202010, EC 1.14.15.4, 8q21, mutations in the genes *CYP11B1* and *CYP11B2*, ρ) that turns dezoxycorticosterone into cortisol. The lack of cortisol leads to disruption of synthesis of epinephrine and metanephrine [*Merke D. et al., 2000*].

- Salt-wasting form is the most severe form of the disease; it develops at insufficiency of ß-dehydrogenase 3 (*201810, EC 1.1.1.210, 1p13.1, mutations in genes HSD3B1, HSD3B2, ρ). The gluco- and mineralocorticoids synthesis is affected; particularly, there is a deficit of aldrosterone, which results in electrolytes loss and dehydration of the organism. Infants with this form of the disease are at high risk of death in the neonatal period or during the first year of life.

In 95% cases CAH is due to 21-hydroxylase deficiency, when the pathway of 17-OHP conversion into cortisol is blocked leading to its accumulation and transformation through an intact pathway with the help of 17, 20-lyase of cytochrome P-450c17. The steroid hormone $\Delta^4$-androstenedione, in its turn, is converted into androgens. Steroids deficiency leads to a disruption of the feedback loop for the pituitary gland and, consequently, to the chronic stimulation of the adrenal cortex adrenocorticotropic hormone and adrenal hyperplasia. As a result of this hormonal imbalance, the virial form of the disease develops. This inherited disorder is autosomal-recessive. In most CAH patients both parents are heterozygous. Approximately 1% mutations occur spontaneously – only one parent is heterozygous [*Krone N. et al., 2000*]. In case when both parents are heterozygous the probability of both mutant alleles inheritance is 25%, the chance of inheriting one mutant allele equals to 50% and implies that the child becomes a carrier, and there is 25% chance for the inheritance of two normal alleles and the birth of a healthy baby. In establishing the heterozygous carrier, there is a sense of conducting prenatal diagnosis in conjunction with prenatal treatment with dexamethasone in case of female fetus, in order to prevent having a child with classic CAH virial form. The excessive synthesis of adrenal androgens leads to virilization, the extent of which depends on the time of disease manifestation.

*CAH congenital form* (classic) is characterized by prenatal virilization of the fetus during the formation of external genitalia leading to the development of female hermaphroditism (significant hypertrophy of the clitoris, fusion of the *labia majora* in the form of scrotum, urogenital sinus). At proper treatment with glucocorticoids and a timely suppression of hypernormal adrenal androgen synthesis the puberty usually occurs at the appropriate chronological age. However, there might be exceptions even among those, who keep control of the disease [*Trinh L. et al., 2007*].

*Non-classical form of CAH* is characterized by a milder enzyme deficiency as compared to the classic form and, in its turn, falls into the following types:

- pubertal type: disease onset is associated with puberty in girls;
- subtle (subclinical), with a late manifestation that can be triggered by sexual debut, stress or pregnancy; and
- latent type with heterozygous carriage of the mutant gene.

Each form of non-classical CAH has a specific clinical picture. Girls suffering from the pubertal form of CAH have correctly developed genital organs; however, there is precocious puberty of heterosexual type and rapid growth of bones, followed by premature closure of a growth plate [*New M., 2006*]. In this case hirsutism, acne, menstrual disorders and late menarche are typical.

Clinical manifestations of the disease in patients suffering from the subtle form of CAH are usually slightly expressed. Very often the only manifestations may be infertility or recurrent pregnancy loss.

Patients with heterozygous carrier state of the mutant gene (the latent form) may have no clinical manifestations of the disease. The only signs of the disease may include miscarriage, stillbirth, death of a child at an early age and delivery of children with the classical form of CAH.

Approximately in 60% of adult women suffering from non-classical form of CAH clinical manifestations of the disease are limited to hirsutism; 10% of the specified cohort have hirsutism and menstrual disorders and about 10% have only menstrual dysfunction. Many patients suffering from this form of the disease have signs of polycystic ovaries revealed by ultra sound investigation. The spontaneous pregnancy rate in women suffering from non-classical form of CAH and not receiving treatment with glucocorticoids is 50% [*Pang S., 1997*].

