

## Случай нефрогенного синдрома неадекватного антидиуреза, обусловленный мутацией рецептора вазопрессина 2-го типа

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Нефрогенный синдром неадекватного антидиуреза (НСНАД) — редкая форма нарушения водного баланса с X-сцепленным типом наследования, впервые описанная у двух неродственных младенцев мужского пола с тяжелой симптоматической гипонатриемией. НСНАД обусловлен активирующими мутациями гена рецептора вазопрессина 2-го типа (*AVPR2*), в результате которых нарушается реабсорбция свободной жидкости, что приводит к повышению осмоляльности мочи, гипоосмолярности плазмы и персистирующей гипонатриемии. Впервые в отечественной литературе приводится описание случая изолированной эуволемической гипоосмолярной гипонатриемии у ребенка с олигодипсией при исключенном гипокортицизме и патологии со стороны почек, что — в отсутствие гиперсекреции антидиуретического гормона — позволило предположить наличие НСНАД. Молекулярно-генетическое исследование выявило новую, не описанную ранее мутацию L312S в седьмом трансмембранном домене гена *AVPR2*, патогенность которой была доказана при проведении функционального исследования. Приводятся клинико-лабораторные характеристики СНАД, основные принципы лечения. Данное заболевание следует учитывать при дифференциальной диагностике синдрома гипонатриемии.

**Ключевые слова:** гипонатриемия, нефрогенный синдром неадекватного антидиуреза, X-сцепленный тип наследования, рецептор вазопрессина 2-го типа (*AVPR2*).

## A case of nephrogenic syndrome of inappropriate antidiuresis caused by a mutation of the vasopressin type 2 receptor

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Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is a rare X-linked disorder of water balance, which was first described in two unrelated male infants with severe symptomatic hyponatremia. NSIAD is caused by activating mutations of the arginine vasopressin receptor 2 (*AVPR2*) gene, resulting in impaired reabsorption of free water, which leads to increased osmolality of urine, plasma hypo-osmolality, and persistent hyponatremia. We report, for the first time in the domestic literature, a case of isolated euvolemic hyposmolality hyponatremia in a child with oligodipsia. Because hypocorticism and renal pathology were excluded, and there was no antidiuretic hormone hypersecretion, NSIAD was suggested. A molecular genetic study revealed a new mutation L312S, not described earlier, in the seventh transmembrane domain of the *AVPR2* gene. Pathogenicity of the mutation was proved by a functional study. We provide the clinical and laboratory characteristics of SIAD and the main principles of treatment. This disease should be considered in the differential diagnosis of hyponatremia syndrome.

**Keywords:** hyponatremia, nephrogenic syndrome of inappropriate antidiuresis, X-linked inheritance, arginine vasopressin receptor 2 (*AVPR2*).

Antidiuretic hormone (ADH) is the main regulator of body fluid homeostasis. Activation of synthesis of this neuropeptide in the supraoptic and paraventricular nuclei of the hypothalamus and its subsequent secretion by the neurohypophysis occur in response to increased plasma osmotic concentration and the reduce volume of circulating blood. At the periphery, ADH binds to vasopressin type 2 receptor, which is expressed in the principal cells of the renal collecting tubules. *AVPR2* is a G-protein-coupled receptor responsible for transmission of the signal from ligand to the nucleus through activation of the adenylate cyclase system. Receptor activation eventually results in translocation of aquaporin 2 protein into the luminal membrane of the principal cells of the collecting tubules, thus increasing permeability of the cells

for water molecules. Free water is reabsorbed, thus increasing osmotic concentration and reducing urine.

Until recently, only two main types of water balance disorders have been known: diabetes insipidus and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). However, Feldman et al. (2005) reported two patients in whom clinical manifestations of SIADH were accompanied by a low level of arginine vasopressin. Association of this condition with activation of the ADH receptor was suggested, which was further confirmed by detecting a mutation in the X-linked gene of the vasopressin type 2 receptor [1]. This disease was called nephrogenic syndrome of inappropriate antidiuresis (NSIAD) [1]. Until recently, no cases of NSIAD have been reported in Russia.

We report a clinical case of NSIAD in a boy with a previously unknown mutation in the *AVPR2* gene.

