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ORIGINAL PAPERS

Features of the Manifestation and Course of the Congenital Adrenal Hyperplasia in Infants

Maryia Simanchyk [1]*, Victoryia Karaga [1]

[1] Pediatric Department, Belarusian State Medical University, Minsk, Belarus

ABSTRACT

Background: In this moment early clinical diagnosis of congenital adrenal hyperplasia (CAH) in the absence of neonatal screening in the Republic of Belarus, prevention of additional therapeutic and psycho interventions associated with the need to change the passport sex and expressed the patient's short stature, a warning of inadequate destination of glucocorticoid drugs is big problem in the practical work of endocrinologists and pediatricians. **Methods:** We analyzed clinical (weight and growth dynamics) and laboratory (potassium (K), sodium (Na), glucose, adrenocorticotropic hormone (ACTH), 17-Hydroxyprogesterone (17-OHP), pH and buffer bases (BE)) parameters of the manifestation of CAH in newborns, evaluated the effectiveness of substitution treatment on the basis of the dynamic of anthropometric, hormonal and metabolic monitoring throughout the year in 32 children with CAC (18 boys and 11 girls with salt-losing form (SLF), 1 boy and 2 girls with virile form (VF)). **Results:** We established 17-OHP and ACTH levels increasing in two forms of CAH and hyperpotassemia, hyponatremia, euglycemia, metabolic acidosis in children with SLF in time of manifestation. Was founded decline of 17-OHP's level and normalization of other indicators through the year of hormone therapy. **Conclusion:** We established late diagnosis of SLF and VF regardless of sex. It's confirmed by clinical and hormonal and metabolic status of patients. There is late detection of SLF in boys due to the lack of the specific symptoms like virilization at birth. Adequate appointment of the doses of glucocorticosteroids and mineralocorticoids ensure normal growth of patients with CAH.

KEYWORDS

Congenital Adrenal Hyperplasia, Hormone Therapy, Glucocorticosteroids, Mineralocorticoids, Newborn

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) shows the spectrum of diseases with an autosomal recessive mode of inheritance caused by defective enzymatic systems that are involved in the biosynthesis of steroid hormones of the adrenal glands. These diseases are accompanied by hyperplasia of the adrenal cortex. The population prevalence of CAH is 1 case per 5,000-60,000 people [1].

In this day early clinical diagnosis of congenital adrenal hyperplasia in the absence of neonatal screening in the Republic of Belarus is big problem in the practical work of endocrinologists and pediatricians [2]. In adulthood, women with CAH closely observed by gynecologists, especially this applies to pregnant women. Unfortunately, patients with this diagnosis are group of risk of psychiatric disorders [3], so psychiatrists can practice their observation too. So priorities for patients are: 1) prevention of additional therapeutic and psycho interventions associated [4] with the dissatisfaction with the quality of life, need to change the passport sex and expressed by short stature, the existence of a disability [5],

2) a warning of inadequate destination of glucocorticoid drugs.

And if the disease can be diagnosed through virilization of the external genitalia in girls the diagnosis VDKN boys often fails during manifestation of CAH in the form of salt-losing crisis. At first, the parents can't pay attention to such non-specific symptoms like belching, fatigue, tearfulness, which may presage the salt-losing crisis. It's medical emergency coerces to start treatment of child with supraphysiological doses of glucocorticoids [6, 7] in intensive care units of specialized hospitals.

So objective of our study was to establish the clinical and laboratory features of CAH manifestation and evaluate the effectiveness of the treatment of SLF and VF in infants.

METHODS

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* Address for Correspondence: Maryia Simanchyk, Lesnaya Street- 42, Zhodino, Minsk region, Republic of Belarus. Tel.: +375293465494; Email: masha_simonchik@mail.ru

We examined 32 children with CAH, who are registered in «The 2nd City Children's Clinical Hospital» in Minsk (2015 – 2016.) We analyzed parameters of the manifestation of SLF and VF:

1) clinical parameters (weight and growth dynamics);

2) laboratory parameters (potassium (K), sodium (Na), glucose, adrenocorticotropic hormone (ACTH), 17-Hydroxyprogesterone (17-OHP), pH and buffer bases (BE);

3) effectiveness of substitution treatment.

Methods of variation statistics were used in processing of results.

RESULTS

In the analyzed group 29 children (18 boys and 11girls) has SLF, 3 patients (1 boy and 2 girls) has VF. The term of manifestation of CAH was 59,41±4,66 days for a boys and 16,3±3,15 for a girls with SLF, 110 days for boy and 285±233,35 days for girls with VF ($p<0,05$).

The 1st stage according to the Prader scale (a mildly large clitoris) was traced in 3 newborn girls, the 2nd stage (macroclitoris) - in 4 patients, the 3rd stage (external genitalia shows a further enlarged phallus with a single urogenital sinus) – in 2 girls; the 4ft stage (external genitalia looks like a penis with narrow urogenital sinus and large lips of pudendum fused like a scrotum) and the 5th stage (male virilization) were not found any patient. This way 9 from 11 girls has indications of the prenatal virilization. According to our data boys with CAH have pigmentation of external genital organs and swelling of penis.