In scientific publications the amount of data on men suffering from non-classical form of CAH is extremely limited. There are signs of early facial hair and rapid growth of penis, however, with rela-

tively small testes. As a rule, they do not have sexual function disorders, and the spermatogenesis is not disrupted [*New M., 2006*]. The main reason for subfertility may be the presence of testicular adrenal tumors and/or hypogonadotropic hypogonadism, which may arise due to the suppression of luteinizing hormone secretion by the pituitary, high concentrations of adrenal androgens and products of aromatization [*Ogilvie C. et al., 2006*]. Only one report on detection of bilateral adrenocortical incidentaloma in adult males suffering from non-classical form of CAH was found in available publications [*Nigawara T. et al., 2008*].

***Among women with CAH*** there is evidence for prevalence of individuals with bisexual and homosexual orientation [*Gastaud F. et al., 2007; Meyer-Bahlburg H., 2008*], whereas among men suffering from CAH this trend was not observed [*Hines M. et al.*, 2004].

***Non-classical form of CAH*** is the most common in clinical picture of infertility and requires a detailed differential diagnosis *versus* other diseases causing reproductive function disorders and having similar clinical and laboratory parameters (hyperandrogenism, hirsutism, menstrual disorders, and ultrasound characteristics of polycystic ovaries). The molecular-genetic testing is the gold standard for this form of CAH, which, unlike the other forms, does not have a pronounced clinical picture.

**Diagnosis setting**

The diagnosis of CAH is made on the basis of molecular-genetic testing on a panel of nine most common mutations. Gene mutation is found in 80-98% patients and carriers. Carefully taking a patient's medical history is of vital importance. Family history may reveal infertility or miscarriage, menstrual disorders and dysfunction, hirsutism, stillbirths, neonatal death of unknown etiology in relatives (first to the third degree of consanguinity). Symptoms like early adrenarche preceding thelarche, rapid growth in the prepubertal period, late menarche (after 14 years) are typical in patients suffering from subclinical forms of adrenal hyperandrogenism. Menstrual cycle in such women is often retained, but extended to 45-50 days. Whereas, the age of menarche in women with polycystic ovary syndrome (PCOS) does not fall out of the population norm, menstrual disorder of oligomenorrhea type with menarche is typical for most women with PCOS.

General examination of patients is carried out to assess the severity of hirsutism, acne, excessive skin oiliness, body fat distribution pattern, body mass index (BMI), peculiarities of the sexual organs development and secondary sexual characters, etc. Hirsutism is characterized by the presence of terminal hair in androgen-sensitive areas, where normally vellus hair grow (face, abdomen, chest, back, hips, shoulders). The manifestation degree of hirsutism varies widely in patients with CAH [*Kashimada K. et al., 2008*]. To evaluate and quantify hirsutism Ferriman-Gallwey scoring system is used [*Ferriman D., Gallwey J., 1961; Goodman N. et al., 2001*]:

- score up to 7 points is the normal range;
- 8-12 points are considered borderline level of body pilosis;
- above 12 points – the degree of excess (for women of Slavic origin).

The degree of lipid metabolism disorders, assessed by BMI, normally should not exceed 25 *kg/m²*. Hormonal assessment on the day 2-3 of the menstrual cycle or menstrual-like reaction reveals increased blood concentrations of the following adrenal androgens: 17-OHP, dehydroepiandrosterone (DHA), DHA-sulfate typical for the virial form of CAH. To diagnose the salt-wasting form, the concentrations of renin and plasma serum electrolytes are defined. The assessment of prenatal masculinization degree in women includes a thorough medical examination of external genitalia and vaginogram to check the anatomy of urethra and vagina.

**Genetic Testing**

Genetic analysis (Table 1) is conducted with the use of the following methods:

*Targeted mutations analysis*: Molecular-genetic testing detects general mutations in 80-98% of patients with CAH. Many of these common mutations are the result of gene conversion. The parents of the majority of patients with CAH in heterogeneous population are heterozygous [*Krone N. et al., 2000*].

*Deletion/Reduplication*: The analysis involves various types of polymerase chain reaction (PCR), such as quantitative PCR, real-time PCR, etc. The effectiveness of the method is also about 80-98%.

*Sequencing*: This method helps revealing mu-

**TABLE 1.**

Nomenclature: initials of *CYP21A2* gene

| Gene symbol | Chromosomal locus | Protein Name | The specific locus | Human gene Mutation Data Base (HGMD) |
|---|---|---|---|---|
| CYP21A2 | 6p21.3 | Cytochrome P450 21 | CYP21A2 @ Cytochrome P450 (CYP) | CYP21A2 |

tations not detected by the first two methods (the efficiency is more than 80-98%) [*Koppens P., 2002; Mao R. et al., 2002*].