### Clinical case

A boy, aged 5 years and 10 months, was admitted for examination in connection with persistent hyponatremia. The child was born to a primigravida mother (uncomplicated full-term pregnancy, unassisted delivery). Child's weight at birth was 2,800 g; height 50 cm. Early psychomotor development was within normal limits. Since the age of 3, the boy has been followed up by a neurologist because of speech delay. His younger sister aged 1 year and 3 months is healthy.

The disease manifested at the age of 5 years and 7 months. Weakness, drowsiness, and then tonic 2–5-min seizures were noted in hot climatic conditions. The boy was admitted to the hospital where a decrease in sodium level to 116 mmol/l was registered. The boy received infusion therapy with water–salt solutions and hydrocortisone. During the therapy, sodium level increased to 136 mmol/l, followed by a decrease to 124 mmol/l.

MRI of the brain and EEG performed in the hospital revealed no pathology. Hypocorticism and the defects of adrenal steroidogenesis were ruled out based on the synacthen test: 0' — cortisol 4.6 µg/dl, 17-OH progesterone 0.01 nmol/l, 60' — cortisol 26.6 µg/dl, 17-OH progesterone 0.2 nmol/l.

The patient was discharged with the blood sodium level of 140 mmol/l. Further child's behavior was adequate; the overall well-being was satisfactory. However, monitoring of the blood electrolyte parameters in dynamics revealed hyponatremia. The boy was readmitted to the Endocrinology Research Center.

Parents mentioned low appetency of the boy to liquids (he almost never asked for water). An analysis of the patient's medical records from the first year of life drew attention to the increased values of the relative density of urine (ranging from 1018 to 1028 g/l).

Biochemical blood assay showed hyponatremia (133.2 mmol/l), the estimated plasma osmotic concentration was 274 mOsm/kg (280–295). The hormonal profile was as follows: aldosterone, 1753 pmol/l (94–756) and PRA, 1.8 ng/ml/h (0.5–6). Clinical urine examination showed the relative density of 1028 g/l. Daily water balance: 700 ml consumed, 500 ml urinated. Orthostatic test: supine BP 90/60 mm Hg, standing BP 100/70 mm Hg.

Taking into account the nature of hyponatremia (euvolemic hypoosmolar hyponatremia in the absence of changes in the levels of other electrolytes), the syndrome of inappropriate antidiuresis (SIADH) was suspected. Provided that there were no clinical or historical grounds for suspecting ADH hypersecretion, it can be caused by an activating mutation in the vasopressin type 2 receptor gene (*AVPR2*).

### Molecular genetic testing

Genomic DNA was isolated from peripheral blood leukocytes using the conventional methods. Fragments

of genomic DNA involving the *AVPR2* gene encoding sequence and the adjacent intronic regions were amplified by polymerase chain reaction (PCR). The PCR products were purified after separation by 1% agarose gel electrophoresis using a Cleanup Standard kit (Eurogene, Russia) and then sequenced on an automated ABI Genetic Analyzer 3130 sequencer («Applied Biosystems», USA).

The following oligonucleotides were used for PCR and subsequent sequencing of the corresponding exons and the adjacent intronic regions: 1F, 5'-GACCCTGGGCCATTGAACTTG -3'; 2F, 5'-CTCTCCATAGTCTTTGTG -3'; 3R, and 5'-CACAG-GCTCTGGCCAATTCTC -3'. The Genbank (<http://www.ncbi.nlm.nih.gov/sites/entrez>) reference was used as the reference sequence of the *AVPR2* gene with ID Z11687.1. Mutations were denoted in accordance with the recommendations given by den Dunnen and Antonarakis [0].

*AVPR2* gene sequencing revealed a hemizygous transition from c. 935T>C in exon 3, which led to the replacement of the codon leucine (TTG) with serine (TCG) at position 312 (p.L312S). Codon L312 is located in the VII transmembrane domain of the receptor. The child's mother was heterozygous for this mutation. The mutation was reported for the first time; its pathogenicity was proved by functional analysis [3].

### Discussion

NSIAD is the disturbance of water balance caused by an activating mutation in the *AVPR2* gene. It is a rare disease: today, only 28 cases have been reported with activating *AVPR2* mutation, most of them being familial variants [4–7].

