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PATIENT WITH COSTELLO SYNDROME: LITERATURE REVIEW AND CLINICAL CASE

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Abstract. Costello syndrome belongs to RAS-pathies and is a multisystem disease based on a heterozygous mutation of the HRAS gene. Frequent characteristic features are a specific phenotype with dysmorphic facial features, delayed mental and psychomotor development, and a tendency to develop neoplasms. The biphasic growth of patients with the development of severe nutritional deficiency after birth causes difficulties in correction of a trophological status. A large number of diseases included in the range of differential diagnosis can cause difficulties in early diagnosis and adequate therapy because of polymorphism of the clinical picture of the disease. The article provides a literature review devoted to the analysis of the mechanisms of development of Costello syndrome, as well as a 4-year observation of a patient whose clinical picture consisted of mental retardation, impaired psychomotor and physical development, severe protein-energy malnutrition, dermatological complications, as well as the development of embryonal rhabdomyosarcoma of the bladder.

Key words: *Costello syndrome; developmental delay; embryonal rhabdomyosarcoma; nutritional status.*

ПАЦИЕНТ С СИНДРОМОМ КОСТЕЛЛО: ОБЗОР ЛИТЕРАТУРЫ И КЛИНИЧЕСКИЙ СЛУЧАЙ

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Резюме. Синдром Костелло относится к RAS-патиям и представляет собой полисистемное заболевание, в основе которого лежит гетерозиготная мутация гена *HRAS*. Частыми характерными особенностями является специфический фенотип с дисморфорическими чертами лица, задержка умственного и психомоторного развития, склонность к развитию новообразований. Двухфазный рост пациентов с развитием после рождения выраженного нутритивного дефицита вызывает трудности в коррекции трофологического статуса. Широкий спектр заболеваний, входящий в круг дифференциальной диагностики при полиморфизме клинической картины заболевания, может вызвать затруднения в ранней диагностике и проведении адекватной терапии. В статье приводится обзор литературы, посвященный анализу механизмов развития синдрома Костелло, а также 4-летнее наблюдение за пациентом, клиническая картина которого заключалась в умственной отсталости, нарушении психомоторного и физического развития, выраженной белково-энергетической недостаточности, дерматологических осложнениях, а также развитии эмбриональной рабдомиосаркомы мочевого пузыря.

Ключевые слова: *синдром Костелло; задержка развития; эмбриональная рабдомиосаркома; нутритивный статус.*

EPIDEMIOLOGY AND PATHOGENESIS

Costello syndrome (OMIM No. 218040) is a unique case of RAS-pathies (retrovirus associated sequences) and a rare polysystemic disease, which is caused by a heterozygous mutation in the *HRAS* gene (190020) on chromosome 11p15. 5. It is characterized by dysmorphic facial features, biphasic growth, motor and mental retardation, ectodermal dysplasia, papillomas. There are also pathological changes in the cardiovascular, endocrine, nervous, and digestive systems, and increased susceptibility to cancer. The mutation of the HRAS gene, which normally encodes guanosine triphosphatase (GTPase), leads to changes in the cascade of mitogen-activated protein kinases (MARK), which determine fundamental biological functions such as cell proliferation, differentiation, and Its survival [1–3].

Costello syndrome (CS) is a rare disease with autosomal dominant de novo mutations with an incidence in live births ranging from 1:300,000 to 1:24,000,000 [4–6]. There is a prenatal large fetus development with subsequent lag in postnatal physical development [7]. A growth retardation is determined by nutritional deficiencies due to feeding difficulties. In 1971, at first, and then in 1977 New Zealand pediatrician Jack Costello described two unrelated children with the syndrome, which included short stature, mental retardation, skin manifestations in the form of excessive skin on the neck, palms, soles of feet and fingers with hyperkeratosis, curly thin hair, papillomas [8, 9].

The main pathogenetic pathways of CS are impaired formation of elastic fibers due to low production of tropoelastin and microfibrillar proteins, its inadequate secretion and extracellular assembly [10]. A. Hinek et al. described causes of CS development in 6 children with confirmed diagnosis. Scientists determined that fibroblasts produced normal levels of soluble tropoelastin, but they were unable to assemble elastic fibers due to secondary deficiency of elastin-binding protein (EBP) [10]. Because the normal association between tropoelastin and EBP can be damaged by contact with fragments containing galactose, and accumulation of chondroitin sulfate-containing proteoglycans and biglycan was noted in fibroblasts from CS patients, it was hypothesized that chondroitin sulfate can induce the release of ESB from cells and prevent normal recycling of reusable tropoelastin chaperone [10, 11].

