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Phenotype of cystic kidney disease in children with orphan diseases and hereditary syndromes due to genetic or chromosomal pathology (description of 9 clinical cases)

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ABSTRACT

The use of DNA diagnostics makes it possible to clarify the clinical diagnosis of hereditary kidney disease, determine a personalized treatment strategy, and predict the patient's health status. Kidney cysts with orphan syndromes and chromosomal mutations are characterized by a high risk of progression of chronic kidney disease to end–stage renal failure in childhood. In 9 patients aged 4 months — 17 years (6 girls and 3 boys) with cystic kidney disease in orphan diseases and hereditary syndromes, assessed the features of the phenotype, the progression of chronic kidney disease. Children over the age of 2 years were stratified with chronic kidney disease stages by NKF–K/DOQI (2002) according to the criterion of glomerular filtration rate calculated by creatinine clearance in the Shwartz formula and the level of microalbuminuria / proteinuria. The description of the phenotype features of kidney cysts in 9 children with orphan diseases and hereditary syndromes is presented: Senior–Løken6 (1), Meckel–Gruber4 (1), CHARGE (1), papillorenal (1), with deletion of the long arm of chromosome 2 (2), microdeletion syndrome 17q12 (2), with deletion of the short arm of chromosome 12 (1). 6 children were diagnosed with cystosis of both kidneys, 2 with unilateral multicystic dysplastic kidney, 1 with non-functioning multicystic and cystic contralateral kidneys. In 2 children aged less than 2 years with a multicystic dysplastic kidney in microdeletion syndrome 17q12 and CHARGE syndromes, renal function is reduced. Of the 6 patients over the age of 2 years, chronic kidney disease was established: stage with preserved renal function in 1, with reduced function in stage 3 in 2, stage 4 in 1 and stage 5 in 2. Two 17-year-old adolescents with an outcome of terminal chronic kidney disease at the age of 12 underwent kidney transplantation. A fatal outcome was found in a proband with nephronophthysis in Meckel–Gruber4 syndrome due mutations of the *CEP290* gene. The features of the clinical phenotype and genotype of cystic kidney diseases associated with orphan syndromes Meckel–Gruber4, Senior–Løken6, CHARGE, papillorenal due to gene mutations and deletion of the long arm of chromosome 2, microdeletion syndrome 17q12 and deletion of the short arm of chromosome 12 in children are described.

Keywords: kidney cysts; orphan hereditary syndrome; gene mutation; chromosome deletion; children.

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Фенотип кистозной болезни почек у детей с орфанными заболеваниями и наследственными синдромами вследствие генной или хромосомной патологии (описание 9 клинических случаев)

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АННОТАЦИЯ

Применение ДНК-диагностики позволяет уточнить клинический диагноз наследственной болезни почек, определить стратегию персонализированного лечения, прогнозировать состояние здоровья пациента. Для кистозной болезни почек при орфанных заболеваниях у детей существует высокий риск прогрессирования хронической болезни почек до терминальной стадии почечной недостаточности.

Клинические случаи. У 9 пациентов в возрасте от 4 мес. до 17 лет (6 девочек и 3 мальчика) с кистозными болезнями почек при орфанных заболеваниях и наследственных синдромах оценены особенности клинического фенотипа, прогрессирования хронической болезни почек. Детям в возрасте более 2 лет проведена стратификация стадий хронической болезни почек в соответствии с классификацией NKF–K/DOQI, 2002 г., по критерию скорости клубочковой фильтрации, рассчитанной по клиренсу креатинина в формуле Шварца и уровню микроальбуминурии/протеинурии.Представлено описание особенностей фенотипа кистоза почек у 9 детей с орфанными заболеваниями и наследственными синдромами: Senior–Løken 6-го типа (1), Меккеля–Грубера 4-го типа (1), CHARGE (1), папиллоренальный (1), при делеции длинного плеча хромосомы 2 (2), синдроме микроделеции 17q12 / микроделеционном синдроме 17q12 (2), при делеции короткого плеча хромосомы 12 (1). У 6 детей диагностирован кистоз обеих почек, у 2 — односторонняя мультикистозная дисплазия почки, у 1 — нефункционирующая мультикистозная и кистозная контралатеральная почка. У 2 детей в возрасте менее 2 лет с мультикистозной дисплазией почки при микроделеционном синдроме 17q12 и CHARGE почечная функция снижена. Из 6 пациентов в возрасте более 2 лет установлена хроническая болезнь почек: стадия I с сохранной функцией почек — у 1, со сниженной функцией — стадия III у 2, стадия IV у 1 и стадия V у 2. Двум подросткам 17 лет с исходом в терминальную почечную недостаточность в возрасте 12 лет проведена трансплантация почки. Летальный исход констатирован у пробанда с нефронофтизом при синдроме Меккеля–Грубера 4-го типа вследствие мутаций в гене *CEP290*. Представлены орфанные синдромы Меккеля–Грубера 4-го типа, Senior–Løken 6-го типа, CHARGE, папиллоренальный вследствие мутаций генов и при делеции длинного плеча хромосомы 2, микроделеционном синдроме 17q12, при делеции короткого плеча хромосомы 12, в структуре которых охарактеризованы особенности фенотипа и генотипа кистозных болезней почек у детей.

