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Development of Polycystic Ovary Syndrome in Patient with a Classic Variant of Congenital Adrenal Dysfunction

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Abstract: ***A retrospective analysis of the viril (simple) form of congenital adrenal dysfunction (CAD) was performed against the backdrop of alternating periods of compensation and decompensation of the disease. During the observation period a number of laboratory and instrumental methods of investigation were performed and evaluated. The importance of hormone replacement therapy for all stages of ontogenesis is shown to prevent the development of complications.***

Keywords: congenital adrenal dysfunction, polycystic ovary syndrome

1. Introduction

CAD is an autosomal recessive disease that occurs with equal frequency among boys and girls. In the European population the frequency of CAD is rather high (1-2.5: 10,000 newborns). The general population frequency ranges from 0.3 to 1%. In the overwhelming number of the enzyme 21-hydroxylase deficiency cases occurs at a frequency of 1:14 000 newborns, and in the Russian Federation 1: 9500 ones. Diagnosis of this disease is important from the first week of the child's life. Other forms of CAD are rare: defect of STAR, deficiency of 11α-hydroxylase, deficiency of 17α-hydroxylase, 3β- hydroxylase[2].

The untimely diagnosis and the absence of hormone replacement therapy at an early stage significantly worsens the prognosis of the disease. Screening of 21-hydroxylase deficiency is performed by determining the level of 17-hydroxyprogesterone (17α-OHP) in the newborn's blood [3, 5].

There are two clinical forms of 21-hydroxylase deficiency: classical (viril and salt-losing or congenital) and nonclassical(later). Congenital forms are accompanied by signs of hermaphroditism and are diagnosed at birth. It is much more difficult to diagnose late and especially latent forms of CAD. The viril form is associated with partial deficiency of 21-hydroxylase, which causes hyperproduction (17α-OHP). Polycystic ovary syndrome (PCOS) develops often with the pubertal form of CAD [1]. In this case a deficiency of 21-hydroxylase and lack of compensation for a lack of cortisol enhances the synthesis of androgens. Adrenal hyperandrogenism develops as a result of which folliculogenesis, ovulation and development of PCOS are suppressed. Adrenal and rogenia is joined by ovarian hyperandrogenia. It has a secondary character and a mixed form [1]. Differential diagnosis of CAD and PCOS is rather complicated in connection with the identity of complaints and clinical symptoms [4]. The relevance of the study of the CAD and PCOS is determined by the violation of menstrual function in combination with hirsutism, miscarriage and infertility, metabolic disorders. These women have a significant impact on the quality of life.

The purpose of the work: to show the complexity of diagnosis and the consequences of the effect of insufficient hormone replacement therapy on the prognosis of the patient with the viril CAD.

2. Materials and Methods

Retrospective analysis of anamnestic data, course of the disease, laboratory, instrumental data and ongoing treatment throughout the life of the patient from birth to 23 years

Anamnesis of the disease

The girl E., 18 years old, in July 2012 appealed to the Endocrinology Department with complaints about the absence of menarche, headaches, acne, excessive growth of hair on the body, rough voice.

Clitoromegalia has been detected since birth. Also, at birth, there was a transient edema of the face, a paresis of the hands and feet. Both parents are heterologous for the defect of the hydroxylase gene 21 (CYP21A2). Father suffers from diabetes. In 2 years 3 months the diagnosis CAD, deficiency of 21-hydroxylase, viril (simple) form was made. At the examination: a significant increase in secretion of 17-CS with urine - 19 μmol / day (the norm was up to 3.5 μmol / day). The genetic study confirmed karyotype 46 XX, 18% sexual chromatin. The gynecologist discovered the penis-like clitoris, urogenital sinus, single dark pubic hair, uterine hypoplasia, which corresponded to 2-3 degrees of virilization by Prader. It was prescribed prednisolone 5 mg / day.

At the age of 2 years 7 months the patient underwent examination at the Endocrin Scientific Center of the Russian Sciences. The previous diagnosis was confirmed: CAD, deficiency of 21-hydroxylase, a simple viril form. The degree of virilization by Prader 2-3. It was recommended to continue treatment with glucocorticoids (GCS)

(prednisolone / hydrocortisone) and mineralocorticoids (florine 0.025 mg per day).

