DOI: https://doi.org/10.17816/PED11435-42

CONGENITAL SODIUM DIARRHEA

© D.O. Ivanov, V.P. Novikova

St. Petersburg State Pediatric Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia

For citation: Ivanov DO, Novikova VP. Congenital sodium diarrhea. *Pediatrician (St. Petersburg).* 2020;11(4):35-42. https://doi.org/10.17816/PED11435-42

Received: 08.06.2020 Revised: 14.07.2020 Accepted: 26.08.2020

Congenital sodium diarrhea (P78.3 according to ICD 10) is a rare autosomal recessive disease, clinically and genetically heterogeneous. The sodium absorption defect is caused by disruption of the intestinal sodium-proton "pump" in the non-syndromic form and in the epithelial sodium channels in the syndromic form. Mutations in 3 genes, *SPINT2* (localization 19q13.2; OMIM code 270420) – syndromic form; *GUCY2C* (localization 12q12.3; OMIM code 601330) and *SLC9A3* (localization 5p15.33; OMIM code 616868) – non-syndromic form, can cause congenital sodium diarrhea. The frequency of the disease is unknown, since it is rare, so far only 50 cases have been described. The classic non-syndromic form of congenital sodium diarrhea is manifested by polyhydramnios, severe secretory diarrhea, severe metabolic acidosis, alkaline pH of feces >7.5 and hyponatremia. The syndrome of congenital sodium diarrhea is also manifested by choanal and/or anal atresia, hypertelorism and erosion of the cornea. Typical laboratory data include metabolic acidosis and alkaline pH of feces (fecal pH >7.5), low Na^+ concentrations. The concentration of Na^+ in the stool is increased. Prenatal ultrasound diagnosis allows you to identify gidroamnion and expansion of intestinal loops, starting from the third trimester of pregnancy. The diagnosis is confirmed by genetic studies. Treatment: complete parenteral nutrition with correction of water-salt metabolism. The forecast is unfavorable.

Keywords: chronic diarrhea; congenital sodium diarrhea; watery diarrhea.

ВРОЖДЕННАЯ НАТРИЕВАЯ ДИАРЕЯ

© Д.О. Иванов, В.П. Новикова

Федеральное государственное бюджетное образовательное учреждение высшего образования «Санкт-Петербургский государственный педиатрический медицинский университет» Министерства здравоохранения Российской Федерации, Санкт-Петербург

Для цитирования: Иванов Д.О., Новикова В.П. Врожденная натриевая диарея // Педиатр. – 2020. – Т. 11. – № 4. – С. 35–42. https://doi.org/10.17816/PED11435-42

Поступила: 08.06.2020 Одобрена: 14.07.2020 Принята к печати: 26.08.2020

Врожденная натриевая диарея (P78.3 по МКБ 10) — редкое аутосомно-рецессивное заболевание, клинически и генетически гетерогенное. Дефект всасывания натрия обусловлен нарушением работы кишечного натрий-протонного «насоса» при несиндромальной форме и эпителиальных натриевых каналов при синдромальной форме. Мутации в 3 генах, *SPINT2* (локализация 19q13.2; код OMIM 270420) — синдромная форма, *GUCY2C* (локализация 12q12.3; код OMIM 601330) и *SLC9A3* (локализация 5p15.33; код OMIM 616868) — несиндромные формы, могут вызвать врожденную натриевую диарею. Частота заболевания неизвестна, поскольку оно встречается редко, всего к настоящему времени описано только 50 случаев. Классическая несиндромная форма врожденной натриевой диареи проявляется полигидрамнионом, выраженной секреторной диареей, тяжелым метаболическим ацидозом, щелочным pH кала >7,5 и гипонатриемией. Синдромная форма врожденной натриевой диареи проявляется также хоанальной и/или анальной атрезией, гипертелоризмом и эрозиями роговицы. Характерные лабораторные данные включают метаболический ацидоз и щелочной pH фекалий (pH кала >7,5), низкие концентрации Na^+. Концентрации Na^+ в стуле при этом повышены. Пренатальная ультразвуковая диагностика позволяет выявить гидроамнион и расширение кишечных петель, начиная с третьего триместра беременности. Диагноз подтверждается генетическими исследованиями. Лечение: полное парентеральное питание с коррекцией водно-солевого обмена. Прогноз неблагоприятный.

Ключевые слова: хроническая диарея; врожденная натриевая диарея; водянистая диарея.

INTRODUCTION

Congenital sodium diarrhea (CSD, P78.3 in International Classification of Diseases 10) is a rare autosomal recessive disease associated with an impairment of the transport protein that enables the exchange of sodium ion for hydrogen ion in the enterocyte [14].