Based on the remaining enzyme activity, the mutations can be grouped into mild and severe ones. In the classical form of CAH severe mutations occur on both alleles of *CYP21A2* gene with the complete cessation of enzyme activity. Individuals suffering from non-classical form of CAH have two mild mutations or one mild and one severe mutation. Parents of about two-thirds of patients with non-classical form of CAH are heterozygous. As a rule, this form of the disease is associated with *p.Pro31Leu* mutations in exon 1 and *p.Val282Leu* – in exon 7. Common grouping of *CYP21A2* mutations, based on the remaining enzyme activity, is presented in Table 2 [*Krone N. et al., 2000*].

**Prevalence**

*The classic forms of CAH*: The CAH classic forms, salt-wasting and virial, occur with a frequency of 1:15,000 live births. Data was obtained from the analysis of almost 6.5 million infants around the world in different population groups [*Pang S., Shook M., 1997; Van der Kamp H., Wit J., 2004*].

The prevalence in specific groups of population is as follows:

- 1:300 in the Eskimos of Alaska;
- 1:5000 in Saudi Arabia;
- 1:10,000-1:16,000 in Europe and North America;
- 1:21,000 in Japan;
- 1:23,000 in New Zeland.

***Non-classical form of CAH*:** The prevalence of CAH non-classical form in the general heterogeneous population of New-York is 1:100. The highest prevalence (1:27) among the studied ethnic groups is detected in Ashkenazi Jews. The prevalence in other ethnic groups varies: the Hispanic Americans (1:40), the "Caucasians" (1:50) and Italians (1:300) [*Speiser P. et al., 1985*]. Among women with hyperandrogenism the percentage of non-classical form of CAH is 1-3%, but in certain populations the percent is much higher. In papers of some authors the percentage of CAH non-classical form among women with hyperandrogenism ranges from 2.2% to 10% [*Dewailly D., 2002; New M., 2006; Escobar-Morreale H. et al., 2008; Fanta M. et al., 2008*].

**Treatment**

Glucocorticoid therapy is aimed to replace the missing steroids and lead to a reduction in adrenal androgens level, thus promoting prevention of virilization, menstrual and reproductive function disorders [*Clayton P. et al., 2002*]. The choice of an

**TABLE 2.**

Grouping of *CYP21A2* mutations on the basis of remaining enzyme activity according to Krone N. et al. (2000)

| Enzymatic activity | Form of the disease | *CYP21A2* Mutations |
|---|---|---|
| 0% | classic | removal of the entire gene (NULL Mutation)<br>large-format genes conversion<br>p.Gly111ValfsX21<br>p.[Ile237Asn; Val238Glu; Met240Lys]<br>p.Leu308PhefsX6 p.Gln319X p.Arg357Trp |
| minimal remaining activity (<1%) | | c.293-13A> G or c.293C> G |
| 2% -11% | | p.Ile173Asn |
| ~ 20% -50% | non-classical | p.Pro31Leu p.Val282L |

adequate therapeutic dose is based on 17-OHP physiological range for a certain age. At times of stress, the dose of glucocorticoids given should be increased. Female patients with classic forms of CAH require lifelong glucocorticoids intake. The non-classical form does not always require treatment. Many women have no symptoms of the disease throughout their lives. The indication for diagnosis and treatment of this form quite often comes to infertility. The dose of the glucocorticoids given is significantly lower in the treatment of non-classical form in comparison with those required during the treatment of classic forms.

Mineralocorticoid therapy is carried out for patients with salt-wasting form of the disease. In rare cases, in patients with severe CAH (*NULL* homozygous mutation) there is a need for bilateral adrenalectomy. It is considered that these patients should be treated by the Addison's disease treatment type, with a mandatory compliance regimen of hormone replacement therapy [*Bachelot A. et al., 2008*]. Only one publication reports on the bilateral adrenalectomy in five patients with severe CAH; surgical indications included infertility, masculinization and obesity [*Ogilvie C. et al., 2006*].