In 2 years and 9 months, an attack accompanied by vomiting, weakness, loss of consciousness, hyponatremia without hyperkalemia, acetonemia was developed. The attacks were eliminated by GCS. There are an episodes of acute adrenal insufficiency. Subsequently, similar crises were repeated 2-3 times a year from 3 to 10 years, started suddenly, early in the morning.

At 3 years 2 months the girl was feminized plastic of the external genitalia (clitorectomy) in one stage. Aldosterone, renin, angiotensin-1 plasma were investigated. The indices were within the normal range. It was recommended to continue therapy with GCS and mineralocorticoids.

3. Objective survey data (July 2012)

The girl has android build (the ratio of the arms of the hips to the hip circumference is 1.1), in spite of the 4-year-old estrogen intake. Height 160 cm, weight 57.8 kg (BMI = 22.5 kg / m2). The projected height of the child is 175 cm. Skin covers of physiological color and moisture. Acne on the face, shoulders, back. Abundant hair of hands and feet, single dark hair around the areola of the nipples, on the back, buttocks. White striae on the anterior-upper surface of the thighs. The mammary glands have increased in size (telarch) at 12 years, at the time of the examination - M1.

Respiratory system: no pathology has been identified. Cardiovascular system: tones are muffled, rhythmic, heart rate = 74 beats per minute. Systolic murmur at the apex of the heart and at the Botkin-Erba point. BP in the sitting position 110/76 mm Hg. in the standing position 93/70 mm Hg. The pathology of the thyroid gland, digestive and genitourinary system was not found.

4. Hormonal status

Since the diagnosis was established, the increase in 17-CS and 17α-OHP from 2 to 3 years, indicating the decompensation of the CAD. These indicators were normalized. The patient was compensated from 3 to 4 years. From the age of 7 to 9, there was also a period of compensation for the levels 17α-OHP. The 17α-OHP again increased from the age of 10 to 17. It was indicated the decompensation of the CAD (Table 1).

FSH and LH were increased in 2005. LH was decreased in 2011. Progesterone and PRL remained within the norm. The total testosterone increased to 1.39 ng / ml (normal level 1.3 ng / ml). From 2008 to 2010 the patient received Estrogel and from 2010 to 2012 - Proginova, but the effect of menarche was not obtained. Serum Estradiol was 200.0 pg / mL in November 2010. Other indicators within the limits of the norm.

When interpreting the indices of the pituitary-adrenal system, it was revealed that ACTH in 2000 was normal. In 2010 it was promoted. The girl had decompensation of CAD.

Table 1: Data from laboratory studies against substitution therapy with gluco- and mineralocorticoids:

Date	ACTH	17α-OHP, ng/ml	Substitution therapy
05.09.1996		>12,8	Prednisolone 5 mg/day Florineff 0,025 mg per day
11.06.1997		0,1	Cortef 15 mg/day Florineff 0,05 mg/day
06.07.2004		22,95	Cortef 15 mg/day Florineff 0,05 mg/day
29.06.2005		26,14	Cortef 20 mg/day Florineff 0,05 mg/day
March 2010		6,7	Cortef 25 mg/day Florineff 0,1 mg/day
March 2012	15,4 pg/ml	17,53	Cortef 20 mg/day Florineff 0,075 mg/day
July 2012	21,63 pg/ml	6,1	Cortef 20 mg/day Cortineff 0,1 mg/day
August	85,45 pg/ml	more than 20 ng/ml	Cortef 20 mg/day Cortineff 0,1 mg/day Dexamethasone 0,25 mg/day
October 2012		2,12 ng/ml	Cortef 20 mg/day Cortineff 0,1 mg/day Dexamethasone 0,5 mg/day
06.09.2013		18,65 ng/ml	Cortef 20 mg/day Cortineff 0,1 mg/day Dexamethasone 0,5 mg/day
23.02.2016		>20 ng/ml	Cortef 20 mg/day Cortineff 0,1 mg/day Dexamethasone 0,05 mg/day
26.07.2016		7,47 ng/ml	Cortef 20 mg/day Cortineff 0,1 mg/day Dexamethasone 0,75 mg/day

5. Instrumental research

According to the ultrasound of the pelvic organs, hypoplasia of the uterus and a decrease in the volume of the ovaries have been repeatedly observed. Against the background of taking estrogens in 2010, single follicles were visualized. It was found that the uterus has always been sharply reduced in volume.