In 1985, two sporadic cases of CSD were described for the first time [18, 32]. In subsequent years, new cases were reported [2, 23, 26, 31, 34, 40, 41] in different countries, which revealed the clinical and genetic heterogeneity of the disease. Mutations in *SPINT2* (serine peptidase inhibitor, type Kunitz; localization 19q13.2; OMIM code 270420, most of the cases described), *GUCY2C* (guanylate cyclase receptor; localization 12q12.3; OMIM code 601330), and *SLC9A3* (Na^+/H^+ transporter family 9; localization 5p15.33; OMIM code 616868) can cause CSD [23, 26, 31, 40, 42, 45]. In 2009, syndromic and non-syndromic forms of CSD were identified. To date, CSD is defined as a disorder of sodium absorption, which is caused by impaired intestinal sodium proton "pump" function in the non-syndromic form and impaired epithelial sodium channel activity in the syndromic form [33].

Given its rarity, the incidence is unknown, and only 50 cases have been described so far.

CLINICAL CHARACTERISTICS

The non-syndromic (classic) and syndromic forms of the disease have distinguishing features. The classic form of CSD is manifested by polyhydramnios, marked secretory diarrhea, severe metabolic acidosis, alkaline stool pH >7.5, and hyponatremia. Mutations in *SLC9A3* and *GUCY2C* genes have been proved as causes of this form. The syndromic form of CSD with choanal atresia and/or proctatresia, hypertelorism, and corneal erosions is associated with mutations in *SPINT2*, which encodes a serine protease inhibitor [33].

To understand the disease pathogenesis, one should note that several interrelated mechanisms are responsible for the absorption of Na^+ and water from the gastrointestinal tract. Postprandial absorption of Na^+ in the small intestine is stimulated by Na^+-dependent glucose and amino acid transporters, whereas two other key nutrient-independent mechanisms in the small intestine and colon involve electrically neutral apical Na^+/H^+ exchange (NHE) and epithelial Na^+ channels (ENaC). NHE, mediated mainly by the apical NHE3 isoform, is responsible for the absorption of NaCl and bicarbonate through the coupled exchange of Na^+/H^+ and Cl^-/HCO_3^- (or Cl^-/OH^-). The latter mechanism is mediated by PAT1 (*SLC26A6*) and suppressed DRA (*SLC26A3*). Electrogenic absorption of Na^+, carried by ENaC (consisting of α-, β-, and γ-ENaC subunits), occurs in the superficial epithelium and superior crypts of the distal middle intestine. These transport mechanisms require a favorable electrochemical gradient supported by basolateral Na^+/K^+-ATPase, Cl^- channels (apical CFTR and basolateral CLC-2), and K^+ channels.

As sodium concentration in the chyme is normally approximately 142 mEq/L (i.e., approximately equal to the content in the plasma), sodium moves inwards along an electrochemical gradient from the chyme through the brush border into the cytoplasm of epithelial cells (the sodium concentration inside the cell is approximately 50 mEq/L), which provides the main transport of sodium ions by epithelial cells into the intercellular space. Water follows passively the movement of ions paracellularly through tight junctions or transcellularly through the cell membrane [29].

In patients with classic sodium diarrhea, studies of membrane transport have revealed a defect in the activity of exchange of sodium ion for hydrogen ion [25, 31, 48]. Subsequently, mutations in *SLC9A3* cause classic sodium diarrhea in approximately 40% of families, and in these families, the disease is autosomal recessively inherited [34]. Deletion of the whole gene, as well as truncated and missense mutations, was detected in nine patients with classic sodium diarrhea in *SLC9A3* (family of dissolved carriers 9, subfamily A, member 3; MIM No. 182307), which is a gene encoding sodium proton antiporter 3 (sodium hydrogen heat exchanger 3 [NHE3]). The deletion of the whole gene and truncated mutations are assumed to disrupt the production of protein from these alleles and cause a decrease in the activity of Na^+/H^+ exchange in *SLC9A3* mutants. Missense mutations showed either decreased transport function or decreased NHE3 surface expression. The decreased surface expression can be explained either by abnormal ion transfer to the membrane or by a decrease in membrane stability [33].