Taking into consideration the hereditary nature of CAH, prenatal diagnosis and prenatal treatment should be performed in case the patients are diagnosed with CAH on a genetic level to prevent the birth of children with life-threatening forms of the disease, as well as the birth of children with false hermaphroditism. In this regard, it is necessary to take measures for the timely identification of patients with both homozygous and heterozygous carriage of the gene *CYP21A2* mutations. This also applies to patients with non-classical form of CAH, taking into account that the majority (from one-half up to two-thirds) of women suffering from this pathology have a combined (compound) mutation with a severe defect in one of the alleles [*Witchel S., Azziz R., 2010*]. When planning a family, genetic counseling is considered appropriate and desirable in order to assess the potential risks to the offsprings.

In international practice, there is a treatment scheme proposed for pregnant women with identified severe defects of the *CYP21A2* gene in both parents. On the basis of this scheme the glucocorticoid therapy is continued during pregnancy [*New M. et al.,* 2003]. At pregnancy weeks 9-11 the fetal karyotyping is carried out: in case of a male administration of dexamethasone is terminated, in case of a female – an additional testing is carried out in order to detect *CYP21A2* mutations. In case the result is positive, dexamethasone intake is continued up to the delivery, in case of a negative result the medication intake is terminated (Figure).

It should be noted that we have not found a similar scheme for patients with non-classical form of CAH; however, given the large percentage of the combined mild and severe mutations, we believe that this group of patients also needs prenatal preventive care in order to control the possibility of having a child with serious disorders of adrenal androgenesis.

Screening of newborns for CAH detection serves the following purposes:

- Early detection of infants with life-threatening salt-wasting form of CAH;
- Early diagnosis of female hermaphroditism;
- Detection of individuals (though not all of them) with non-classical form of CAH [*Votava F. et al., 2005*].

Adequate prenatal glucocorticoid treatment proves effective in preventing virilization. Prenatal treatment with dexamethasone is usually well tolerated by both mother and fetus [*New M. et al.,* 2003]**.** According to the results of large-scale trials, no differences were detected in the incidence of congenital anomalies of the fetus, its weight or growth, as compared to the control group not receiving glucocorticoid therapy, provided that the mother and the doctor follow recommended therapeutic doses [*Forest M. et al., 1989*; *Lajic S. et al., 1998*; *New M. et al., 2001;* 2003]. It should be also noted that long-term studies showed that prenatal treatment promotes normal growth and sexual maturation in girls suffering from specified pathology [*Trautman P. et al., 1995; Forest M.*, 1998; *Lajic S. et al., 1998*]. It was also pointed out that most of the puberty age girls suffering from non-classical form of CAH had normal menstrual cycle and an intact reproductive function, if timely initiated appropriate treatment was arranged. However, the total fertility rate was reported to remain low in this group of patients [*Lo J. et al., 1999*].

Considering literature data, we conducted genotyping of two polymorphisms of the *CYP21A2* gene (*Pro31Leu* and *Val282Leu*) in order to reveal the prevalence of CAH non-classical form in Armenian women and to identify the incidence of the geneti-

cally confirmed CAH in their hyperandrogenism structure. Among 86 infertile women, who applied to the Department of Human Reproduction of "Shengavit" Medical Center (Yerevan), molecular-genetic testing was performed. The comparison group involved 30 fertile women. Overall, 116 blood samples were analyzed through mini-sequencing matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF) mass spectrometry method based on molecules identification *via* measurements of their mass to charge (m/z) ratio in the ionized state on mass spectrometer AUTOFLEX-III™ ("Bruker Daltonics" GmbH, Germany).