Table 2: Ultrasound of the pelvic organs

Year of the survey	Uterus	Right ovary	Left ovary
1996	V=2,21 ml N	Not visualized	V=1,4 ml ↓
2005	V=4,83 ml ↓	V= 1,7 ml ↓	V=2,3 ml ↓
2008	Signs of hypoplasia (dimensions not indicated)		
2010	V=9,25 ml ↓	2,7×1,4 с несколькими фолликулами	2,8×1,5 с несколькими фолликулами
2011	V=8,33 ml ↓	V=1,5 ml ↓	V=1,1 ml ↓
March 2012	V=10,1 ml ↓	1,7×1,1 ↓	1,6×1,0 ↓
June 2012	V=16,8 ml ↓	V=7,3 ml ↓	V=3,1 ml ↓
19.10.2012	V=12,4 cm³ M-Echo - 4,7 mm	V=3,4 cm³ antrum follicles 3-4 mm throughout the body	V=4,1 cm³ with antral follicles throughout the body

According to the data of ultrasound of the adrenal glands, a multiple increase in their dimensions without volume formations was revealed, which also testified in favor of decompensation of the CAD. Since 1997, the diffuse heterogeneity of their parenchyma was noted, which indicated the development of adenomatosis. (Table 3).

Table 3: Instrumental studies of the adrenal gland

Research Date	Results
1996	The right adrenal gland is not enlarged, the left adrenal gland is slightly enlarged - 1,9x0,7 cm
1997	Signs of an increase in both adrenal glands
2005	Pathologies not detected
July 2012	Symptoms of diffuse adrenal enlargement (CT)
28.03.2016	Pathology is not detected (ultrasound)
29.07.2016	Pathology is not found on a spiral tomograph

The pathology of the thyroid gland has never been found.

Data of the primary treatment at the Department of Endocrinology

At the primary reference to the Department of Endocrinology in July 2012 received Cortef 20 mg / day, Cortinefff 0.1 mg /day, proginova. There was a rising of 17-OP and testosterone. In the biochemical analysis of blood, hyperuricemia was noted, which indicates the development of the metabolic syndrome.

On ultrasound of the pelvic organs in July 2012, hypoplasia of the uterus and ovaries was noted (Table 2).

Diagnosis (July 2012): CAD, deficiency of 21-hydroxylase, simple viril form, uncompensated. Adenomatosis of the adrenal glands and pituitary gland is not excluded. Dysplasia of connective tissue (bend of the neck of the gallbladder in the lower third, flat feet) is not excluded.

The following studies were commissioned: MRI of the pituitary gland, CT scan of the adrenal glands, ultrasound of the genitals, ultrasound of the heart, blood electrolytes (sodium, potassium, chlorides, calcium, magnesium, phosphorus, zinc), 17-OP and ACTH.

It was recommended to continue treatment under the former scheme with the previous dosages: Cortef 20 mg / day, Cortineff 0.1 mg / day, proginova, 1 tab/day

In the second visit, the 17-OP and ACTH blood counts were again increased, which confirmed the decompensation of the CAD. In the study of blood electrolytes, there were no deviations from the norms. MRI data of the pituitary gland without contrast are presented in Table 4, CT scan of the adrenal glands in Table 3.

Table 4: Magnetic resonance imaging of the pituitary gland

Research date	Results
July 2012	Dimensions of the pituitary gland - 4 × 11 × 12 mm, in the left lobe of a rounded shape 4 mm in diameter (microadenoma).
29.07.2016	The pituitary gland has dimensions of 11 * 13 * 4 mm. There is no microadenoma.