Dominant activating mutations in the GC–C receptor (MIM No. 601330), encoded by the *GUCY2C* gene, cause classic sodium diarrhea in 20% of families with this disorder [40]. These mutations were identified by whole-exome sequencing in four unrelated patients, and all four heterozygous mutations arose in patients *de novo*. The mode of transmission of *GC–C* mutations to the next generation will be autosomal dominant. GC–C is the

highest expressed transmembrane guanylate cyclase in the intestinal tract. Uroguanylin, guanylin, and a thermostable toxin produced by enterotoxigenic *Escherichia coli* are represented by luminal ligands that can stimulate intracellular production of cyclic guanosine monophosphate upon binding as part of one of the several signaling pathways that exist in enterocytes [17]. *GC–C* mutations in a patient increased basal level and stimulated intracellular level of cyclic guanosine monophosphate [40], which inhibits NHE3 by its phosphorylation by GMP kinase II (MIM No. 601591), thereby providing an explanation for secretory diarrhea by reversing the Na^+ absorption [17, 20, 21]. Classic CSD thus results from the loss of NHE3 function, which leads to impaired Na^+ absorption, increased fluid secretion, and diarrhea. In subgroup 1 of patients with CSD, "primary" NHE3 deficiency is caused by recessive mutations in *SLC9A3*, resulting in a missing or non-functional protein. In subgroup 2 of patients with CSD, "secondary" NHE3 deficiency is the result of suppression by increased intracellular levels of cGMP caused by activating and hyperstimulating *GUCY2C* mutations. Currently, both phenotypes cannot be clinically distinguished due to the small number of registered patients [40, 48]. Approximately 40% of patients with classic sodium diarrhea had neither *SLC9A3* nor *GUCY2C* mutations, which indicates that other genes are responsible for the disease in these patients and that there is significant heterogeneity of the genetic locus for this disease.

Approximately one-third of patients have congenital malformations and manifested superficial punctate keratitis, that is, a syndromic form of sodium diarrhea, which can be distinguished from its non-syndromic (classic) form. This form of CSD is also referred to as a syndromic form of congenital tufting enteropathy or dysplasia of the intestinal epithelium, because it is often accompanied by clustered enterocytes that form bundles with branching crypts in histological examination [44, 46]. Sodium diarrhea syndrome is caused by mutations in *SPINT2*, which encodes Kunitz type 2, a serine protease inhibitor. The SPINT2 protein is involved in the regulation of the ENaC, which is required for sodium reabsorption in the distal colon. The activity of the ENaC depends on its proteolytic activation by a system consisting of two serine proteases, namely, matriptase and prostasin, and their inhibitor SPINT2 [24, 28, 47]. Moreover, the etiology of syndromic signs that occur in patients with *SPINT2* mutations has not been clarified. Both the number of recognized forms of CDD and genes of the underlying disease are gradually increasing.

A classic disease form can be suspected prenatally in the third trimester of pregnancy, since secretory diarrhea begins *in utero*, and ultrasound examination can detect dilated and fluid-filled intestinal loops, as well as polyhydramnios. Mothers often had a history of preterm labor between weeks 32 and 35 of gestation and the weight and length of the newborn were appropriate for the gestational age. After birth, there is usually marked bloating, pseudoascites, and secretory diarrhea. Watery diarrhea is observed immediately after birth and is independent of breastfeeding or infant's food intake. Diarrhea is described as "continuous," and the stool is very watery that it can be mistaken for urine. Meconium discharge was never reported. Furthermore, in some patients, diarrhea may have varying severity. Resonant intestinal peristalsis (borborygmus) is noted. Dehydration of varying severity, metabolic acidosis, and protein–calorie deficiency develop. Babies become irritable and later apathetic. Untreated disease can be life threatening. Even with treatment, various levels of mental and physical development impairment can occur in the future. Persistent intractable diarrhea from birth, increased fecal sodium excretion, hyponatremia, and metabolic acidosis are of diagnostic value. Symptoms are similar to those of congenital chloride diarrhea. Table 1 presents distinguishing features. Patients with syndromic disease form may have additional genetic defects, such as choanal atresia, proctatresia, corneal epithelial erosion, hypertelorism, cleft palate, and polydactyly [2, 14, 15, 18, 23, 26, 31, 32, 34, 40, 41].

LABORATORY AND INSTRUMENTAL STUDIES

Serum samples taken prior to infusion therapy show low Na^+ concentrations. Fecal Na^+ concentrations are increased (stool Na^+ >70 mmol/L), and they are most often increased after initiation of therapy with fluids and electrolytes. Fecal Na^+ concentrations may be normal when sodium loss in the body has progressed over time. Urinary Na^+ concentration, as a marker of Na^+ depletion in the body, is sometimes low before and during inadequate fluid and sodium intake. Fractional sodium excretion may be the best marker of sodium status in these patients, since it is independent of urine flow [22, 30]. Other characteristic laboratory findings include metabolic acidosis and alkaline fecal pH (fecal pH >7.5). With the classic phenotype, no endoscopic or histological changes in the intestinal mucosa are usually observed, with rare partial

Table 1 / Таблица 1

Differential diagnosis of congenital sodium diarrhea
Дифференциальный диагноз врожденной натриевой диареи