Expressing metabolical disbalance was traced among the patient of both sex in the manifestation of SLF: hyperpotassemia (5.66±0.25 mmol/l, $p<0.01$), hyponatremia (130.19±1.81 mmol/l, $p<0.005$), pH

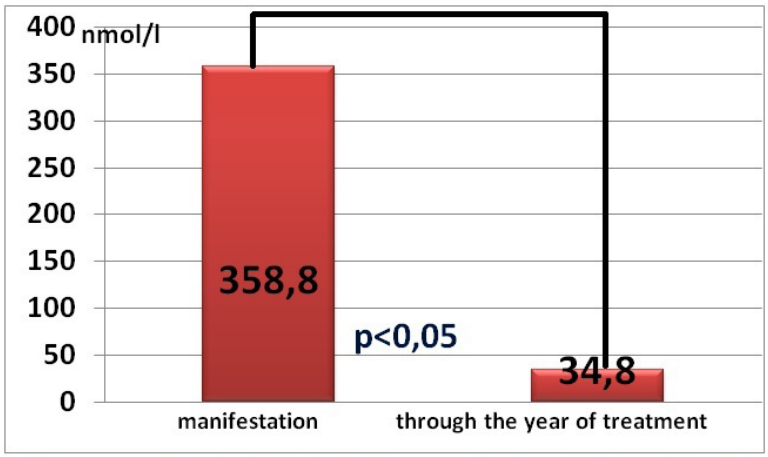

Fig. 1. 17-OHP lebel dynamics in children with SLF

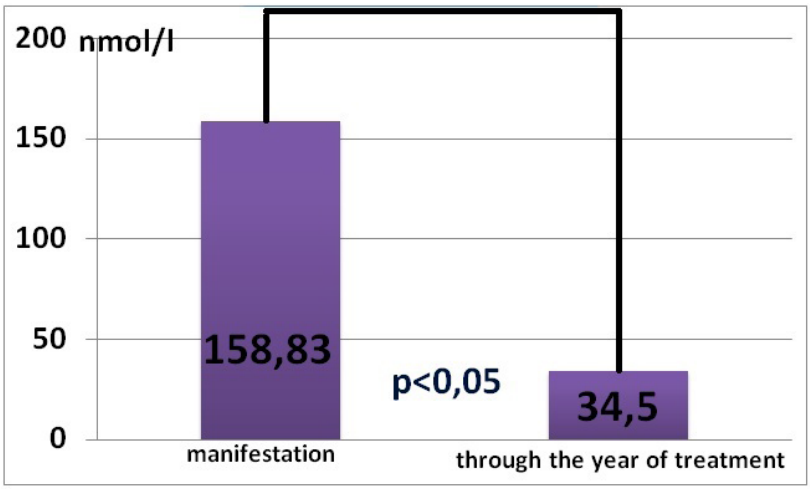

Fig. 2. 17-OHP lebel dynamics in children with VF

7,31±0,02, BE=-7,96±0,77 mmol/l (p<0,05). The pathology of carbonic link wasn't found – euglycemia (4,57±0,1 mmol/l).

All patients had hormonal disbalance in our research, which specific for SLF. Level of 17OHP was 358.8±39,12 nmol/l (p<0.05) (normal 0-3 nmol/l). Level of ACTH was 69,6±7,95 pg/ml (normal 50 pg/ml , p<0,05).

Increased level of 17OHP without salt-losing crisis is the laboratory standart of the virile form. Increase of the 17OHP concentration was traced in our research at the manifestation - 158,83±15,11 nmol/l (p<0,05). Level of ACTH exceeded the norm too (63,00±0,79 pg/ml, p<0,05). Serum values of electrolytes (potassium and sodium) corresponded to standard.

Starting daily doses of glucocorticoid and mineralocorticoids in the manifestation of SLF were: hydrocortisone - 26,09 ± 2,82 mg/m2, fludrocortisone - 0,46 ± 0,03 mg / m2 per day. Patients received an initial dose of hydrocortisone to 15.35 ± 3.80 mg / m2 per day at the virile form CAH. Correction doses of drugs was carried out individually, taking into account the indicators of metabolic and hormonal status.

Serum potassium levels became normal after a year of treatment of patients with SLF - 4,32±0,10 mmol/l (p<0,01) and sodium - 138,2±0,84 mmol/l (p<0,005).

Increasing the confidence level of 17OHP retained relative to the diagnostic standards - 34,80±7,00 10 nmol/l (p<0,05) in the normalization of ACTH secretion, that indicating a state of metabolic diseases subcompensation. Patients growth rates decreased by an average of the -1 sigma deviation against glucocorticoid therapy.

