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THE RESULTS OF THERAPY OF CONGENITAL ADRENAL HYPERPLASIA IN CHILDREN IN PERM REGION

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Background. Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders. About 90% of all children with CAH have 21-hydroxylase deficiency which is required for the synthesis of glucocorticoids and mineralocorticodes. The salt-wasting form of CAH develops with a deficiency of both types of hormones. This form of CAH results in infant death if not treated, therefore early disease detection and start of treatment are very important.
Aim of research is to study the clinical features of the course of the disease and evaluate the treatment efficacy of children with salt-wasting form of CAH in the Perm region.

Materials and methods. We conducted an analysis of the clinical features of the salt-wasting form of CAH in 40 children of the Perm region. To evaluate the treatment efficacy following symptoms were analyzed: salty food craving, hyperpigmentation of skin, hirsutism, delayed or accelerated growth, etc. and parameters of water-electrolytic balance, the level of 17-hydroxyprogesterone, adrenocorticotropic hormone, renin.

Results and discussion. Despite the modern possibilities of diagnosing and treating CAH, the complete control of the disease can't be achieved in all children. Almost all the children examined had either symptoms of replacement therapy failure or overdose symptoms. Hormonal imbalance disorders were performed by a few children without any symptoms of the disease.

Conclusion. During our research we concluded that young children often have issues with an overdose of hormonal drugs and frequent occurrence of salt-wasting crises against the background of associated diseases, while for teenagers, problems associated with an insufficient dose of glucocorticoid drugs are relevant. Also, significant difficulties in the treatment of children with CAH are associated with the short action of hydrocortisone. One way to solve these problems is to organize a school for parents of children with CAH. Creating motivation, explaining the principles of treatment and importance of regular taking of drugs, as well as algorithm in medical emergency is an important step in achieving control for the disease.

Keywords: salt-wasting form of congenital adrenal hyperplasia; hyperandrogenism; main clinical manifestations; electrolyte imbalance; reasons of decompensation.

РЕЗУЛЬТАТЫ ЛЕЧЕНИЯ ДЕТЕЙ С ВРОЖДЕННОЙ ДИСФУНКЦИЕЙ КОРЫ НАДПОЧЕЧНИКОВ, ПРОЖИВАЮЩИХ В ПЕРМСКОМ КРАЕ

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Введение. Врожденная дисфункция коры надпочечников (ВДКН) — это группа аутосомно-рецессивных заболеваний. Около 90 % всех детей с ВДКН имеют недостаточность фермента 21-гидроксилазы, который необходим для синтеза глюкокортикоидов и минералокортикоидов. Сольтеряющая форма ВДКН формируется при дефиците и глюкокортикоидов, и минералокортикоидов. Отсутствие лечения при данной форме приводит к гибели ребенка уже в младенчестве, а потому раннее выявление и начало лечения чрезвычайно важно.

Цель исследования: изучить клинические особенности течения заболевания и оценить эффективность лечения детей с сольтеряющей формой ВДКН в Пермском крае.

Материалы и методы. Проведен анализ клинических особенностей течения заболевания у 40 детей с сольтеряющей формой ВДКН, проживающих в Пермском крае. Для оценки адекватности подобранной терапии были проанализи-

рованы клинические проявления: тяга к соленой пище, гиперпигментация кожных покровов, гирсутизм, нарушение роста и другие симптомы, а также показатели электролитного баланса, уровень 17-гидроксипрогестерона, адренокортикотропного гормона, ренина.

Результаты и обсуждение. Несмотря на современные возможности диагностики и лечения при ВДКН, полной компенсации заболевания удается добиться далеко не во всех случаях. Почти у всех обследованных детей встречались либо симптомы недостаточности заместительной терапии, либо признаки передозировки. У ряда детей, не имеющих клинических проявлений заболевания, были выявлены отклонения в гормональном профиле.