Ключевые слова: кистозы почек; орфанный наследственный синдром; мутация гена; делеция хромосомы; дети.

Как цитировать

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ЭКО•ВЕКТОР

INTRODUCTION

Molecular genetic testing has exposed the heterogeneity of hereditary kidney diseases, as defects in different genes can lead to phenotypically similar or even indistinguishable conditions [9]. Pathogenic mutations in genes responsible for the development of orphan syndromes with cystic kidney disease (renal cysts) have been identified. Chromosomal deletions result in the loss of genes involved in the embryogenesis of multiple organ systems, contributing to the phenotypic heterogeneity of hereditary syndromes and orphan diseases. The characterization of genotypes in cystic kidney diseases within the structure of orphan syndromes has rarely been the subject of dedicated discussion [8, 9]. Cystic kidney diseases exhibit a wide range and severity of clinical phenotypes, often involving congenital anomalies of multiple organs and systems. In cases of renal oligohydramnios, Potter phenotype may develop, accompanied by acute kidney injury (AKI), necessitating a personalized, multisystem approach to diagnosis, management, and treatment [3–6, 8, 9].

Kidney cysts associated with hereditary syndromes and chromosomal mutations pose a high risk of chronic kidney disease (CKD) progression to end-stage renal disease in childhood.

CKD in children and adults ranks as the sixth leading cause of death worldwide. Since 2006, World Kidney Day has been organized annually at the initiative of the International Society of Nephrology and the International Federation of Kidney Foundations to raise awareness among the global community and policymakers about the importance of kidney health. The campaign aims to enhance public understanding of the significance and consequences of congenital, hereditary, and acquired kidney diseases, as well as CKD in both children and adults, and to promote strategies aimed at reducing their incidence, severity, and impact on health and quality of life [7].

Early subclinical diagnosis relies on imaging techniques such as ultrasound and magnetic resonance imaging (MRI). Molecular genetic tests have identified gene and chromosomal mutations that determine the pathogenesis, phenotype, and genotype of orphan diseases associated with kidney cysts, such as juvenile nephronophthisis. These mutations are documented in the Online Mendelian Inheritance in Man (OMIM) database [10], the Orphanet portal on rare diseases and orphan drugs (ORPHA)*, and various publications [8, 9, 12, 17].

The clinical phenotype and progression of CKD were studied in nine patients (six girls and three boys) aged 4 months to 17 years with cystic kidney diseases associated with hereditary syndromes and genetic or chromosomal mutations.

CKD staging in children older than 2 years was performed according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF–K/DOQI, 2002) classification, based on the estimated glomerular filtration rate (eGFR) calculated using the Schwartz formula for creatinine clearance, as well as microalbuminuria and/or proteinuria levels [16].

Molecular genetic, cytogenetic, and molecular cytogenetic studies were conducted in laboratories licensed for medical practice and DNA testing, using medical equipment registered in Russia. These laboratories included the Molecular Pathology Laboratory at OOO "Genomed" Medical Genetic Center, OOO "Genotek" Laboratory, the AO "First Genetics" Laboratory, the Molecular Diagnostics Laboratory with an Extended Ecogenetics Group at the Research Center of Saint Petersburg State Pediatric Medical University, and the Laboratory of the Saint Petersburg State Budgetary Healthcare Institution "Diagnostic Center (Medical-Genetic)."

The inclusion criteria for the study were the presence of multiple round formations — cysts — in the parenchyma of one or both kidneys, with no blood flow and no connection to the pelvicalyceal system, as detected by ultrasound. The presence of more than three cysts in the kidney parenchyma was classified as multiple cysts.

Cystic kidney disease was diagnosed in patients with cystic kidneys, whereas unilateral multicystic dysplasia was established in cases of a nonfunctioning kidney (determined by renal scintigraphy and/or intravenous urography) without parenchyma, containing a conglomerate of multiple, closely packed, thin-walled cysts of varying sizes, lacking blood flow and not communicating with each other, as confirmed by ultrasound with blood flow assessment [2].