Differential diagnostic signs / Дифференциально-диагностические признаки	Classical sodium diarrhea / Классическая натриевая диарея	Syndromic sodium diarrhea / Синдромальная натриевая диарея	Congenital chloride diarrhea / Врожденная хлоридная диарея	Microvillus inclusion disease / Болезнь цитоплазматических включений микроворсинок	Epithelial dysplasia (tufting enteropathy) / Эпителиальная дисплазия (тафтинговая энтеропатия)
Polyhydramnion / Полигидрамнион	Characteristically / Характерно	Characteristically / Характерно	Characteristically / Характерно	Usually absent / Обычно отсутствует	Usually absent / Обычно отсутствует
Abdominal enlargement due to enlarged fluid-filled intestinal loops (pseudoascites) / Увеличение живота из-за расширенных заполненных жидкостью петель кишечника (псевдоасцит)	Characteristically / Характерно	Characteristically / Характерно	Characteristically / Характерно	Absent / Отсутствует	Absent / Отсутствует
Extraintestinal manifestations / Внекишечные проявления	Absent / Отсутствует	Atresia of the choan, anal atresia, erosion of the corneal epithelium hypertelorism, cleft palate, polydactyly / Атрезия хоан, анальная атрезия, эрозии эпителия роговицы, гипертелоризм, волчья пасть, полидактилия	Absent / Отсутствует	Absent / Отсутствует	Absent / Отсутствует
Morphological data / Морфологические данные	No specific data / Нет специфических данных	Atrophy of the villi and the presence of focal epithelial “tuft” / Атрофия ворсинок и наличие фокальных эпителиальных «пучков»	No specific data / Нет специфических данных	Atrophy of villi and loss of microvilli. Included microvilli and secretory granules by electron microscopy / Атрофия ворсинок и потеря микроворсинок. Включенные микроворсинки и секреторные гранулы на электронной микроскопии	Atrophy of the villi and the presence of focal epithelial “tuft” / Атрофия ворсинок и наличие фокальных эпителиальных «пучков»
Mutant gene / Мутантный ген	*SLC9A3* (NHE3) *GUCY2C* (GC-C)	*SPINT2*	*SLC26A3* (DRA)	*MYO5B, STX3*	*EPCAM*

atrophy of the villi [33]. In syndromic cases, villous atrophy and focal epithelial bundles may occur [44, 46]. Prenatal ultrasonography may detect hydramnion and enlargement of intestinal loops, starting from the third trimester of pregnancy [33]. The diagnosis is confirmed by genetic studies with the identification of mutations in genes *SPINT2, GUCY2C,* and *SLC9A3*. New-generation sequencing is used, and in unclear cases, targeted genetic testing (Sanger sequencing) or whole-exome sequencing is applied.

Differential diagnostics with various diseases is necessary[1, 3, 4, 7, 13, 35, 45]. Classic sodium diarrhea requires differential diagnostics with congenital chloride diarrhea (MIM No. 214700) [13, 35], which is characterized by high fecal Na^+ loss and metabolic acidosis as opposed to alkalosis. Sodium diarrhea differs from enterocyte differentiation and polarization disorders such as microvillus inclusion disease (MIM No. 251850) [11, 48] and non-syndromic tufting enteropathy [35, 45]

in terms of histopathology. Differential diagnostics is also performed with the salt-wasting form of adrenogenital syndrome [7, 10] and malabsorption of di- and monosaccharides [8, 9, 12]. The table 1 presents the differential diagnostics with the most similar diseases.

Severe profuse diarrhea and dehydration require referral of the child to complete parenteral nutrition with correction of water–salt metabolism [5, 14, 15]. To replenish sodium losses, sodium citrate and glucose–salt solutions are prescribed [6]. In the course of treatment, the child's condition improves mildly, although persistent diarrhea is still noted. Oral electrolyte supplementation (sodium and bicarbonate) helps some children grow normally [23].

The prognosis is unfavorable, and persistent secretory diarrhea is still noted, although it is often not life threatening after a long period of parenteral nutrition. This disease can be life threatening if left untreated. Immediately after birth, pseudoobstruction caused by the expansion of fluid-filled bowel loops may require surgical treatment [33]. Even with adequate therapy in the future, various levels of mental and physical development impairment can occur.

In recent years, follow-up has shown that six of 36 patients with dominant *GC–C* mutations and two of nine patients with recessive *SLC9A3* mutations developed inflammatory bowel disease (IBD) [27, 34, 40]. The association between NHE3 function loss and IBD is supported by a number of experimental and clinical studies [16, 19, 36, 39, 43]. NHE3 activity is reduced both in ulcerative colitis and Crohn's disease, in cases of inactive colitis, and in cases of active inflammation [37, 38]. In addition, monogenic defects have been found to alter intestinal immune homeostasis through several mechanisms, which can lead to disruption of the epithelial barrier and epithelial response. NHE3 may play a critical role in the composition of the intestinal microbiota, and its deficiency may contribute to dysbiosis in patients with IBD [49]. Thus, in patients with IBD, the genetic, environmental, and microbial influences of the host are combined and lead to dysregulation of the mucosal immune response against the commensal gut microbiota. Mutations of *GUCY2C* and *SLC9A3* represent monogenetic variants that provide a high risk for early- and late-onset IBD [33].