In the group of fertile women the molecular-ge-

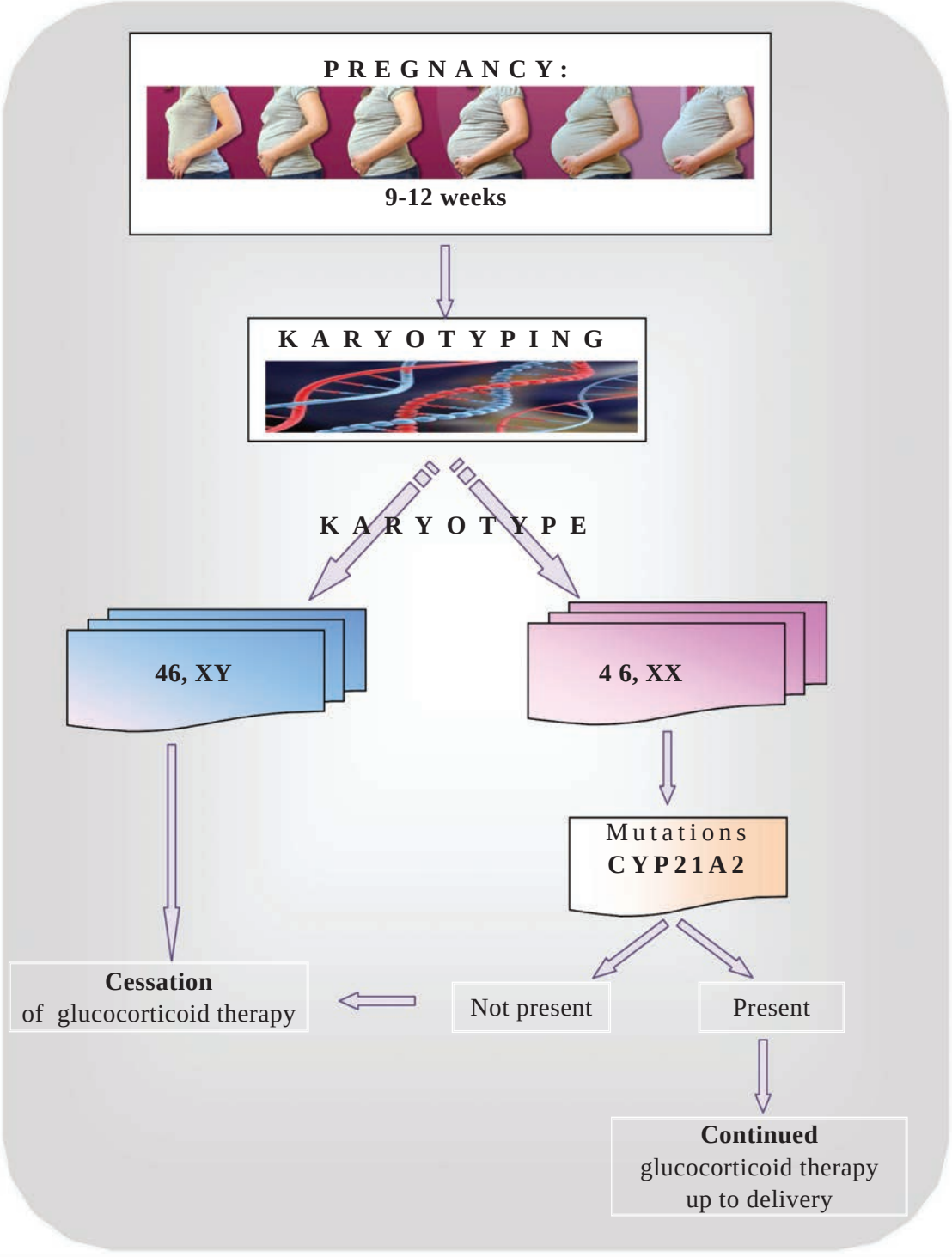


**Figure.** *The algorithm for management of pregnancy in women diagnosed with the classical form of Congenital Adrenal Hyperplasia.*

netic testing did not detect patients with either homozygous, or heterozygous carrier state of *Pro-31Leu* and *Val282Leu* mutations of *CYP21A2* gene. The mutations of those 2 polymorphisms were detected at 10.3% rate only in the group of patients with biochemical signs of adrenal hyperandrogenism. The clinical picture of the disease, as well as the 17-OHP elevation degree did not allow differentiating the latent form of the non-classical 21-hydroxylase deficiency from other forms of endocrine disorders accompanied by hyperandrogenism.

Generally, the prevalence of heterozygous carrier state of CAH in all the patients, who underwent the molecular-genetic testing for identification of mutations of polymorphisms *Pro31Leu* and *Val282Leu* of the *CYP21A2* gene (n=116) was 5.2% (1:22).

**CONCLUSION**

Taking into consideration the above-mentioned, molecular-genetic testing should by all means be introduced to the examination scheme of Armenian women with biochemical signs of adrenal hyperandrogenism, as the clinical picture does not allow differentiation between latent and subclinical forms of non-classical 21-hydroxylase deficiency *versus* other forms of endocrine disorders accompanied by hyperandrogenism. This approach will allow selection of a pathogenetically justified tactics of infertility treatment. Furthermore, hereditary nature of CAH dictates the need for prenatal diagnosis and prenatal treatment of patients diagnosed with CAH at the genetic level in order to prevent the birth of children with life-threatening forms of the disease, as well as the birth of children with false hermaphroditism. Moreover, newborn screening is required for the identification and early treatment of CAH. The screening of adolescent girls would allow to highlight the reproductive disorders risk group and, if necessary, to conduct an adequate corrective treatment.