The clinical diagnosis of nephronophthisis in children was based on the presence of anemia, growth retardation, and secondary tubulointerstitial damage (polyuria, polydipsia, hyposthenuria). Ultrasound criteria included increased echogenicity of the kidney parenchyma with loss of corticomedullary differentiation, small, predominantly medullary renal cysts, and either a decreased (in the juvenile form) or increased (in the infantile form) kidney volume. Disease progression to end-stage renal disease was also a diagnostic criterion.

Ophthalmology, otolaryngology, neurology, and cardiology appointments were scheduled for children as clinically indicated.

Among the nine children aged 4 months to 17 years with cystic kidney diseases, the following rare hereditary disorders were identified: Senior–Løken syndrome 6 (one case), Meckel–Gruber syndrome type 4 (one case),

* The portal for rare diseases and orphan drugs. Juvenile-nephronophthisis [Internet]. Available from: https://www.orpha.net/en/disease/classification/list/name/Juvenile-nephronophthisis?orphaCode=93592 (cited: 29 May 2024).

CHARGE syndrome (one case), papillorenal syndrome (one case), chromosome 2 long-arm deletion (two cases), chromosome 17q12 microdeletion syndrome (two cases), and chromosome 12 short-arm deletion (one case).

CLINICAL PHENOTYPE IN CHILDREN WITH CYSTIC KIDNEY DISEASE IN RARE DISORDERS AND HEREDITARY SYNDROMES

Proband: a 7-month-old girl. Multicystic dysplasia of the left kidney. A single functioning cystic right kidney in 17q12 microdeletion syndrome

A 7-month-old girl from a family with a history of autosomal dominant polycystic kidney disease (maternal lineage) was prenatally diagnosed with increased echogenicity of the right kidney parenchyma and multiple cysts in the left kidney on ultrasound. After birth, multicystic dysplasia of the nonfunctioning left kidney was confirmed, along with an enlarged cystic right kidney containing predominantly subcapsular cysts measuring 2–5 mm, with the largest reaching 12×8 mm.

The neonatal clinical phenotype was characterized by anemia, a right ovarian cyst, inferior vena cava thrombosis, and stage 3 AKI, complicated by incomplete recovery of kidney function despite peritoneal dialysis. Molecular genetic testing confirmed a 1,258,684-base pair deletion in the long arm of chromosome 17 (nucleotides 36,486,450–37,745,134), encompassing the *HNF1B* gene.

At 7 months, ultrasound of the proband revealed involution of the multicystic left kidney (volume: 6 cm^3) and an increase in the volume of the cystic right kidney (37 cm^3), along with the progression of CKD (eGFR: 20 mL/min/1.73 m^2).

Proband: a 1-year-old boy. Multicystic dysplasia of the right kidney. A single functioning left kidney in CHARGE syndrome

Prenatal ultrasound at 23 weeks of gestation detected multicystic dysplasia of the right kidney, polyhydramnios, and an extremely short umbilical cord. The boy was born at term but developed progressive respiratory distress within 10 h. Mechanical ventilation was required for 7 days, followed by respiratory oxygen support. Due to persistent respiratory and feeding difficulties, a tracheostomy and percutaneous gastrostomy were performed. The characteristic phenotype met the major criteria for CHARGE syndrome. *C* for Coloboma: Bilateral choroidal coloboma, left optic nerve coloboma, gaze nystagmus, and hypermetropia in the right eye. *H* for Heart Defects: Congenital heart defect — atrial septal defect. *A* for Atresia of Choanae: Bilateral choanal stenosis, ethmoid cell dystopia. *R* for Retardation of Growth and Development: Delayed physical, psychomotor, and speech development; right facial nerve paresis; pseudobulbar syndrome; residual central nervous system involvement; facial asymmetry; dysphagia; and hearing impairment. *G* for Genital and Urinary Anomalies: Micropenis, cryptorchidism (inguinal ectopia of the right testis). *E* for Ear Abnormalities and Deafness: Bilateral sensorineural hearing loss (grade 3–4). Additional findings included segmental stenosis of the right middle lobe bronchus, atelectasis of the right lower lobe, type 3 laryngomalacia, and nonfunctioning multicystic dysplasia of the right kidney.

At 5 months of age, the proband was diagnosed with CHARGE syndrome. Molecular genetic testing identified a mutation in the *CHD7* gene (c.469C>T p.Arg157*), mapped to chromosome 8q12.2.

At 1 year of age, ultrasound revealed compensatory hypertrophy of the contralateral (left) kidney, with a reduced eGFR of 58 mL/min/1.73 m^2.

