Non-classical congenital adrenal hyperplasia.
Clinical case


Abstract. Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease emerging from mutations of genes for enzymes that lead to the biochemical shifts in the production of glucocorticoids, mineralocorticoids, or sex steroids from cholesterol by the adrenal glands. Universal newborn screening for CAH is recommended for early diagnosis and initiation of therapy. The development of CAH is due to a defect in the CYP21 gene, which encodes 21-hydroxylase enzyme involved in the synthesis of cortisol. This leads to an increase in the secretion of adrenocorticotropic hormone and the accumulation of cortisol precursors, which are converted into adrenal androgens — the classical form of the disease develops. With a point mutation of the CYP21 gene, an incomplete defect occurs in 21-hydroxylase, which leads to an unpronounced disorder of adrenal steroidogenesis — a non-classical form of congenital adrenal hyperplasia, which happens more often. In this form, the clinical symptoms are erased with moderate hirsutism, acne vulgaris, infertility. In comparison to the classical form of the disease, which is diagnosed at birth or during the neonatal period because of ambiguous genitalia and/or salt-wasting symptoms or through screening programs used in some countries, most cases of non-classical CAH are not easy to detect. Additionally, many individuals remain asymptomatic during childhood and adolescence, have normal reproductive function, and only become aware of non-classical CAH due to the diagnosis of another family member and consequent testing. However, most women with non-classical CAH seek medical assistance when they experience symptoms of androgen excess and, when clinical suspicion prompts testing, elevated basal 17-OH progesterone levels may primarily point to the diagnosis of non-classical CAH. A case of a non-classical form of the disease which manifested itself in infertility is given. Pregnancy occurred after 4 months treatment with prednisolone (5 mg/day).

Keywords: non-classical congenital adrenal hyperplasia; diagnosis; pregnancy; treatment; clinical case

Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders affecting cortisol biosynthesis that lead to the biochemical steps of production of glucocorticoids, mineralocorticoids, or sex steroids from cholesterol by the adrenal glands [1]. Most of these diseases involve the excessive or deficient production of sex steroids that can alter the development of primary or secondary sex characteristics in some affected infants, children, or adults [2]. Sometimes, deficient production of mineralocorticoids can lead to severe salt-wasting, increasing neonatal morbidity, and mortality. Universal newborn screening for CAH is recommended for early diagnosis and institution of therapy [3].

Reduced activity of an enzyme required for cortisol production leads to chronic overstimulation of the adrenal cortex and accumulation of precursors proximal to the blocked enzymatic step. The most common form of CAH is caused by steroid 21-hydroxylase deficiency due to mutations in CYP21A2. Numerous new developments include more detailed understanding of steroidogenic pathways, refinements in neonatal screening, improved diagnostic measurements utilizing chromatography and mass spectrometry coupled with steroid profiling, and improved genotyping methods. Clinical trials of alternative medications and modes of delivery have been recently completed or are under way. Genetic

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and cell-based treatments are being explored. A large body of data concerning long-term outcomes in patients affected by CAH, including psychosexual well-being, has been enhanced by the establishment of disease registries [2].

The clinical features associated with each disorder of adrenal steroidogenesis represent a clinical spectrum that reflect the consequences of the specific mutations. Treatment goals include normal linear growth velocity and “on-time” puberty in affected children. For adolescent and adult women, treatment goals include regularization of menses, prevention of progression of hirsutism, and preservation of fertility. For adolescent and adult men, prevention and early treatment of testicular adrenal rest tumors is beneficial [4, 5].

Clinical case
We report the case of a 25-year-old women height 170 cm, BMI — 24 kg/m². Sent by a gynecologist about infertility, married for two years. Menstruation since 14 years of age according to the type of 24/7 days. Physical development corresponds to age, successfully completed 11 classes. Objective status is without abnormalities. The thyroid gland is not palpated. Blood pressure — 110/65 mm Hg. The skin and visible mucous membranes are pale pink. On the upper lip there is blonde fuzzy hair, individual hairs on the chin and sparse hair on the shoulders and along the midline of the abdomen, thighs. The mother of the patient has moderate hirsutism, there was miscarriage during the first pregnancy.

