Редкий вариант врожденной дисфункции коры надпочечников вследствие доминантно-негативной мутации в гене *STAR*

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Острый регулятор стероидогенеза (StAR) играет ключевую роль в транспортировке холестерина, главного предшественника всех стероидных гормонов, с наружной мембраны митохондрии на внутреннюю, где начинается синтез стероидных гормонов. Нарушения в работе этого транспортного белка, вследствие мутации в гене *STAR,* приводят к развитию одной из самых редких и тяжелых форм врожденной дисфункции коры надпочечников — липоидной гиперплазии коры надпочечников, характеризующейся минерало- и глюкокортикоидной недостаточностью с первых дней жизни ребенка в сочетании с нарушением формирования пола у лиц с кариотипом 46XY или первичной недостаточностью яичников у лиц с кариотипом 46XX. Особенностью данной формы ВДКН является то, что она обусловлена не ферментным дефектом, для которых характерен только аутосомно-рецессивный тип наследования. К нарушению транспортной функции белка могут приводить и гетерозиготные мутации в гене *STAR*. В литературе имеются редкие описания развития липоидной гиперплазии надпочечников вследствие аутосомно-доминатной мутации в гене *STAR*. В данной публикации представлен уникальный случай дефекта белка StAR у пациента с кариотипом 46XY, обусловленного доминантно-негативной мутацией в *STAR.*

Ключевые слова: врожденная дисфункция коры надпочечников, дефект белка StAR, нарушение формирования пола.

The rare form of congenital adrenal hyperplasia caused by an autosomal dominant form of *STAR* deficiency

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The steroidogenic acute regulatory protein (StAR) is crucial for transport of cholesterol to mitochondria where biosynthesis of steroids is initiated. Loss of StAR function due to autosomal-recessive mutations in the *STAR* gene leads to lipoid congenital adrenal hyperplasia (LCAH) which is characterized by impaired synthesis of adrenal and gonadal steroids, which causes adrenal insufficiency, primary ovarian failure in 46XX patients, or 46XY disorder of sex development (DSD). However, there were a few reports of 46 XY DSD patients with LCAH caused by a heterozygous mutation in the *STAR* gene. Here, we describe another rare case of LCAH in a 46XY patient with DSD and primary adrenal insufficiency due to an autosomal-dominant mutation in the *STAR* gene.

Keywords: steroidogenic acute regulatory protein, lipoid congenital adrenal hyperplasia, adrenal insufficiency, sex development disorders.

Background

Congenital adrenal dysfunction (adrenogenital syndrome, congenital adrenal hyperplasia) is a group of autosomal recessive disorders resulting from the deficiency of one of the enzymes or transport proteins required for cortisol synthesis in the adrenal cortex [1]. Seven forms of congenital adrenal hyperplasia (CAH) have been described to date: lipoid congenital adrenal hyperplasia (LCAH) is caused by mutations in the StAR transport protein (steroidogenic acute response protein involved in a rapid steroidogenic stress response), whereas other forms of CAH involve a deficiency of an enzyme involved in the synthesis of cortisol.

The StAR protein plays a key role in the initiation of steroidogenesis and regulates transport of cholesterol from the outer mitochondrial membrane into the inner mitochondrial membrane, where the enzymes involved in the conversion of cholesterol to steroid hormones are located [2]. Mutations in the *STAR* gene lead to lipoid adrenal hyperplasia characterized by impaired synthesis of all adrenal and gonadal steroid hormones, which causes primary adrenal insufficiency in conjunction with primary hypogonadism in patients with karyotype 46 XX and disorder of sex development (DSD) in patients with karyotype 46 XY [3]. All forms of CAH, including LCAH with mutant StAR protein, are inherited in an autosomal recessive manner. However, there were a few reports of genetic defects in the StAR protein caused by a heterozygous polymorphism in the *STAR* gene [4].

Here we also present a unique case of chronic adrenal insufficiency and DSD 46 XY caused by dominant-negative mutation in the *STAR* gene.

Case description

Medical record: the child was born to nonblood-related parents. It was the first delivery; the child was born large (weight 4110 g, height 54 cm) at 41 week. The Apgar score was 7/8 points. Ambiguous genitalia were obvious at birth: the penis-like clitoris, the scrotum was not formed; the urethra opened under the clitoral head, bilateral absence of testicles, urogenital sinus. The condition