Proband: a 17-year-old girl. Multicystic dysplasia of the right kidney and left renal artery stenosis associated with papillorenal syndrome

Prenatal ultrasound at 32 weeks of gestation detected multiple cysts in the right kidney. After birth, the girl was diagnosed with bilateral coloboma of the optic nerve discs and chorioretinitis. At 5 years of age, leukocyturia, proteinuria, hematuria, nonfunctioning multicystic dysplasia of the right kidney, and reduced eGFR (63 mL/min/1.73 m^2) were detected.

At 8 years of age, the patient underwent a right-sided nephrectomy. Histological examination confirmed renal involution (size: 5×2.5×1.5 cm), multicystic dysplasia, and abnormal ureteral and arterial structure. The girl was found to have a splice-site mutation in a heterozygous state: a nucleotide substitution, IVS6–2G>C, in intron 6 of the *PAX2* gene, located at 10q24.31 and inherited in an autosomal dominant manner. The same mutation was confirmed in the father and sibling.

A distinctive feature of this case is the autosomal dominant inheritance pattern from the proband's paternal line: the grandmother had optic nerve coloboma, hearing loss, and stage 5 CKD, which led to a fatal outcome at the age of 38 years; the father has hypertension. The proband presents with ocular anomalies, including bilateral coloboma of the optic nerve discs, a choroidal epibulbar dermoid on the left, chorioretinitis in the scarring stage, horizontal nystagmus, concomitant exotropia, and progressive myopia in both eyes. Stable severe renovascular hypertension is present due to left renal artery stenosis and hypoplasia of the right vertebral artery. At the age of 12, the proband was diagnosed with end-stage renal disease. At 13, she underwent a living-donor kidney transplantation. At 17, kidney graft function remains preserved (eGFR92 mL/min/1.73 m^2), with sufficient blood flow confirmed by ultrasound.

Proband: a 4-month-old girl. Nephronophthisis (infantile) in Meckel–Gruber syndrome type 4

At 4 months of age, a girl was diagnosed with nephronophthisis-associated Meckel–Gruber syndrome type 4 due to a compound heterozygous mutation in the *CEP290* gene, including a known pathogenic mutation (p.Ser1387fs) and a previously unknown pathogenic mutation (p.Leu993fs), with an autosomal recessive inheritance pattern. There was no family history of renal cysts. Infantile nephronophthisis is characterized by multiple diffuse small (1–3 mm) cysts in the parenchyma of both enlarged, nodular kidneys.

In the newborn, the following findings were noted: Potter phenotype (prenatal oligohydramnios, Potter facies, pulmonary hypoplasia with grade 3 respiratory failure, AKI, valgus foot deformity); occipital meningocele, aplasia of the 12th pair of ribs, and cerebellar hypoplasia with vermian aplasia. The cause of death in the proband was stage 3 AKI, with no recovery of renal function despite renal replacement therapy via peritoneal dialysis.

Proband: a 4-year-old girl. Nephronophthisis (infantile) in Senior–Løken syndrome 6

A 4-year-old girl was diagnosed with nephronophthisis (with infantile onset) caused by a homozygous deletion at 12q21.32 involving the *CEP290* gene as part of nephronophthisis-associated Senior–Løken syndrome type 6 with an autosomal recessive inheritance pattern.

Diffuse changes in the parenchyma of both fetal kidneys and polyhydramnios were detected by ultrasound at 30–32 weeks of gestation. The girl was born to healthy parents, and no signs of renal failure were detected at birth. Postnatal ultrasound confirmed increased echogenicity and multiple small parenchymal cysts in both kidneys, polycystic liver disease, signs of cavernous transformation of the portal vein, and porto-caval anastomosis, which required differential diagnosis with autosomal recessive polycystic kidney disease [4].

At 2 months of age, the child was diagnosed with lack of visual fixation. At 4 months, horizontal nystagmus, partial optic nerve disc atrophy, mild iron deficiency anemia, delayed psychomotor development, and kidney enlargement were noted on ultrasound.

At 2 years of age, the girl was found to have significant kidney enlargement, increased parenchymal echogenicity, a single unilateral 5 mm cyst, signs of cholangitis, and thickening of the intrahepatic bile duct walls on ultrasound. Leber congenital amaurosis, craniosynostosis, and hydrocephalus were confirmed.

At 4 years of age, the patient presented with moderate anemia, polydipsia, polyuria, glucosuria, proteinuria, hypertension complicated by left ventricular myocardial hypertrophy, multiple small (2–5 mm) parenchymal cysts in both enlarged kidneys on ultrasound, and liver fibrosis and cystic changes complicated by portal hypertension syndrome.