Gynecological consultation: primary infertility. Sexual hair growth occupies the entire suprapubic area. The clitoris is somewhat enlarged, the labia minora are underdeveloped. Internal genital organs are developed normally. The nipples of the mammary glands with a diameter of 1.5 cm are pigmented, slightly pigmented areolae and micromastia stand out around them.

Thyroid function analysis presented that the thyroid-stimulating hormone (TSH) level was 4.5 µIU/ml (normal range 0.5–4.5 µIU/ml). Other hormonal tests demonstrated that the adrenocorticotropic hormone (ACTH) level was 69.8 pg/ml (normal range 8.3–57.8 pg/ml), free testosterone level was 2.5 ng/dl (normal range 0.70–1.48 ng/ml), the prolactin level was 15.1 ng/ml (normal range 2.58–18.2 ng/ml). The patient’s cortisol level was 4.7 µg/dl (normal range 95.8–511.7 µg/dl), the 17-ОН progesterone level was 720.3 µg/dl (normal range ≤ 2.0 ng/ml). The patient’s cortisol level was 4.7 µg/dl (normal range 95.8–511.7 µg/dl), the 17-ОН progesterone level was 720.3 µg/dl (normal range ≤ 2.0 ng/ml). The patient’s cortisol level was 4.7 µg/dl (normal range 95.8–511.7 µg/dl), the 17-ОН progesterone level was 720.3 µg/dl (normal range ≤ 2.0 ng/ml).

Consequently, a decrease in blood cortisol level, an increase in ACTH, free testosterone, androstenedione, DHEAS and 17-ОН progesterone levels are characteristic of adrenal hyperandrogenism. Laboratory indicators of 21-hydroxylase deficiency may not go beyond the reference values, with the exception of 17-ОН progesterone, which is considered a marker of deficiency of this enzyme: its blood content of > 100 ng/ml indicates the classic version of CAH (normally < 2.0 ng/ml), and a level of 10–100 ng/ml confirms the diagnosis of CAH [6, 7].

The ultrasound examination of the internal organs of the female genitourinary system visualizes such conditions: ovaries up to 6 cm³, oval shape, protein lining is not thickened, the echogenicity of the stroma is normal, the follicles are placed randomly, up to 5 mm in diameter, varying degrees of maturity. The uterus is underdeveloped. CT demonstrated moderate bilateral hyperplasia.

Clinical diagnosis: non-classical congenital adrenal hyperplasia, primary infertility.

Ultrasound of the internal genital organs and CT of the adrenal glands confirm the diagnosis.

Treatment of the classic forms of congenital adrenal hyperplasia due to 21-ОН deficiency is based on two pillars: the first is glucocorticoid and mineralocorticoid replacement and the second is androgen control [5, 6].

The requirements and effects of glucocorticoid replacement therapy and androgen concentrations vary depending on patients’ age. The recommended glucocorticoid in infants, children, and adolescents (until final height has been reached) is hydrocortisone, which minimizes the negative effects of treatment on growth. Hydrocortisone preparations used for children are tablets or extemporaneous capsules prepared to provide low doses [7, 8]. New therapies for congenital adrenal hyperplasia seek to diminish the daily requirement of glucocorticoids by optimizing the pharmacokinetics of glucocorticoid replacement or reducing hyperandrogenism, independent of the suppressive effect of glucocorticoids on adrenocorticotropic hormone [5].

Reduced fertility and adverse pregnancy outcomes have been reported [9, 10], such as an increase in the number of children being small for gestational age or with congenital anomalies born to mothers with classic congenital adrenal hyperplasia. Primary caesarean deliveries are common among women with congenital adrenal hyperplasia, because genital virilization or previous genital surgery might complicate vaginal delivery. Genital surgery and the associated psychological burden might negatively affect sexual life, body image, and self-confidence. The imbalance of steroid hormones due to congenital adrenal hyperplasia causes menstrual disturbances in up to 30–60 % of female patients not on contraceptives.

In case the woman is not interested in pregnancy, and the main complaints are hirsutism, pustular skin rash or irregular periods, oral contraceptives are recommended. In asymptomatic nonpregnant individuals with non-classical congenital adrenal hyperplasia we recommend against glucocorticoid treatment [1].