Taking into account the results of the studies, correction of drug therapy was made: proginova was withdrawn, Dexamethasone 0.25 mg (1/2 tablets) was added per day), glucocorticoid activity of which is 30 times higher than Cortef. It is also recommended to continue taking Cortef 20 mg per day and Cortineff 0.1 mg per day under the control of ACTH, 17-OP blood. It is strongly recommended to do heart ultrasound to confirm connective tissue dysplasia.

A month later, due to lack of effectiveness, the dose of Dexamethasone was increased to 0.5 mg (1 tablet) per day. In October, menarche appeared, the menstrual cycle recovered at a normal level of 17-OP (2.12 ng / ml).

Visit 07.04.2016 (in the dynamics)

Complaints: disturb irregular menstruation - alternation of opso- and hyperpolymenorrhea, poor tolerance of exercise. Gluco-and mineralocorticoids take irregularly. At weekends she taking medication from 7 in the morning to 12-13 hours. Notes a significant reduction in hair growth on the hands, but intensive growth continues on the hips.

BMI = 19.8 kg / m2 (lost weight by 2 kg). Blood pressure sitting was at 103/62 mm Hg. Standing was at 92/75 mm Hg. Pulse was 100 beats per minute.

Ultrasound of the genitals

Date	Uterine	Rigt ovary	Left ovary
28.03.2016 28th day of the ovarian-menstrual cycle(OMC)	V=34.6 cm³ M-echo - 3mm	V=14 cm³	V=10,7 cm³
		The follicular apparatus differs indistinctly, in the body of both ovaries 10 or more follicles 3-5 mm in size	

Diagnosis (07.04.2016): CAD (deficiency of 21-hydroxylase), classical variant, viril form, uncompensated. The emerging polycystic ovary syndrome. Oligo-opsomenorea alternating with hyperpolymenorea. The relative deficiency of vitamin D. Syndrome of undifferentiated connective tissue dysplasia?

Recommendations

High-protein diet with a high content of dairy products, butter, fried eggs, bread, meat. Add weight of 3 kg, Cortef, 10 mg - 1t. at 7:00 h, ½ table. at 16 hours and 21:00 h, Cortineff, 0.1 mg - 1 table. at 7:00 h, Dexamethasone, 0.5 mg - 1.5 tablets. at 7:00. After 3 months, examine 17-OP, HbA1C, 25 (OH) D3, calcium, phosphorus, magnesium, albumin, TTG, PRL, ultrasound of the genitals on the 2nd-5th day of O.M.C., ultrasound of the heart with M-echo. It is strongly recommended to take gluco- and mineralocorticoids at the same hours and without omissions.

Visit 03.08.2016

She took drugs-gluco- and mineralocorticoids- at the same hours and without omissions. Ovarian-menstrual cycle (OMC) is recovered.

The results of the survey in dynamics (July 26, 2016): TTG - 3.75 IU / L, PRL - 703.4 μIU / ml, 17-OP - 7.47 ng / ml - N, Vitamin D total - 20.9 ng / ml, albumin - 40,8 g / l, calcium - 2,34 mMol / l, magnesium - 0,7 mMol / l, phosphorus - 1,11 mMol / l, HbA1c - 5,4%.

Echo-KS: mitral valve prolapse in the left atrium cavity 3 mm. Regurgitation on the valve of the pulmonary artery and mitral valve.

Ultrasound of the genitals

Date	Uterine	Rigt ovary	Left ovary
03.08.2016 The third day of OMC	V=27,6 см³ Endometrial = 5mm	V=3,79 см³ Follicles to 7mm in diameter,to 5 in a cut	V=4,62 см³ Follicles to 8 mm, to 5 in a cut

Diagnosis (03.08.2016): CACD (deficiency of 21-hydroxylase), classical variant, viril form, compensated. Syndrome of connective tissue dysplasia. Adrenal adenomatosis and pituitary microadenoma, polycystic ovary syndrome disappeared against the background of the normal 17-OP level