The consequences of organic central nervous system damage included atonic-astatic syndrome (inability to sit or walk), delayed speech development, and dysfunction of pelvic organs characterized by a lack of control. At 4 years of age, the proband was diagnosed with the progression of CKD to stage 4 (eGFR20 mL/min/1.73 m^2) and albuminuria. Renal replacement therapy via dialysis was proposed.

Proband: a 7-year-old boy. Cystic kidney disease in deletion of the short arm of chromosome 12

On day 24 of life, a male newborn was diagnosed with acute pyelonephritis with AKI (serum creatinine 171 μmol/L) and multiple small cysts (up to 3.5 mm in the right kidney, up to 2 mm in the left) in the parenchyma of both hypoplastic kidneys. Congenital heart defects (atrial septal defect) and laryngeal malformations (laryngomalacia) were identified, along with microglossia, micrognathia, esotropia, torticollis, growth retardation (microsomia, grade 2 hypotrophy), psychomotor developmental delay, and signs of rickets. Karyotype analysis revealed an abnormal male karyotype with a *de novo* structural rearrangement of the short arm of chromosome 12:46, XY, der(12)de novo.

A molecular cytogenetic test (FISH) confirmed an interstitial deletion of the short arm of chromosome 12, clarifying the nature of the structural anomaly. FISH: der(12)de novo, del(12)(p)ish12psubtel(8M16/SP6X2), 12qsubtel(VIJyRM2196X2)del(12)(p)ish12(wep12++).

At 7 years of age, kidney ultrasound revealed a decrease in total kidney volume (11 cm^3) and multiple parenchymal cysts measuring 5–7 mm, with progression of CKD to stage 3 (eGFR33 mL/min/1.73 m^2).

Proband: an 8-year-old boy. Cystic kidney disease in 17q12 microdeletion syndrome

The clinical phenotype of cystic kidney disease in the 8-year-old boy was characterized by multiple small (3–5 mm) parenchymal cysts, increased cortical echogenicity, and reduced kidney volume (65 cm^3). CKD was at stage 1, with an eGFR within the normal range (107 mL/min/1.73 m^2), along with extrarenal manifestations, including pancreatic hypoplasia with hypoinsulinemia (without hyperglycemia or glucosuria), thyroid cysts, hypomagnesemia, and delayed speech development.

The family history is burdened with single and multiple kidney cysts, kidney hypoplasia, and CKD in maternal relatives across three generations. Whole-genome sequencing (performed at AO "First Genetic") identified a 17q12 deletion of approximately 1.6 Mb in the proband, spanning positions 36,486,698–38,136,480 and including the *HNF1b* gene.

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Proband: a 17-year-old girl. Nephronophthisis (juvenile) due to a deletion in the long arm of chromosome 2

The proband, a girl, was born to healthy, nonconsanguineous parents. At age 8, ultrasound revealed a single 6-mm kidney cyst, which increased to 8 mm by age 10. At age 12, the patient was diagnosed with moderate anemia, decreased eGFR (14 mL/min/1.73 m^2 by the Schwartz formula, 8 mL/min by the Rehberg test), proteinuria, and hyposthenuria. Ultrasound and MRI showed reduced kidney volume, decreased corticomedullary differentiation, and multiple bilateral parenchymal cysts (<1 cm). Echocardiography detected a congenital heart defect (1.2-mm patent ductus arteriosus with minimal shunting), which did not require surgical correction. Whole-genome sequencing using the MGISEQ2000 platform (conducted at AO "First Genetic," with >10× effective target nucleotide coverage) identified a ~115-kb homozygous deletion in the long arm of chromosome 2, encompassing the *NPHP1* gene.

At the age of 12, the girl was diagnosed with end-stage renal disease, and renal replacement therapy with hemodialysis was initiated. That same year, she underwent deceased-donor kidney allotransplantation into the right iliac region; however, transplant nephrectomy was performed on postoperative day 11 due to renal vein thrombosis and acute transplant injury. One month later, a second deceased-donor kidney transplant was performed in the left iliac region.

At the age of 17, with a functioning kidney transplant for five years, the patient was diagnosed with chronic allograft nephropathy, presenting with hypertension, mild anemia, decreased eGFR (53 mL/min/1.73 m^2), proteinuria, and hyposthenuria. Ultrasound revealed an increased transplant volume (135 cm^3) without structural parenchymal changes and with uniform blood flow.

Sibling of the proband, a 10-year-old girl. Nephronophthisis (juvenile) due to a deletion in the long arm of chromosome 2

The sibling of the proband, a 4-year-old girl, underwent evaluation in the nephrology department due to a family history of CKD stage 5 in her older sister, resulting from juvenile nephronophthisis caused by a deletion in the long arm of chromosome 2. Her eGFR was 123 mL/min/1.73 m^2, and renal ultrasound showed a total kidney volume of 63 cm^3 with no parenchymal abnormalities.