Dispensary follow-up is performed by a genetic scientist and a gastroenterologist. Since patients with classic sodium diarrhea often did not have known mutations, this indicates that other genes are responsible for the disease and its genetic heterogeneity. Progress in the development of genetics should motivate further search for mutations in sodium diarrhea, and further research of drugs and peptides to restore or enhance Na^+ absorption in diarrheal disorders is needed [33]. Preventive measures have not been developed.

CONCLUSION

Despite the rarity of CSD, pediatricians should be informed about the characteristics of this disease for its timely diagnosis and treatment.

REFERENCES

1. Губернаторова Т.Ю., Сидорова И.В. Энтеропатический акродерматит // Медицина: теория и практика. – 2020. – Т. 4. – № 1. – С. 71–79. [Gubernatorova TYu, Sidorova IV. Acrodermatitis enteropathica. *Medicine: theory and practice*. 2020;4(1):71-79. (In Russ.)]
2. Думова Н.Б., Арсентьев В.Г., Богданов И.Ю., Иванов Д.В. Врожденная натриевая диарея // Педиатрия. – 2017. – Т. 96. – № 6. – С. 173–176. [Dumova NB, Arsentiev VG, Bogdanov IY, Ivanov DV. Congenital sodium diarrhea. *Pediatriia*. 2017;96(6):173-176. (In Russ.)]. https://doi.org/10.24110/0031-403X-2017-96-6-173-176.
3. Иванов Д.О., Новикова В.П., Прокопьева Н.Э. Врожденная диарея с гипериммуноглобулинемией Е и отсутствием островков Лангерганса // Медицина: теория и практика. – 2019. – Т. 4. –№ 1. – С. 92–94. [Ivanov DO, Novikova VP, Prokopyeva NE. Enteropathy. X-linked syndrome. *Medicine: theory and practice*. 2019;4(1):92-94. (In Russ.)]
4. Иванов Д.О., Новикова В.П., Замятина Ю.Е. Синдромальная (фенотипическая) диарея — трихогепатоэнтерический синдром // Медицина: теория и практика. – 2019. – Т. 4. – № 1. – С. 95–100. [Ivanov DO, Novikova VP, Zamyatina JuE. Syndromic diarrhea/tricho-hepato-enteric syndrome. *Medicine: theory and practice*. 2019;4(1):95-100. (In Russ.)]
5. Иванов Д.О. Нарушения кислотно-основного состояния // Иванов Д.О., Аврелькина Е.В., Александрович Ю.С., и др. Руководство по перинатологии. В 2-х т. – СПб.: Информ-Навигатор, 2019. – С. 122–155. [Ivanov DO. Disorders of the acid-base state. In: Ivanov DO, Avrel'kina EV, Aleksandrovich YuS, et al. Rukovodstvo po perinatologii. Saint Petersburg: Inform-Navigator; 2019. P. 122-155. (In Russ.)]
6. Иванов Д.О. Нарушения обмена натрия // Иванов Д.О., Аврелькина Е.В., Александрович Ю.С., и др. Руководство по перинатологии. В 2 т. – СПб.: Информ-Навигатор, 2019. – С. 242–280. [Ivanov DO. Disorders of sodium metabolism. In: Ivanov DO, Avrel'kina EV, Aleksandrovich YuS, et al. Rukovodstvo

po perinatologii. Saint Petersburg: Inform-Navigator; 2019. P. 242-280. (In Russ.)]