6. Recommendations

High-protein diet with a high content of dairy products, butter, fried eggs, bread, meat. Add weight of 3 kg, Cortef, 10 mg - 1t. at 7:00 h, ½ table. at 16 hours and 21:00 h, Cortineff, 0.1 mg - 1 table. at 7:00 h, Dexamethasone, 0.5 mg - 1.5 tablets. at 7:00; Aquadetrim, 3 drops for lunch; Magnerot ,2tab * 3 times a day 1 month, 2tab * 2times a day a second month, 2 tab * once a day the third month. After 3 months, examine 17-OP, HbA1C, 25 (OH) D3, calcium, phosphorus, magnesium, albumin, TTG, PRL, ultrasound of the genitals on the 2nd-5th day of O.M.C., ultrasound of heart with M-echo. It is strongly recommended to take gluco- and mineralocorticoids at the same hours and without omissions.

7. Discussion

Since our diagnosis, frequent changes in the periods of decompensation and compensation of CAD have been observed in our patient. There was an increase in 17-OP from 2 to 3 years, which indicated the decompensation of the disease, and in the age groups from 3 to 4 years and from 7 to 9 years, these indicators were normalized and the patient was compensated. On the contrary, the entire period of prepubertate and pubertal decompensation of CAD took place, as evidenced by the level of 17-OP, exceeding the normal values. When interpreting the indices of the pituitary-adrenal system, it was revealed that ACTH in 2000 was normal. In 2010 ACTH was increased. It confirms the decompensation of CAD at the age of 14 years. This can be explained by pubertal and the lack of adequate correction of the dose of GCS. High doses of GCS in adolescence can lead to obesity and delay in menarche and puberty with sexual infantilism. Inadequate low doses of the latter leads to premature puberty, low growth. The patient had a telarche at 12 years old. She taking estrogens from two years from 16 to18 years old, but the menarche was absent.

Increased ACTH, adrenal hyperplasia, pituitary microadenoma confirmed the long absence of an adequate dose of GCS and the development of central and peripheral adenomatosis.

In March 2016 the ovary enlargement in the volume from 10 to 14 cm3 and the presence of 10 or more follicles 3-5 mm in a cut by genitals ultrasound was recorded for the first time. There was a violation of the menstrual cycle- oligo-opsomenorrhea alternating with hyperpolymenorrhea. These changes indicated the emerging syndrome of polycystic ovaries. Why did this happen? Was the increased level of 17-OP the main reason? But also earlier to 18 years of age against a background of elevated levels of 17-OP this syndrome did not develop and the ovaries were hypoplastic. It can be assumed that the administration of Dexamethasone suppressed ACTH and the production of androgens in the adrenal glands. This led to a relative increase in estrogen. Given the irregular intake of gluco-and-mineralocorticoids, this contributed to the fluctuations of LH and FSH in the pituitary gland in the direction of a larger increase in LH and a decrease in FSH. Most likely, all these changes and caused the development of PCOS in this patient. More research is needed.

The patient was diagnosed with connective tissue dysplasia, Marfanoid appearance. Magnesium preparations, vitamins B, C, E is needed to normalize the synthesis and maturation of collagen and elastin. These medicines reduce the degree of dysplastic processes in the heart, leveling signs of autonomic dysfunction.

On the example of this patient, the importance of compensation of CAD at all stages of ontogenesis is shown to prevent the development of complications, in particular, acute hypocorticism, low growth, hyperplastic processes in the adrenal glands and pituitary gland up to tumor degeneration, PCOS formation. After the growth zones are closed, translation into synthetic analogues of GCS (prednisolone) is possible. Dexamethasone may be added in the evening. Based on the observation of our patient, apparently to maintain stable hormonal and physical status, it is necessary to recommend the level of 17-OP in 1,5-2 times above the upper limit of the norm.

8. Conclusion

The importance of compensation of CAD at all stages of ontogenesis is shown on the example of our patient. Compensation of CAD prevents the development acute hypocorticism, low growth, hyperplastic processes in the adrenal glands and pituitary gland up to tumor degeneration, PCOS formation

Estrogens can be added to the treatment of CAD if a satisfactory girl estrogenization is not achieved at normal levels of 17-OP. We believe that it is necessary recommend the level of 17-OP in 1,5-2 times above the upper limit of the norm. The observation of our patient proves our assumption.

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