At the age of 10, the girl was first noted to have a decline in eGFR (52 mL/min/1.73 m^2), anemia, polydipsia, polyuria, hyposthenuria, increased echogenicity of the renal parenchyma, kidney enlargement (158 cm^3), and growth retardation (appropriate for age 8.5–9 years). No definitive evidence of cysts in the kidneys (cysts <1 mm not excluded), liver, pancreas, thyroid gland, or spleen was obtained. No hypertension was detected.

The patient underwent echocardiography at the age of 10, which revealed a congenital heart defect — patent ductus arteriosus with a minor left-to-right shunt — followed by endovascular embolization. Ophthalmologic examination identified simple myopic astigmatism in both eyes. No evidence of pigmentary retinitis or optic disc coloboma was found.

At the age of 10, digital droplet polymerase chain reaction detected a large deletion involving the *NPHP1* gene in a homozygous state. Based on the examination results, juvenile nephronophthisis due to a deletion in the long arm of chromosome 2 was diagnosed, with progression to CKD stage 3. The mother (aged 48 years) and father (aged 46 years) of the two sisters (the 17-year-old proband and her 10-year-old sibling) are healthy. No abnormalities were detected on kidney and abdominal ultrasound. Digital droplet polymerase chain reaction identified a large deletion in the long arm of chromosome 2 involving the *NPHP1* gene in a heterozygous state in both parents.

A table summarizing genetic or chromosomal abnormalities in nine children with hereditary orphan diseases associated with cystic kidney disease is presented below.

DISCUSSION

A description of the phenotypic presentation of kidney cysts in the context of rare syndromes is provided for nine pediatric patients.

A case of unilateral nonfunctioning multicystic dysplastic kidney in children with CHARGE syndrome (1) and papillorenal syndrome (1) is presented. In a 17-year-old female proband with a nonfunctioning multicystic right kidney and renal artery stenosis of the contralateral kidney, CKD stage 5 was diagnosed in the context of papillorenal syndrome due to a heterozygous *PAX2* mutation (IVS6–2G>C in intron 6). Forero-Delgadillo et al. [14] identified a pathogenic *de novo* c.94C>T (p.Pro32Ser) variant in the *PAX2* gene, which resulted in severe kidney cystic disease with Potter phenotype and AKI without renal function recovery in a newborn.

The article presents a description of 17q12 deletion syndrome in a 7-month-old female patient with unilateral nonfunctioning multicystic dysplastic kidney and a functioning contralateral cystic kidney, as well as in an 8-year-old male patient with cystic kidney disease. Clinical features of kidney cysts in pediatric patients with 17q12 deletion/microdeletion syndrome have been reported in the literature [11, 13]. The association of 17q12 deletion syndrome with multicystic dysplastic kidney phenotype has been confirmed in studies [11–13, 15, 19, 20].

The phenotype of bilateral kidney cysts in four children has been characterized in the context of hereditary

Table. Characteristics of genetic or chromosomal pathology in 9 children with hereditary orphan diseases with kidney cysts

Таблица. Характеристика генной или хромосомной патологии у 9 детей при наследственных орфанных заболеваниях с кистозом почек