7. Иванов Д.О., Мавропуло Т.К. Нарушения функций надпочечников // Иванов Д.О., Атласов В.О., Бобров С.А., и др. Руководство по перинатологии. В 2-х т. – СПб.: Информ-Навигатор, 2019. – С. 946–962. [Ivanov DO, Mavropulo TK. Adrenal dysfunction. In: Ivanov DO, Avrel'kina EV, Aleksandrovich YuS, et al. Rukovodstvo po perinatologii. Saint Petersburg: Inform-Navigator; 2019. P. 946-962. (In Russ.)]
8. Иванов Д.О., Новикова В.П. Врожденная мальабсорбция глюкозы и галактозы // Иванов Д.О., Аврелькина Е.В., Александрович Ю.С., и др. Руководство по перинатологии. В 2-х т. – СПб.: Информ-Навигатор, 2019. – С. 920–924. [Ivanov DO, Novikova VP. Congenital malabsorption of glucose and galactose. In: Ivanov DO, Avrel'kina EV, Aleksandrovich YuS, et al. Rukovodstvo po perinatologii. Saint Petersburg: Inform-Navigator; 2019. P. 920-924. (In Russ.)]
9. Иванов Д.О., Новикова В.П., Петренко Ю.В. Мальабсорбция лактозы // Иванов Д.О., Аврелькина Е.В., Александрович Ю.С., и др. Руководство по перинатологии. В 2-х т. – СПб.: Информ-Навигатор, 2019. – С. 911–919. [Ivanov DO, Novikova VP, Petrenko YuV. Lactose malabsorption. In: Ivanov DO, Avrel'kina EV, Aleksandrovich YuS, et al. Rukovodstvo po perinatologii. Saint Petersburg: Inform-Navigator; 2019. P. 911-919. (In Russ.)]
10. Карева М.А., Чугунов И.С. Федеральные клинические рекомендации — протоколы по ведению пациентов с врожденной дисфункцией коры надпочечников в детском возрасте // Проблемы эндокринологии. – 2014. – Т. 60. – № 2. – С. 42–50. [Kareva MA, Chugunov IS. Federal clinical practice guidelines on the management of the patients presenting with congenital adrenal hyperplasia. *Problems of Endocrinology*. 2014;60(2):42-50. (In Russ.)]. https://doi.org/10.14341/probl201460242-50.
11. Новикова В.П., Воронцова Л.В. Болезнь цитоплазматических включений микроворсинок // Иванов Д.О., Аврелькина Е.В., Александрович Ю.С., и др. Руководство по перинатологии. В 2-х т. – СПб.: Информ-Навигатор, 2019. – С. 940–945. [Novikova VP, Vorontsova LV. Disease of cytoplasmic inclusions of microvilli. In: Ivanov DO, Avrel'kina EV, Aleksandrovich YuS, et al. Rukovodstvo po perinatologii. Saint Petersburg: Inform-Navigator; 2019. P. 940-945. (In Russ.)]
12. Новикова В.П., Воронцова Л.В., Тихомирова К.К. Врожденная недостаточность сахаразы-изомальтазы у новорожденных // Иванов Д.О., Аврелькина Е.В., Александрович Ю.С., и др. Руководство по перинатологии. В 2-х т. – СПб.: Информ-Навигатор, 2019. – С. 925–928. [Novikova VP, Vorontsova LV, Tikhomirova KK. Congenital insufficiency of sucrose-isomaltase in newborns. In: Ivanov DO, Avrel'kina EV, Aleksandrovich YuS, et al. Rukovodstvo po perinatologii. Saint Petersburg: Inform-Navigator; 2019. P. 925-928. (In Russ.)]
13. Новикова В.П., Воронцова Л.В., Тихомирова К.К. Врожденная хлоридная диарея // Иванов Д.О., Аврелькина Е.В., Александрович Ю.С., и др. Руководство по перинатологии. В 2-х т. – СПб.: Информ-Навигатор, 2019. – С. 929–931. [Novikova VP, Vorontsova LV, Tikhomirova KK. Congenital chloride diarrhea. In: Ivanov DO, Avrel'kina EV, Aleksandrovich YuS, et al. Rukovodstvo po perinatologii. Saint Petersburg: Inform-Navigator; 2019. P. 929-931. (In Russ.)]
14. Шабалов Н.П. Детские болезни. 8-е изд. В 2 т. Т. 1. – СПб.: Питер, 2017. – С. 684–685. [Shabalov NP. Detskie bolezni. 8th ed. Vol. 1. Saint Petersburg: Piter; 2017. P. 684–685. (In Russ.)]
15. Шабалов Н.П., Цвелев Ю.В., Кира Е.Ф., и др. Основы перинатологии: учебник для студентов медицинских вузов. 3-е изд. – М., 2004. – 633 с. [Shabalov NP, Tsvelev YuV, Kira EF, et al. Osnovy perinatologii: uchebnik dlya studentov meditsinskikh vuzov. 3rd ed. Moscow; 2004. 633 p. (In Russ.)]
16. Anderson CA, Boucher G, Lees CW, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet*. 2011;43(3):246-252. https://doi.org/10.1038/ng.764.
17. Arshad N, Visweswariah SS. The multiple and enigmatic roles of guanylyl cyclase C in intestinal homeostasis. *FEBS Lett*. 2012;586(18):2835-2840. https://doi.org/10.1016/j.febslet.2012.07.028.
18. Booth IW, Stange G, Murer H, et al. Defective jejunal brush-border Na^+/H^+ exchange: a cause of congenital secretory diarrhoea. *Lancet*. 1985;1(8437):1066-1069. https://doi.org/10.1016/s0140-6736(85)92369-4.
19. Camilleri M, Carlson P, Acosta A, et al. RNA sequencing shows transcriptomic changes in rectosigmoid mucosa in patients with irritable bowel syndrome-diarrhea: a pilot case-control study. *Am J Physiol Gastrointest Liver Physiol*. 2014;306(12): G1089-G1098. https://doi.org/10.1152/ajpgi.00068.2014.
20. Cha B, Kim JH, Hut H, et al. cGMP inhibition of Na^+/H^+ antiporter 3 (NHE3) requires PDZ domain adapter NHERF2, a broad specificity protein kinase G-anchoring protein. *J Biol Chem*. 2005;280(17): 16642-16650. https://doi.org/10.1074/jbc.M500505200.
21. Chen T, Kocinsky HS, Cha B, et al. Cyclic GMP Kinase II (cGKII) inhibits NHE3 by altering its trafficking and phosphorylating NHE3 at three required sites: identification of a multifunctional phosphorylation site. *J Biol Chem*. 2015;290(4):1952-1965. https://doi.org/10.1074/jbc.M114.590174.