Выводы. В ходе нашего исследования установлено, что для детей младшего возраста характерны симптомы передозировки глюко- или минералокортикоидами, а также частое возникновение сольтеряющих кризов на фоне присоединения интеркуррентных заболеваний, тогда как для детей подросткового возраста актуальны проблемы, связанные с недостаточной дозой глюкокортикоидных препаратов. Существенные трудности терапии детей с ВДКН также связаны с коротким действием гидрокортизона (Кортефа®). Один из способов решения этих проблем — организация школы для родителей детей, больных ВДКН. Создание мотивации, объяснение принципов лечения и важности регулярного приема препаратов, а также объяснение алгоритма действий при неотложных состояниях — важный шаг в достижении компенсации заболевания.

Ключевые слова: сольтеряющая форма врожденной дисфункции коры надпочечников; основные клинические проявления; гиперандрогения; электролитные нарушения; причины декомпенсации.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of diseases with an autosomal recessive inheritance mechanism that is caused by a congenital disorder of steroidogenesis due to enzymatic system deficiency.

Approximately, 90% of all pediatric patients with CAH have a deficiency of the enzyme 21-hydroxylase (a mutation in the *CYP21* gene), and <10% have a deficiency of 11β-hydroxylase (a defect in the *CYP11B1* gene). The rest of the forms are extremely rare [5, 9]. Insufficient 21-hydroxylase causes glucocorticosteroid (GCS) and mineralocorticoid deficiency, and less often glucocorticoid deficiency. Compensatory adrenal cortex hyperstimulation with adrenocorticotrophic hormone (ACTH) leads to excess androgens and cortisol synthesis precursors, 17-hydroxyprogesterone (17-OH-progesterone) [1, 3, 7, 10]. Based on the decreased severity in 21-hydroxylase activity, 3 disease forms are distinguished, which are simple or virile, salt-wasting, and obliterated or non-classical [6, 4, 10]. In the salt-wasting form, the decisive role in the clinical presentation of the disease is played by aldosterone deficiency and the salt-wasting crises arising in this situation, which is lethal in infancy if left untreated. With virile form, the clinical presentation is due to androgen hyperproduction with low cortisol levels. In the non-classical form, the enzyme deficiency is not pronounced, thus the clinical presentation is obliterated. The salt-wasting and virile forms of CAH are characterized by an impaired external genital organ (EGO) formation in girls, as manifested by virilization of varying severity. In boys, macrogenitosomia is registered at birth but is usually disregarded.

In Russia, the incidence of CAH among children is 1:9500 [1, 5, 6]. By the end of 2019, 122 children were registered with the diagnosis of CAH in the Perm Region.

Since March 2006, neonatal screening has been introduced in Russia, during which the blood level of 17-OH-progesterone is examined. This study identified pediatric patients with CAH in the first days of life, but it is considered ineffective in the non-classical, and in some cases, in the virile forms [2, 6, 9]. To date, the most informative method for all CAH forms is molecular genetic research by an allele-specific polymerase chain reaction to detect point mutations in the *CYP21* gene [9]. However, this method is only available in large endocrinological centers.

The only possible method to correct hormonal disorders in CAH is hormone replacement therapy with glucocorticoids and mineralocorticoids. Feminizing plastic surgery is indicated for girls with signs of EGO virilization, of which the timing is determined based on virilization degree [8]. In the future, constant monitoring of the adequacy of the selected therapy and changing the dose of hormonal drugs based on the age and bodyweight of the child is required. Additionally, the dosage should be adjusted in the presence of intercurrent diseases.

This study aimed to analyze the clinical aspects of the disease course and evaluate the efficiency of treatment of children with a salt-wasting form of CAH who live in the Perm Region.

MATERIALS AND METHODS

The case histories of 40 children aged 1–15 years (6.6 ± 3.8 years) with a salt-wasting form of CAH,

who were treated at the endocrinology department of the Regional Children's Clinical Hospital in 2017–2019 were analyzed. Under follow-up were 23 girls and 17 boys. CAH diagnosis was established based on the neonatal screening results in 38 patients and was suspected based on clinical manifestations of a salt-wasting crisis in the first month of life in 2 boys born before the introduction of screening. On urgent grounds, 7 children were hospitalized, whereas the remaining 33 were admitted on a scheduled basis. The molecular genetic examination was conducted on 11 children in the laboratory of the genetics of monogenic diseases, "National Medical Research Center of Endocrinology" of the Ministry of Health in Russia.