Proband (age at the time of catamnesis) / Пробанд (возраст к моменту катамнеза)	Description of kidney cysts. Renal function / Описание кистоза почек. Почечная функция	Etiology of the disease / Этиология заболевания	Diagnosis (OMIM, ORPHA) / Диагноз (OMIM, ORPHA)
Unilateral non-functioning multicystic dysplastic kidney and a single functioning contralateral cystic kidney / Односторонняя нефункционирующая мультикистозная дисплазия почки и функционирующая кистозная контралатеральная почка			
Girl, 7 months / Девочка, 7 мес.	Multicystic dysplastic left kidney. A single functioning cystic right kidney (GFR20 ml/min×1.73 m^2) / Мультикистозная дисплазия левой почки. Единственная функционирующая кистозная правая почка (СКФ 20 мл/мин×1,73 м^2)	17q12del(~1258684 p. n.): 36486450–37745134 / 17q12del(~1258684 п. н.): 36486450–37745134	Microdeletion syndrome 17q12 (OMIM:614527, ORPHA:261265) / Микроделеционный синдром 17q12 (OMIM:614527, ORPHA:261265)
Unilateral non-functioning multicystic dysplastic kidney / Односторонняя нефункционирующая мультикистозная дисплазия почки			
Boy, 1 year / Мальчик, 1 год	Multicystic dysplastic right kidney. A single functioning left kidney (GFR58 ml/min×1.73 m^2) / Мультикистозная дисплазия правой почки. Единственная функционирующая левая почка (СКФ 58 мл/мин×1,73 м^2)	CHD7 8q12.2 c.469C>T p.Arg157*, AD / CHD7 8q12.2 c.469C>T p.Arg157*, АД	CHARGE syndrome (OMIM:214800, ORPHA:138) / CHARGE-синдром (OMIM:214800, ORPHA:138)
Girl, 17 year / Девочка, 17 лет	Multicystic dysplastic right kidney, condition after nephrectomy. Stenosis of the left renal artery. CKD5 (at 12 years old), recipient of a related kidney transplant. Graft function is preserved (GFR92 ml/min×1.73 m^2) / Мультикистозная дисплазия правой почки, состояние после нефрэктомии. Стеноз левой почечной артерии. Реципиент родственного трансплантата почки в связи с исходом в ХБПС5 (в 12 лет). Функция трансплантата сохранна (СКФ 92 мл/мин×1,73 м^2)	PAX2 10q24.31 IVS6–2G>C, heterozygous splicing-mutation in intron 6, AD / PAX2 10q24.31 IVS6–2G>C, гетерозиготная сплайсинг-мутация в 6-м интроне, АД	Papillorenal syndrome (OMIM:120330, ORPHA:1475) / Папиллоренальный синдром (OMIM:120330, ORPHA:1475)
Bilateral multiple parenchymal cysts of kidneys / Двусторонние множественные паренхиматозные кисты почек			
Girl, 4 months / Девочка, 4 мес.	Nephronophthysis (infantile). Acute kidney injury, III stage / Нефронофтиз (инфантильный). Острое повреждение почек, III стадия	CEP290, Compound-heterozygosity 12: c.2978dupT (p.Leu993fs), 12: c.4159dupA (p.Ser1387fs), AR / CEP290 Компаунд-гетерозигота 12: c.2978dupT (p.Leu993fs), 12: c.4159dupA (p.Ser1387fs), АР	Meckel–Gruber 4 syndrome (OMIM:611134, ORPHA:564) / индром Меккеля–Грубера, 4-й тип (OMIM:611134, ORPHA:564)
Girl, 4 year / Девочка, 4 года	Nephronophthysis (infantile). CKD4 (GFR20 ml/min×1.73 m^2) / Нефронофтиз (инфантильный). ХБПС4 (СКФ 20 мл/мин×1,73 м^2)	CEP290 homozygous deletion 12q21.32, AR / CEP290 гомозиготная делеция 12q21.32, АР	Senior–Løken 6 syndrome (OMIM:610189, ORPHA:3156) / Синдром Senior–Løken, 6-й тип (OMIM:610189, ORPHA:3156)

Table (continued) / Продолжение таблицы

Proband (age at the time of catamnesis) / Пробанд (возраст к моменту катамнеза)	Description of kidney cysts. Renal function / Описание кистоза почек. Почечная функция	Etiology of the disease / Этиология заболевания	Diagnosis (OMIM, ORPHA) / Диагноз (OMIM, ORPHA)
Boy, 7 year / Мальчик, 7 лет	Cystic kidney disease. CKD3 (GFR33 ml/min×1.73 m^2) / Кистозная болезнь почек. ХБПС3 (СКФ 33 мл/мин×1,73$м^2$)	Karyotype: 46,XY, der(12)denovo, FISH: der(12)de novo, del(12)(p)ish12psubtel(8M16/SP6X2),12qsubtel(VIJyRM2196X2) del(12)(p)ish12(wep12++) / Кариотип: 46,XY, der(12)denovo. FISH: der(12)denovo, del(12)(p) ish12psubtel(8M16/SP6X2), 12qsubtel(VIJyRM2196X2)del(12) (p)ish12(wep12++)	Deletion of the short arm of chromosome 12 (del12p) (ORPHA:316244) / Делеция короткого плеча хромосомы 12 (del12p) (ORPHA:316244)
Boy, 8 year / Мальчик, 8 лет	Cystic kidney disease. CKD1 (GFR107 ml/min×1.73 m^2) / Кистозная болезнь почек. ХБПС1 (СКФ 107 мл/мин×1,73 $м^2$)	17q12del (~1.6 Mb): 36486698–38136480	Microdeletion syndrome 17q12 (OMIM:614527, ORPHA:261265) / Микроделеционный синдром 17q12 (OMIM:614527, ORPHA:261265)
Girl, 17 year (proband, the older sister) / Девочка, 17 лет (пробанд, старшая сестра)	Nephronophthysis (juvenile). CKD5, recipient of repeated (cadaveric) kidney allotransplantation (at 12 years old). Chronic transplant nephropathy (GFR53 ml/min×1.73 m^2) / Нефронофтиз (ювенильный). Реципиент повторной аллотрансплантации трупной почки в связи с исходом в ХБП V стадия (в 12 лет). Хроническая трансплантационная нефропатия (СКФ 53 мл/мин×1,73 $м^2$)	2qdel (~115Kb): 110097497–110212771, with *NPHP1* gene involvement, homozygote / 2qdel (~115 Kb): 110097497–110212771, с захватом гена *NPHP1* в гомозиготном состоянии	Nephronophthysis (juvenile) due to deletion of the long arm of chromosome 2 (OMIM:256100 ORPHA:655, 93592) / Нефронофтиз (ювенильный) вследствие делеции длинного плеча хромосомы 2 (OMIM:256100 ORPHA:655, 93592)
Girl, 10 year (sibs, the younger sister) / Девочка, 10 лет (сибс, младшая сестра)	Nephronophthysis (juvenile). CKD3 (GFR52 ml/min×1.73 m^2) / Нефронофтиз (ювенильный). ХБПС3 (СКФ 52 мл/мин×1,73 $м^2$)	Extended deletion with *NPHP1* gene involvement, homozygote / Обнаружена протяженная делеция с вовлечением гена *NPHP1* в гомозиготном состоянии	Nephronophthysis (juvenile) due to deletion of the long arm of chromosome 2 (OMIM:256100 ORPHA:655, 93592) / Нефронофтиз (ювенильный) вследствие делеции длинного плеча хромосомы 2 (OMIM:256100 ORPHA:655, 93592)