22. Coates AJ, Crofton PM, Marshall T. Evaluation of salt supplementation in CF infants. *J Cyst Fibros*. 2009;8(6):382-385. https://doi.org/10.1016/j.jcf.2009.08.006.
23. Dimitrov G, Bamberger S, Navard C, et al. Congenital Sodium Diarrhea by mutation of the SLC9A3 gene. *Eur J Med Genet*. 2019;62(10):103712. https://doi.org/10.1016/j.ejmg.2019.103712.
24. Faller N, Gautschi I, Schild L. Functional analysis of a missense mutation in the serine protease inhibitor SPINT2 associated with congenital sodium diarrhea. *PLoS One*. 2014;9(4):94267. https://doi.org/10.1371/journal.pone.0094267.
25. Fell JM, Miller MP, Finkel Y, et al. Congenital sodium diarrhea with a partial defect in jejunal brush border membrane sodium transport, normal rectal transport, and resolving diarrhea. *J Pediatr Gastroenterol Nutr*. 1992;15(2):112-116. https://doi.org/10.1097/00005176-199208000-00002.
26. Fiskerstrand T, Arshad N, Haukanes BI, et al. Familial diarrhea syndrome caused by an activating GUCY2C mutation. *N Engl J Med*. 2012 Apr 26;366(17):1586-95. doi: 10.1056/NEJMoa1110132.
27. Fiskerstrand T. Diagnostic success with pitfalls [Editorial]. *Tidsskr Nor Laegeforen*. 2015 Nov 03; 135(20):1812. doi: 10.4045/tidsskr.15.1062.
28. Friis S, Sales KU, Schafer JM, et al. The protease inhibitor HAI-2, but not HAI-1, regulates matriptase activation and shedding through prostasin. *J Biol Chem*. 2014;289(32):22319-22332. https://doi.org/10.1074/jbc.M114.574400.
29. Ghishan FK, Kiela PR. Small intestinal ion transport. *Curr Opin Gastroenterol*. 2012;28(2):130-134. https://doi.org/10.1097/MOG.0b013e32834e7bc3.
30. Heinz-Erian P, Akdar Z, Haerter B, et al. Decreased urinary sodium-to-urinary creatinine ratio identifies sodium depletion in pediatric acute gastroenteritis. *Klin Padiatr*. 2016;228(1):24-28. https://doi.org/10.1055/s-0035-1559689.
31. Heinz-Erian P, Muller T, Krabichler B, et al. Mutations in SPINT2 cause a syndromic form of congenital sodium diarrhea. *Am J Hum Genet*. 2009;84(2):188-196. https://doi.org/10.1016/j.ajhg.2009.01.004.
32. Holmberg C, Perheentupa J. Congenital Na^+ diarrhea: a new type of secretory diarrhea. *J Pediatr*. 1985;106(1):56-61. https://doi.org/10.1016/s0022-3476(85)80465-0.
33. Janecke AR, Heinz-Erian P, Müller T. Congenital sodium diarrhea: a form of intractable diarrhea, with a link to inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2016;63(2):170-176. https://doi.org/10.1097/MPG.0000000000001139.
34. Janecke AR, Heinz-Erian P, Yin J, et al. Reduced sodium-proton exchanger NHE3 activity causes congenital sodium diarrhea. *Hum Mol Genet*. 2015;24(23): 6614-6622. https://doi.org/10.1093/hmg/ddv367.
35. Thiagarajah JR, Kamin DS, Acra S, et al. Advances in evaluation of chronic diarrhea in infants. *Gastroenterology*. 2018;154(8):2045-2059.e6. https://doi.org/10.1053/j.gastro.2018.03.067.
36. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012;491(7422): 119-124. https://doi.org/10.1038/nature11582.
37. Kiela PR, Laubitz D, Larmonier CB, et al. Changes in mucosal homeostasis predispose NHE3 knockout mice to increased susceptibility to DSS-induced epithelial injury. *Gastroenterology*. 2009;137(3):965-975. https://doi.org/10.1053/j.gastro.2009.05.043.
38. Larmonier CB, Laubitz D, Hill FM, et al. Reduced colonic microbial diversity is associated with colitis in NHE3-deficient mice. *Am J Physiol Gastrointest Liver Physiol*. 2013;305(10):667-677. https://doi.org/10.1152/ajpgi.00189.2013.
39. Laubitz D, Larmonier CB, Bai A, et al. Colonic gene expression profile in NHE3-deficient mice: evidence for spontaneous distal colitis. *Am J Physiol Gastrointest Liver Physiol*. 2008;295(1):63-77. https://doi.org/10.1152/ajpgi.90207.2008.
40. Müller T, Rasool I, Heinz-Erian P, et al. Congenital secretory diarrhea caused by activating germline mutations in GUCY2C. *Gut*. 2016;65(8):1306-1313. https://doi.org/10.1136/gutjnl-2015-309441.
41. Muller T, Wijmenga C, Phillips AD, et al. Congenital sodium diarrhea is an autosomal recessive disorder of sodium/proton exchange but unrelated to known candidate genes. *Gastroenterology*. 2000;119(6): 1506-1513. https://doi.org/10.1053/gast.2000.20514.
42. Online Mendelian Inheritance in Man database. Available from: http://www.ncbi.nlm.nih.gov/omim.
43. Rajendran VM, Kumar NS, Tse CM, et al. Na-H exchanger isoform-2 (NHE2) mediates butyrate-dependent Na^+ absorption in dextran sulfate sodium (DSS)-induced colitis. *J Biol Chem*. 2015; 290(42):25487-25496. https://doi.org/10.1074/jbc.M115.654277.
44. Salomon J, Goulet O, Canioni D, et al. Genetic characterization of congenital tufting enteropathy: epcam associated phenotype and involvement of SPINT2 in the syndromic form. *Hum Genet*. 2013;133(3):299-310. https://doi.org/10.1007/s00439-013-1380-6.
45. Sivagnanam M, Janecke AR, Müller T, et al. Case of syndromic tufting enteropathy harbors SPINT2 mutation seen in congenital sodium diarrhea. *Clin Dysmorphol*. 2010;19(1):48. https://doi.org/10.1097/MCD.0b013e328331de38.
46. Sivagnanam M, Mueller JL, Lee H, et al. Identification of EpCAM as the gene for congenital tufting enteropathy.