## *REFERENCES*


1. *Bachelot A., Chakthoura Z., Rouxel A., Dulon J., Touraine P.* Classical forms of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults. Horm. Res. 2008; 69: 203-211.
2. *Clayton P.E., Miller W.L., Oberfield S.E., Ritzén E.M., Sippell W.G., Speiser P.W.* ESPE/LWPES CAH Working Group; Consensus statement on 21-hydroxylase deficiency from the European society for pediatric endocrinology and the Lawson Wilkins pediatric endocrine society. Horm. Res. 2002; 58: 188-195.
3. *Dewailly D.* Nonclassic 21-hydroxylase deficiency. Semin. Reprod. Med. 2002; 20(3): 243-248.
4. *Escobar-Morreale H.F., Sanchón R., San Millán J.L.* A prospective study of the prevalence of nonclassical congenital adrenal hyperplasia among women presenting with hyperandrogenic symptoms and signs. J. Clin. Endocrinol. Metab. 2008; 93: 527-533.
5. *Fanta M., Cibula D., Vrbíková J.* Prevalence of nonclassic adrenal hyperplasia (NCAH) in hyperandrogenic women. Gynecol. Endocrinol. 2008; 24: 154-157.
6. *Ferriman D., Gallwey J.D.* Clinical assessment of body hair growth in women. Journal of Clinical Endocrinology. 1961; 21: 1440-1447.
7. *Forest M.G.* Prenatal diagnosis, treatment, and outcome in infants with congenital adrenal hyperplasia. Curr. Opin. Endocrinol. Diab.1998; 4: 209-217.
8. *Forest M.G., Bétuel H., David M.* Prenatal treatment in congenital adrenal hyperplasia due to 21-hydroxylase deficiency: up-date 88 of the French multicentric study. Endocr. Res. 1989; 15: 277-301.
9. *Gastaud F., Bouvattier C., Duranteau L., Brauner R., Thibaud E., Kutten F., Bougnères P.* Impaired sexual and reproductive outcomes in women with classical forms of congenital adrenal hyperplasia. J. Clin. Endocrinol. Metab. 2007; 92: 1391-1396.
10. *Goodman N., Bledsoe M., Cobin R., Futterweit W., Goldzieher J., Petak S., Smith K., Steinberger E.* "American Association of Clinical Endocrinologists Hyperandrogenism Guidelines". Endocrine Practice. 2001; 7(2): 120-134.

11. *Hines M., Brook C., Conway G.S.* Androgen and psychosexual development: core gender identity, sexual orientation and recalled childhood gender role behavior in women and men with congenital adrenal hyperplasia (CAH). J. Sex Res. 2004; 41: 75-81.

12. *Kashimada K., Ono M., Onishi T., Koyama S., Toyoura T., Imai K., Saisho S., Mizutani S.* Clinical course of patients with nonclassical 21-hydroxylase deficiency (21-OHD) diagnosed in infancy and childhood. Endocr. J. 2008; 55: 397-404.

13. *Koppens P.F., Hoogenboezem T., Degenhart H.J.* Duplication of the CYP21A2 gene complicates mutation analysis of steroid 21-hydroxylase deficiency: characteristics of three unusual haplotypes. Hum. Genet. 2002; 111: 405-410.

14. *Krone N., Braun A., Roscher A.A., Knorr D., Schwarz H.P.* Predicting phenotype in steroid 21-hydroxylase deficiency? Comprehensive genotyping in 155 unrelated, well defined patients from southern Germany. J. Clin. Endocrinol. Metab. 2000; 85: 1059-1065.

15. *Lajic S., Wedell A., Bui T.H., Ritzén E.M., Holst M.* Long-term somatic follow-up of prenatally treated children with congenital adrenal hyperplasia. J. Clin. Endocrinol. Metab. 1998; 83: 3872-3880.

16. *Lo J.C., Schwitzgebel V.M., Tyrrell J.B., Fitzgerald P.A., Kaplan S.L., Conte F.A., Grumbach M.M.* Normal female infants born of mothers with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. 1999; 84: 930-936.