Note: AD, autosomal dominant type of inheritance; AP, autosomal recessive type of inheritance; GFR, glomerular filtration rate; CKD, chronic kidney disease (C1–5, stages I–V).
Примечание: АД — аутосомно-доминантный тип наследования, АР — аутосомно-рецессивный тип наследования, СКФ — скорость клубочковой фильтрации, ХБП — хроническая болезнь почек (С1–5 — стадии I–V).

syndromes, including Meckel–Gruber syndrome type 4 (1) and Senior–Løken syndrome 6 (1), both associated with mutations in the *CEP290*gene; deletion of the long arm of chromosome 2 (2); and 17q12 microdeletion syndrome (1). The literature provides data on the kidney cyst phenotype associated with *CEP290* mutations [10, 17, 21]. For the first time, multiple congenital anomalies with bilateral kidney cysts have been described in a 7-year-old male proband with a deletion of the short arm of chromosome 12 [1].

Scientific and practical interest lies in the combination of juvenile nephronophthisis and a congenital heart defect (patent ductus arteriosus) associated with a homozygous deletion of the long arm of chromosome 2 involving the *NPHP1* gene in two sisters, aged 17 and 10 years. Their parents were confirmed to be heterozygous carriers of the same chromosomal deletion. The 17-year-old proband underwent a first kidney transplantation, which was complicated by renal vein thrombosis, followed by a second deceased-donor kidney transplantation that has been

functioning for five years. Other authors have reported a case of successful living-related kidney transplantation in monozygotic twins with a heterozygous *NPHP1* gene deletion and a nephronophthisis phenotype [18].

CONCLUSION

Heterogeneity of the clinical phenotype of cystic kidney disease was identified in nine children with rare syndromes, including Meckel–Gruber syndrome type 4, Senior–Løken syndrome 6, CHARGE syndrome, and papillorenal syndrome, caused by pathogenic variants in the *CEP290, CHD7, and PAX2* genes, as well as deletions of the long arm of chromosome 2, the short arm of chromosome 12, and 17q12 deletion syndrome. An unfavorable renal prognosis was confirmed in seven of nine children with cystic kidney disease associated with rare diseases and hereditary syndromes due to genetic or chromosomal abnormalities.

The diversity and severity of cystic kidney phenotypes in rare syndromes and chromosomal disorders, along with congenital malformations affecting multiple organs and systems, necessitate a multisystem approach to diagnosis and a personalized management strategy based on CKD stage.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from the patients for publication of relevant medical information within the manuscript.

Ethics approval. The present study protocol was approved by the Ethics Committee of the Saint Petersburg State Pediatric Medical University, Ministry of Health of the Russian Federation (Protocol No. 10/8, dated 2020 Oct 19).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие законных представителей пациентов на публикацию медицинских данных.

Этический комитет. Протокол исследования был одобрен этическим комитетом ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России (Протокол № 10/8 от 19.10.2020).

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