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of the child rapidly deteriorated on the second postnatal day: hypoglycemia 0.6—1 mmol/l, hyponatremia 118—121 mmol/l (the normal range is 135—150), hyperkalemia 8—8.5 mmol/l (3.8—5.5), and increasing dehydration. The condition stabilized secondary to intramuscular injection of Solu-Cortef. On examination: ACTH level – 238 pg/ml (10—185), 17-OH progesterone – 1.5 ng/ml (0.1—2.7). Karyotype 46XY. Ultrasound adrenal gland examination revealed bilateral adrenal gland hypoplasia. An attempt to cancel glucocorticoid therapy deteriorated the condition and aggravated electrolyte disturbances (hyponatremia, hyperkalemia). On repeated examination, after cessation of glucocorticoids: cortisol – 0.8 μg/dl (the normal range is 3.7—19.4), ACTH — 654 pg/ml (0—46), aldosterone – 31 pg/ml (25.6—445), renin > 500 μU/ml (4.4—46.1). Ultrasound imaging of the scrotum and the small pelvis visualized the right and left testicles over the entrance to the inguinal canal. A diagnosis was established: "Sex development disorder 46XY, primary adrenal insufficiency". A permanent glucocorticoid and mineralocorticoid replacement therapy was indicated.

A low requirement for glucocorticoid and mineralocorticoids was noted when the patient was monitored at the place of residence: at the age of 1 year 3 months upon application of Cortef at a daily dose of 8.3 mg/m^2 and Cortineff at a daily dose of 125 μg: ACTH <5 pg/ml (0—46), renin 1.01 μIU/ml (4.4—46.1). At age of 2 years 4 months upon application of Cortef at a dose of 6.5 mg/m^2/day and Cortineff 50 μg/day: ACTH <5 pg/ml and renin 4.4 μIU/ml, bone age — 1.5 years.

Due to a rare combination of DSD 46XY with primary chronic adrenal insufficiency which was corrected with low doses of glucocorticoids, the child was admitted to Endocrinology Research Centre, Moscow. On admission: ambiguous genital organs — significantly underdeveloped penis (length < 1 cm, severely hypoplastic cavernous bodies, weakly developed penis head), hypoplastic scrotum; no palpable testicles in the scrotum and regions of inguinal canals. The HCG treatment did not increase the testosterone level – 0.05 nmol/l (negative sample). With suppression of ACTH (2.7 pg/ml) in response to Cortef administration at a dose of 6.5 mg/m^2/day and absence of severe worsening of adrenal insufficiency symptoms (adrenal crisis) over the entire follow-up, hydrocortisone dose was reduced to 5.35 mg/m^2/day and was subsequently decreased to 3.75 mg/m^2/day due to sustained low level of ACTH. Despite low doses of hydrocortisone, the condition of the child remained stable; there were no instances of glucocorticoids deficiency.

Diagnostic laparoscopy was performed at the age of 3 years. On revision, the internal inguinal rings were not obliterated. Gonads were located in the abdomen. The right testicle (0.5×0.7 cm) was located at a distance of 1 cm from the deep inguinal ring, the left (0.4×0.5 cm) — at a distance of 1.5 cm from the deep inguinal ring. The right testicle was descended into the scrotum; during testicular descent a decreased density of the testicle and severe hypoplasia were noted.

Descent of the left testicle into the scrotum was performed at the age of 3.5 years and a significant decrease in gonad density was observed.

Due to the presence of a rare combination of primary adrenal insufficiency with DSD 46XY, molecular-genetic assay using high-throughput parallel sequencing (Ion Torrent) was performed using an author's panel "Adrenal Insufficiency, Electrolytic Disorders" which was created in Endocrinology Research Centre, Moscow. A heterozygous mutation c.65-2A>G was revealed in the *STAR* gene that disrupts splicing site. This mutation was not detected in the mother and the father suggesting its *de novo* emergence. A similar heterozygous mutation in the *STAR* gene was previously described by Baquedano et al. [4], wherein the mutant protein exhibited reduced StAR activity in a dominant-negative manner.

CONCLUSION

this case report is unique as it involves a rare type of a mechanism in development of congenital adrenal hyperplasia associated with a heterozygous mutation in the *STAR* gene. Enzymes are known to rely upon the quantity of enzymes in the development of a disease whereas transport proteins for normal function are more dependent on dimensional configuration which is formed by both alleles. In our patient, mutation in one allele was responsible for the development of the disease. Abnormal protein structure instead of total lack of the protein accounts for a low glucocorticoid requirement in the patient, which indicates incompletely impaired transport of cholesterol into the inner mitochondrial membrane.

This case report focuses on the importance of molecular-genetic diagnostics of rare combinations of sex development disorder with impaired adrenal function. Molecular-genetic diagnostics can predict the course of disease and be used in medical-genetic counseling.

Additional information

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Consent of the patient. A legally authorized representative of the patient signed an informed consent on the publication of medical data in this paper in the journal Problems of Endocrinology.

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interests on the publication of this paper.

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