Gastroenterology. 2008;135(2):429-437. https://doi.org/10.1053/j.gastro.2008.05.036.
47. Szabo R, Uzzun Sales K, Kosa P, et al. Reduced prostasin (CAP1/PRSS8) activity eliminates HAI-1 and HAI-2 deficiency-associated developmental defects by preventing matriptase activation. *PLoS Genet*. 2012;8(8):1002937. https://doi.org/10.1371/journal.pgen.1002937.
48. Wiegerinck CL, Janecke AR, Schneeberger K, et al. Loss of syntaxin 3 causes variant microvillus inclusion disease. *Gastroenterology*. 2014;147(1):65-68. https://doi.org/10.1053/j.gastro.2014.04.002.
49. Yeruva S, Farkas K, Hubricht J, et al. Preserved $Na^{(+)}/H^{(+)}$ exchanger isoform 3 expression and localization, but decreased NHE3 function indicate regulatory sodium transport defect in ulcerative colitis. *Inflamm Bowel Dis*. 2010;16(7):1149-1161. https://doi.org/10.1002/ibd.21183.

◆ Information about the authors

Dmitry O. Ivanov — MD, PhD, Dr Med Sci, Professor, Rector. St. Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: doivanov@yandex.ru.

Valeria P. Novikova — MD, PhD, Dr Med Sci, Professor, Head of the Laboratory of Medical and Social Problems in Pediatrics, Head of the Department of Propedeutics of Childhood Diseases. St. Petersburg State Pediatric Medical University, Russian Ministry of Health, Saint Petersburg, Russia. E-mail: novikova-vp@mail.ru.

◆ Информация об авторах

Дмитрий Олегович Иванов — д-р мед. наук, профессор, ректор, заслуженный врач РФ, главный внештатный специалист-неонатолог Минздрава России. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: doivanov@yandex.ru.

Валерия Павловна Новикова — д-р мед. наук, профессор, заведующая кафедрой пропедевтики детских болезней с курсом общего ухода за детьми, заведующая лабораторией медико-социальных проблем в педиатрии, НИЦ. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: novikova-vp@mail.ru.