After a year of follow-up, 6 children (4 boys and 2 girls) observed a decrease in the growth rate of 3 sigma deviations due to inadequate correction dose glucocorticoid drugs and the lack of achievement of the metabolic compensation.

17OHP levels were increased after 1 year of treatment in children with SLF and VF in comparison to initial one: 34.8±7 and 34.5±4.08 respectively, (nmol/l, p<0.05) had decreased growth rate (under 3) after 1 year of ofpharmaceutical treatment. growth rates have increased relative to the average age norms in this group of patients after a year of substitution treatment.

Maintenance hydrocortisone and fludrocortisone doses after one year of treatment were in patients with SLF: 13.28±1.14 mg/m2/d and 0.2±0.02 mg/m2/d respectively; hydrocortisonedoses in patients with VF were 12.68±3.85 mg/m2/d relative to the starting value (p <0.05).

At our work maintenance doses of drugs when administered in full compliance with the doses recommended by the international consensus on the

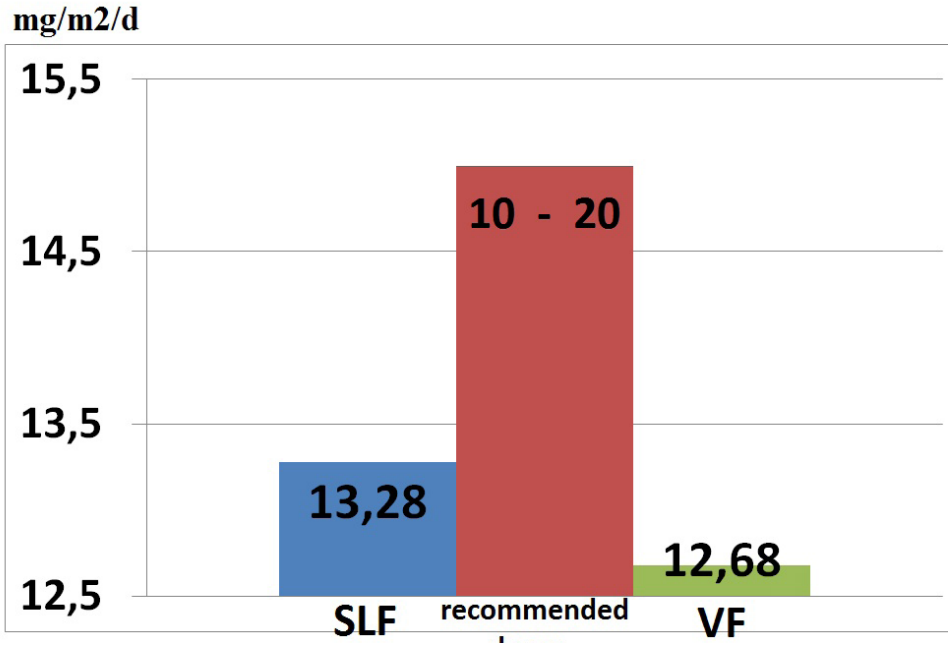

Fig. 3. Comparison of the recommended and achived doses of glucocorticosteroids

diagnosis and treatment of 21-hydroxylase deficiency in children (2002) adopted at the joint congress of the European Society for Pediatric Endocrinology and the Society of Pediatric Endocrinology Lawson Wilkins (USA) [8].

We found negative correlations between the age of manifestation of the disease and initial mineralocorticoid dose (r=-0.37, p<0.001) in patients with SLF, initial glucocorticoid dose and 17OHP levels - in children with SLF (r=-0.3, p<0.05), initial glucocorticoid dose and rate of growth in patients with SLF and VF (r=-0.3, p<0.01) were noticed in our work.

DISCUSSION

In the study, we have significant correlations:

1) between age of manifestation SLF and starting dose of mineralocorticoids (r=-0,37; p<0,001);

2) between dose of glucocorticosteroid drugs and levels of 17-OHP (SLF; r=-0,3; p<0,05);

3) between dose of glucocorticosteroid drugs and growth rate of patients with SLF and VF (r=-0,3; p<0,01) have been identified.

We came to the following conclusions:

1. There is late diagnosis of SLF and VF regardless of sex in Republic of Belarus. It's confirmed by clinical and hormonal and metabolic status of patients.

2. There is late detection of SLF in boys due to the lack of the specific symptoms like virilization at birth.

3. In time of CAH manifestation patients with SLF and VF took supraphysiological doses of glucocorticoids. It was due to the severity of clinical symptoms, particularly a salt-losing crisis. Significant reduction in the dose of hydrocortisone have been achieved to the recommended values for the correction of the treatment over time.

4. Adequate appointment of the doses of glucocorticosteroids and mineralocorticoids ensure normal growth of patients with CAH.

CONFLICT OF INTEREST

Authors confirm that this article content has no conflicts of interest.

ORCID

Maryia Simanchyk *http://orcid.org/0000-0002-0736-331X*

Viktoryia Karaga *http://orcid.org/0000-0003-4856-8001*

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