Clinical manifestations were analyzed, namely craving for salty food, skin hyperpigmentation, hirsutism, impaired growth, and other symptoms, as well as laboratory parameters, namely serum levels of potassium and sodium and their ratio, the serum levels of 17-OH-progesterone, ACTH, and renin, to assess the adequacy of the selected therapy.

The average ages of patients, as well as the average doses of drugs, are presented as the arithmetic mean values and standard deviations ($M \pm \delta$). The indicators that characterize the qualitative characteristics were determined as a percentage. Microsoft Excel 2016 was used for the statistical data analysis.

RESULTS AND DISCUSSION

All children from the first weeks of life received hormonal therapy, which prevented the formation of a salt-wasting crisis at the disease onset. Cortef® (a tablet form of hydrocortisone) was prescribed at 5.7–19.23 mg/m^2 per day (12.41 ± 3.38 mg/m^2 per day) to correct glucocorticoid deficiency. Mineralocorticoid deficiency was corrected with Cortineff (fludrocortisone, a drug with mineralocorticoid activity) at 25–150 μg/day (74.46 ± 33.10 μg/day). According to the Federal Clinical Recommendations, the recommended dose of Cortef is 10–15 mg/m^2 per day, whereas that of Cortineff is 50–150 μg/day [5]. Excessive Cortef dosage was noted in 7 patients (17.5%), whereas 10 received lower than prescribed doses (25%). An insufficient dose of Cortineff (<50 μg/day) was prescribed to 5 children (12.5%).

Due to the disease decompensation with acute respiratory infections, 7 patients were hospitalized, of whom 3 vomited 1–8 times a day, 5 had loose stools, and most had signs of dehydration. All children have severe electrolyte imbalance (hyperkalemia, hyponatremia, and potassium/sodium ratio of 1:29–1:20). Two patients had an increased ACTH (215–294 pg/ml) and 17-OH-progesterone (76.3–123 nmol/L) and 5 patients had increased renin (62.7–336 IU/L). No distinct endocrine disorders were determined in 2 patients.

Before the arrival of the ambulance team, most parents did not change the dose of hormonal drugs; Solu-Cortef® was injected in only 2 children due to the rapid deterioration in their condition. In the hospital, Solu-Cortef (an injectable form of hydrocortisone) was prescribed to 6 children, with an average age of 3.7 ± 1.9 years.

On a scheduled basis, 33 children were admitted, of whom 7 had complete compensation without significant clinical and laboratory manifestations. In 5 children, laboratory abnormalities were revealed as increased ACTH, 17-OH-progesterone, and renin, although they did not present any complaints.

Clinical signs of an increased level of androgens in various combinations were registered in 11 children, namely hyperpigmentation in 9 (27.3%), hirsutism in 3 (9.1%), acne in 2 (6%), and signs of false precocious sexual development (PSD) in 1 (3%). Advancement of bone age by >2 years and a slight acceleration of growth rates for the first years of life, followed by a slowdown toward puberty, was registered in 8 (24.2%) patients.

Hyperandrogenism was confirmed by increased blood levels of 17-OH-progesterone in all children (46.6–202.5 nmol/L), ACTH in 9 patients (104–845 pg/ml), and testosterone in 2 girls (10.4–11.5 nmol/ml). These disorders were found mainly in children of puberty, with an average age of 10.7 ± 2.8 years due to the untimely adjustment of hormonal drug doses as the children grow older.

Cravings for salty foods were noted in 6 (18%) children. One girl was diagnosed with hyponatremia with normal potassium and electrolyte ratios. Impaired K^+ and Na^+ ratios were registered in 5 children (1:27–1:23). All pediatric patients showed increased renin from 50.0 to 313.8 mIU/L, which was a sign of insufficient mineralocorticoid replacement therapy. The dose of Cortineff in these children was 25–100 μg. The average age of this group of children was 6.1 ± 2.8 years.