Our patient received glucocorticoid replacement therapy (prednisolone 5 mg) in the morning. In women with non-classical congenital adrenal hyperplasia who are infertile or have a history of prior miscarriage, we recommend treatment with glucocorticoid that does not traverse the placenta [6].

With the onset of pregnancy, the dosage of prednisolone is the same (5 mg/day). Blood level control of 17-ОН progesterone was carried out every month.

Clinicians should evaluate the need for an increase in glucocorticoid during the second or third trimester and administer stress doses of glucocorticoids during labor and delivery [8, 10]. It should be borne in mind that in such cases, with the onset of labor, it is recommended to prescribe hydrocortisone. After childbirth, the question of further treatment tactics will be resolved. In patients with non-classical congenital adrenal hyperplasia, we suggest hydrocortisone.
stress dosing for major surgery, trauma, or childbirth only if a patient has a suboptimal cortisol response to cosyntropin or iatrogenic adrenal suppression [1].

Non-classical congenital adrenal hyperplasia is considered to be a common monogenic inherited disease, with an incidence range from 1:500 to 1:100 births worldwide. However, despite the high incidence, there is a low genotype-phenotype correlation, which explains why non-classical congenital adrenal hyperplasia diagnosis is usually delayed or even never carried out, since many patients remain asymptomatic or are misdiagnosed as suffering from other hyperandrogenic disorders. For affected adolescent and adult women, it is crucial to investigate any suspicion of non-classical congenital adrenal hyperplasia and determine a firm and accurate diagnosis [11].

Conclusions

A case of a non-classical congenital adrenal hyperplasia, which manifested as infertility, is given. Pregnancy occurred as a result of prednisolone treatment. In the future, it is important genetically consultation future parents with clinical manifestations of hyperandrogenism to assess the possible development of a similar pathology in their offspring. We recommend that screening laboratories employ a second-tier screen by liquid chromatography–tandem mass spectrometry in preference to all other (e.g., genotyping) to improve the positive predictive value of congenital adrenal hyperplasia screening. We advise that research protocols for prenatal therapy include genetic screening for Y-chromosomal DNA in maternal blood to exclude male fetuses from potential treatment groups.

References


Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.
Клінічний випадок

Клінічний випадок рекомендований для ранньої діагностики та призначення терапії. Розвиток вродженої гіперплазії надниркових залоз зумовлений ферментом гену CYP21, який кодує фермент 21-гідроксилазу, що береться у синтезі кортисолу. Це призводить до підвищення секреції адренокортикотропного гормону й накопичення попередників кортисолу, що перетворюються в андрогени, з розвитком класичної форми захворювання. При точковій мутації гена CYP21 виникає неповний дефект ферменту 21-гідроксилази, що обумовлює невиражене порушення стероїдогенезу у надниркових залозах із розвитком некласичної форми вродженої гіперплазії надниркових залоз, яка трапляється часто. При цьому клінічні симптоми стерті, спостерігається помірній гіпергідротазм, вульгарні вугри, безпліддя. Класичну форму захворювання діагностують при народженні або в період новонародженості по зовнішніх статевих органах проміжного типу та/або симптомах втрати солі або за допомогою програм скринінгу, що застосовуються в деяких країнах. Порівняно з цим більшість випадків некласичної вродженої гіперплазії надниркових залоз виявлять не просто. Крім того, багато людей залишаються безсимптомними в дитинстві та підлітковому віці, мають нор- мальну репродуктивну функцію і дізнаються про некласичну вроджену гіперплазію надниркових залоз, лише коли хворобу діагностують в іншого члена сім’ї та проводять подальше тестування. Однак більшість жінок із некласичною вродженою гіперплазією надниркових залоз звертаються по медичну допомогу, відчуваючи симптоми надлишку андрогенів. Коли клінічна підозра спонукає до обстеження, підвищення базальніх рівнів 17-OH прогестерону насамперед може вказати на діагноз некласичної вродженої гіперплазії надниркових залоз. Наведено випадок некласичної форми захворювання, що проявилися безпліддям. Вагітність настала через 4 місяці лікування преднизолоном (5 мг/добу).

Ключові слова: некласична вроджена гіперплазія надниркових залоз; діагностика; вагітність; лікування; клінічний випадок