A total of 4 activating *AVPR2* mutations that cause NSIAD are known: R137L, R137C, F229V, and I130N [1,6–8]. A clinical case of NSIAD with a mutant V266A receptor has been also reported; its functional analysis has proved its intactness: the disease was apparently caused by a defect at the level of aquaporin 2 [10].

The disease is X-linked; it is more common among men: a total of 8 women with activating *AVPR2* mutation have been reported, of which only 5 had the clinical and laboratory presentation of NSIAD [4, 11, 12]. The plasma sodium level in the mother of our patient, which was assessed for the first time in connection with the boy's disease, lied within normal limits.

Inappropriate antidiuresis developing in the presence of an excessive level of ADH or upon constitutional (ligand-independent) activation of the *AVPR2* receptor is unregulated fluid reabsorption, which increases urine osmotic concentration on the one hand, while reducing its volume. On the other hand, it increases body fluid volume, resulting in development of hyponatremia and hypoosmolality. Moreover, an increase in the extracellular fluid volume results in activation of the atrial natriuretic

peptide, thus increasing excretion of sodium ions with urine [11].

Criteria of inappropriate antidiuresis [14]:

- euvolemic hyposmolar hyponatremia;
- more than 20 mmol/l increase in Na<sup>+</sup> excretion at normal level of fluid and salt intake;
- more than 100 mOsm/kg increase in urine osmotic concentration;
- hypocorticism and hypothyroidism were ruled out;
- undisturbed renal function; diuretics have not been administered.

PRA in these patients is reduced; aldosterone lies within normal limits [1, 15]. The decrease in the activity of the renin–angiotensin system is expected to be due to the increased circulating blood volume. However, hyposmolar hyponatremia stimulates aldosterone secretion [16].

Differential diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and NSIAD is based on the ADH level. An analysis of the *AVPR2* gene is appropriate when this parameter cannot be evaluated (as it is in our case).

Clinical manifestations of NSIAD are caused by hyponatremic encephalopathy: nausea, vomiting, impaired consciousness, and seizures. Severity of clinical signs and time of NSIAD manifestation vary greatly: from hyponatremic seizures appearing in childhood to asymptomatic hyponatremia with oligodipsia [4, 5]. Hyponatremia can occur only in case of significant water loading, both in hemizygous (in men) and heterozygous mutations (in women) [15].

In our case, there was asymptomatic chronic hyponatremia, which most likely was aggravated by water loading in hot climatic conditions.

Based on the pathogenesis of the disease, fluid restriction (50–70 ml/kg/day) is a mandatory therapeutic

measure, which is usually easily tolerated by patients. Urea, which causes osmotic diuresis, has proven its efficiency for being used both in adults and children at a dose of 0.1 to 2 g/kg/day [4, 15].

Vaptans, ADH antagonists, have proved to be ineffective in R137L/C mutation both during clinical use [9] and *in vitro* [17]. However, a functional study of the F229V mutation *in vitro* showed a decrease in the cAMP level in response to administration of ADH antagonists [6]. Thus, activating *AVPR2* mutations can lead to various changes in the receptor structure, which is important in assessment of the possibility of therapeutic application of ADH antagonists.

Taking into account mild hyponatremia in our patient, treatment measures were limited to reducing the amount of consumed liquid and monitoring the blood sodium level in dynamics. Thus, the case of NSIAD associated with mutation in the vasopressin type 2 receptor gene has been reported for the first time in Russian practice.

## Conclusion

Nephrogenic syndrome of inappropriate antidiuresis should be included in the algorithm of differential diagnosis of hyponatremia syndrome in children. Molecular genetic testing allows one to make a correct diagnosis and provides evidence for the need of long-term fluid restriction.

### ADDITIONAL INFORMATION

**Conflict of interests.** The authors declare no obvious or potential conflict of interests regarding this publication.

**Patient's informed consent.** Patient's legal representatives gave written informed consent for publication of the medical data within the framework of this article.

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#### ABBREVIATIONS

AVPR2 — vasopressin type 2 receptor

ADH — antidiuretic hormone

NSIAD — nephrogenic syndrome of inappropriate antidiuresis

SIADH — syndrome of inappropriate antidiuretic hormone secretion

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