Symptoms of an overdose with GCS drugs were noted in 9 patients (27%). Seven children had a slowdown in growth rates, 1 girl was overweight, 4 were obese with degrees 1–3, and 3 children had striae in the lower abdomen, inner surface of the shoulders, and thighs. Increased blood pressure was recorded in 3 children (Fig. 1). Clinical manifestations were confirmed by laboratory data, thus 6 pediatric patients showed a decreased ACTH (<8.7 pg/ml). In the same children, 17-OH-progesterone was at the

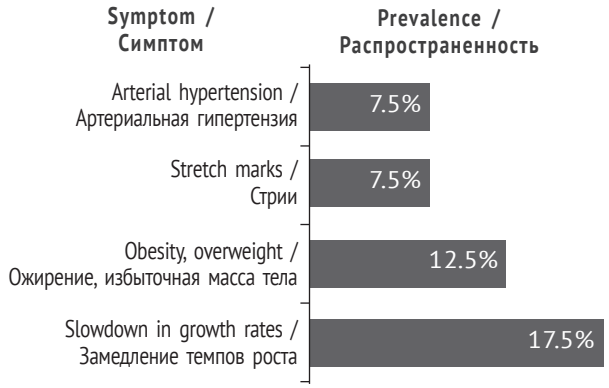

Fig. 1. The main clinical manifestations of glucocorticoid drugs overdose in 33 patients with Congenital adrenal hyperplasia hospitalized on a planned basis

Рис. 1. Основные клинические проявления передозировки глюкокортикостероидов у 33 пациентов с сольтеряющей формой дисфункции коры надпочечников, госпитализированных в плановом порядке

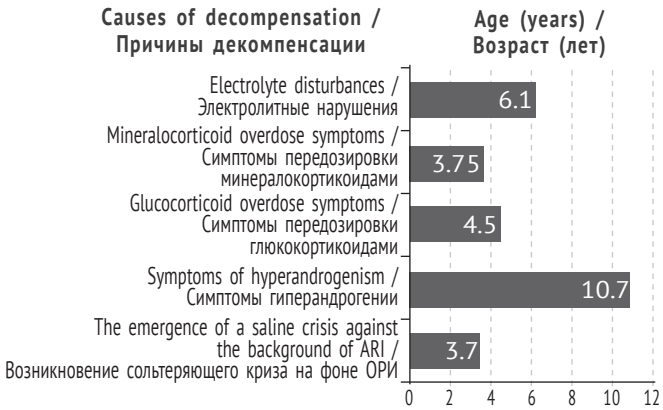

Fig. 2. The average age of children with various causes for the decompensation of CAH, admitted in a planned and emergency manner. ARI — acute respiratory infection

Рис. 2. Средний возраст детей, имеющих различные причины декомпенсации ВДКН, поступивших в плановом и экстренном порядке. ОРИ — острая респираторная инфекция

lower normal limit (the target 17-OH-progesterone level was the upper normal limit or slightly higher).

Sharp renin suppression was noted in 3 children. One girl aged 3 years 9 months was diagnosed with hypokalemia, which might be a sign of mineralocorticoid overdose.

Before a hospitalization, pediatric patients received Cortef at 10.7–19.23 mg/m^2 per day and Cortineff at 37.5–50.0 μg/day. Symptoms of drug overdose were detected mainly in preschool children (mean age 4.5 ± 1.2 years).

Figure 2 illustrates the main causes of disease decompensation and the distribution of these causes by age groups.