17. *Mao R., Nelson L., Kates R., Miller C.E., Donaldson D.L., Tang W., Ward K.* Prenatal diagnosis of 21-hydroxylase deficiency caused by gene conversion and rearrangements: pitfalls and molecular diagnostic solutions. Prenat. Diagn. 2002; 22: 1171-1176.

18. *Merke D.P., Chrousos G.P., Eisenhofer G., Weise M., Keil M.F., Rogol A.D., Van Wyk J.J., Bornstein S.R.* Adrenomedullary dysplasia and hypofunction in patients with classic 21-hydroxylase deficiency. N. Engl. J .Med. 2000; 343: 1362-1388.

19. *Meyer-Bahlburg H.F., Dolezal C., Baker S.W., New M.I.* Sexual orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess. Arch. Sex Behav. 2008; 37: 85-99.

20. *New M.I.* Extensive clinical experience: nonclassical 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. 2006; 91: 4205-4214.

21. *New M.I., Carlson A., Obeid J., Marshall I., Cabrera M.S., Goseco A., Lin-Su K., Putnam A.S., Wei J.Q., Wilson R.C.* Prenatal diagnosis for congenital adrenal hyperplasia in 532 pregnancies. J. Clin. Endocrinol. Metab. 2001; 86: 5651-5657.

22. *New M.I., Carlson A., Obeid J., Marshall I., Cabrera M.S., Goseco A., Lin-Su K., Putnam A.S., Wilson R.C.* Update: Prenatal diagnosis for congenital adrenal hyperplasia in 595 pregnancies. The Endocrinologist. 2003; 13: 233-239.

23. *Nigawara T., Kageyama K., Sakihara S., Takayasu S., Kawahara M., Imai A., Ohyama C., Usui T., Sasano H., Suda T.* A male case of nonclassical 21-hydroxylase deficiency first manifested in his sixties with adrenocortical incidentaloma. Endocr. J. 2008; 55: 291-297.

24. *Ogilvie C.M., Crouch N.S., Rumsby G., Creighton S.M., Liao L.M., Conway G.S.* Congenital adrenal hyperplasia in adults: a review of medical, surgical and psychological issues. Clin. Endocrinol. Oxford. 2006; 64: 2-11.

25. *Ogilvie C.M., Rumsby G., Kurzawinski T., Conway G.S.* Outcome of bilateral adrenalectomy in congenital adrenal hyperplasia: one unit's experience. Eur. J. Endocrinol. 2006; 154: 405-408.

26. *Pang S.* Congenital adrenal hyperplasia. Endocrinol. Metab. Clin. North Am. 1997; 26: 853-891.

27. *Pang S., Shook M.K.* Current status of neonatal screening for congenital adrenal hyperplasia. Curr. Opin. Pediatr. 1997; 9: 419-423.

28. *Speiser P., Dupont B., Rubinstein P., Piazza A., Kastelan A., New M.* High frequency of nonclassical steroid 21-hydroxylase deficiency. Am. J. Hum. Genet. 1985; 37: 650-667.

29. *Trautman P.D., Meyer-Bahlburg H.F., Postelnek J., New M.I.* Effects of early prenatal dexametha-

sone on the cognitive and behavioral development of young children: results of a pilot study. Psychoneuroendocrinology. 1995; 20: 439-449.

30. *Trinh L., Nimkarn S., New M.I., Lin-Su K.* Growth and pubertal characteristics in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J. Pediatr. Endocrinol. Metab. 2007; 20(8): 883-891.

31. *Van der Kamp H.J., Wit J.M.* Neonatal screening for congenital adrenal hyperplasia. Eur. J. Endocrinol. 2004; 151(Suppl. 3): U71-U75.

32. *Votava F., Török D., Kovács J., Möslinger D., Baumgartner-Parzer S.M., Sólyom J., Pribilincová Z., Battelino T., Lebl J., Frisch H., Waldhauser F.* Estimation of the false-negative rate in newborn screening for congenital adrenal hyperplasia. Eur. J. Endocrinol. 2005; 152: 869-874.

33. *Witchel S., Azziz R.* Nonclassic congenital adrenal hyperplasia. Int. J. Pediatr. Endocrinol. 2010; 2010: ID 625105; doi: 10.1155/2010/625105.