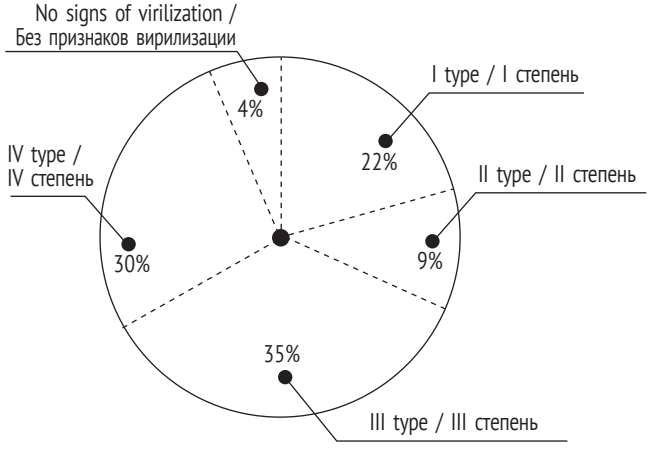

Fig. 3. Virilization of the external genitals in 23 girls participating in this study (percentage of different degrees of virilization)

Рис. 3. Вирилизация наружных гениталий у 23 девочек, участвовавших в данном исследовании (процентное соотношение различных степеней вирилизации)

Impaired EGO structure was noted in 22 of 23 girls, of whom 5 had a degree I virilization (hypertrophy of the clitoris without changing the vaginal orifice or its slight narrowing), 2 had degree II (hypertrophy of the clitoris, underdevelopment of the labia, their partial fusion, and funnel-shaped narrowing of the vaginal orifice), 8 had degree III (hypertrophy of the clitoris with urogenital sinus), and 7 had degree IV (urogenital sinus, opening at the base of the clitoris, and partial fusion of the labia). Degree V virilization (fusion of the labia with the formation of a scrotal resemblance and opening of the urethra at the apex of the hypertrophied clitoris) was not recorded (Fig. 3).

Figure 3 shows that the virile syndrome was manifested (degree II–IV virilization) in 74% of girls, thus a careful genital examination in most cases enables to suspect CAH in girls already in the first hours of life.

Feminizing plastic surgery was performed in 19 girls (stage 1 was performed in 16 cases, 2 stages of surgical treatment in 2 cases, and only clitoris resection in 1 girl). Surgical treatment is planned for 2 patients. The parents of 1 girl (4 years old) refuse to undergo feminizing plastic surgery.

Thus, at present, with the use of neonatal screening, the primary diagnostics of the salt-wasting form of CAH is performed promptly; however, the subsequent correction of GCS doses, which is required as the child grows up, often causes difficulties.

Severe disease decompensation that requires urgent hospitalization is usually due to the addition of respiratory infections with insufficient adjustment hormonal drug doses and a deficiency of mineralo-

corticoids. More often, a similar situation is noted in children of early and preschool age.

The need for mineralocorticoids in children decreases with age, thus in older patients, especially in adolescents, insufficient compensation, often without clear clinical manifestations, is in most cases due to an inadequate glucocorticoid dosage.

Our data revealed that less than a quarter of patients who are admitted to the hospital on a scheduled basis did not have clinical manifestations.

The active growth of a child requires constant correction and control of corticosteroids dosage, which are not always promptly performed. Due to inadequate replacement therapy, signs of overdose or symptoms of hyperandrogenism occur with insufficient suppression of the androgen-producing function of the adrenal glands.

The absence of prolonged forms of hormones complicates the replacement therapy since the three-time intake of Cortef provokes frequent misses of the next dose. "Windows" occur when the body does not have the proper level of glucocorticoids, which leads to an increased release of ACTH, adrenal cortex stimulation, and active androgen synthesis. Hyperandrogenism provokes the progression of bone age, early closure of growth zones, and subsequent short stature. With an increased dose and subsequent regular intake of drugs, glucocorticoid overdosage occurs, which also results in early growth zone closures.

CONCLUSIONS

During periods of apparent well-being, a significant proportion of patients have signs of insufficient disease compensation due to inadequate corticosteroid dosages. Our study established that young children are characterized by symptoms of corticosteroid overdosage, as well as the frequent occurrence of salt-wasting crises with intercurrent diseases.

For adolescent patients, the most important cause of decompensation is insufficient glucocorticoid drug dosage and signs of androgen overproduction.

Significant difficulties in the treatment of pediatric patients with CAH are associated with the short action of hydrocortisone (Cortefa) and the need to prescribe it in 3 doses. Insufficient family compliance leads to missed regular hormone intake, which complicates the selection of adequate doses.

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