Correlations between genotype changes and corresponding phenotypic features were proved [12]. Patients with HRAS mutation and Costello syndrome more often have polyuria, ulnar deviation, growth hormone deficiency and tachycardia, than patients with *BRAF* or *MEK1* mutations [13]. Moreover, patients with *G13C* alterations also show polymorphism (polyhydramnios, macrocephaly, delayed physical and mental development, hypertrophic cardiomyopathy, and posterior fossa crowding) in clinical picture [14]. However, patients with *p.G12A* or *p.G12C HRAS* alteration have more severe phenotypic and morphofunctional manifestations than patients with other *HRAS* mutations [15]. Regardless of the mutation, severity did not significantly increase over time. Almost all of literature sources shows that there is no specific therapy for CS. The symptomatic treatment is used in therapy of CS. The treatment is aimed at nutritional support, prevention and therapy of emerging cardiac, gastrointestinal, and respiratory disorders.

The appearance of papillomas has been noted in children mainly on the face (a projection of the nasolabial triangle) and perianal area [16–18]. A mental retardation in various extents is an important diagnostic and sometimes prognostic factor in the structure of CS [19]. Children with CS are more susceptible to the development of autism spectrum disorders, especially children of 2–4 years old [20, 21]. The cause of CS development is associated with mutations in the HRAS gene, but it was found that patients may show signs of cardio-facio-cutaneous syndrome (CFC), and also referred to RAS-pathies [22, 23].

Di Rocco et al. were the first who wrote about oral-motor apraxia and associated malnutrition in patients with CS [24]. The case analysis showed marasmus-type of growth chart changes in the postnatal period in the majority of SC patients [4, 25, 26]. S. Umans et al. described a case of oropharyngeal dysphagia in the structure of CS [27]. The concomitant cause of trophoblastic deficiency was a severe gastroesophageal reflux disease in some patients [28]. In addition, a tendency to stomach and duodenum ulcerative process was described [29]. Problems of patient feeding and the need for artificial feeding with high-calorie formulas through a tube are posed by H. Kawame [30]. The dysphagia syndrome usually resolves in 4-yaers old children with CS [9, 31].

Clinical forms of CS with cardiovascular pathology, specifically rhythm disturbances and extrasystoles, as well as mitral valves thickening, pulmonary artery stenosis or hypertrophic cardi-

omyopathy, were described [32–34]. Therefore, the routine follow-up of cardiovascular system is recommended for all patients with CS.

A growth retardation in these patients is often associated with growth hormone deficiency [35]. Decreased cortisol concentrations and hypoglycemia also was noted [36–38].

An increased risk of malignant neoplasms, mainly in muscle tissues, was observed in patients with CS [39]. Thus, M. Feingold et al. reported about a child with confirmed CS who had alveolar rhabdomyosarcoma of the right foot which appeared in infancy [40]. B. Kerr et al. not only reported about two children with CS, who developed retroperitoneal embryonal rhabdomyosarcoma in infancy, but also associated an increased risk of malignization as a structural part of Costello syndrome [41]. K.W. Gripp et al. in 2002 also described 5 cases of abdominal, pelvic or urogenital rhabdomyosarcoma in patients with CS [42]. The literature review shows that all patients with CS and *p.Gly12Ser* or *p.Gly12Ala* genotype variants developed cancer [14, 43]. An intrathoracic ganglioneuroblastoma and bladder carcinoma were also detected in children with CS [44–46].

The issues of prenatal diagnosis have not been developed because the syndrome is rare, as well as the lack of specific signs of fetal phenotype was found [47, 48].

CLINICAL CASE

We present our own 4-year observation of a patient with Costello syndrome. The typical course of CS included in addition to mental retardation, disorders of psychomotor and physical development, marked malnutrition, and dermatologic manifestations, was accompanied by embryonal rhabdomyosarcoma of the bladder. Its surgical treatment leaded to recurrent vesico-uretero-renal reflux.

Patient M., born in 2015, was observed in the clinic from January 2019 to November 2022. At first he was admitted to the hospital at the age of 3 years 11 months in a serious condition with complaints of recurrent urinary tract infections, which have developed because of a pelvic and abdominal neoplasm compressing the left ureter. It was complicated with the ureterohydronephrosis on the left side. The accompanying diagnosis was Costello syndrome. The patient was transferred from a multidisciplinary hospital for left ureter stenting as part of preoperative preparation.

Anamnesis vitae. The child from the fourth pregnancy, which was without complications, second childbirth at 37 weeks (1 — medical abortion; 2 — healthy premature boy 3700 g, 53 cm, then he was a healthy child, 3 — missed abortion at 8/9 weeks). No fetal pathology was detected by prenatal testing. The birth weight was 4750 g (7^{th}-centile corridor (c.c.), Z-score — 2.55). The birth length was 54 cm (7^{th} c.c., Z-score — 2.17). An Apgar score was 7/8 points. The child's parents were healthy; they did not have any chronic somatic or diagnosed hereditary diseases. The marriage was unrelated.

A pseudobulbar syndrome and motor disorders were diagnosed in the early neonatal period. Multiple small developmental anomalies (keel-shaped deformation of the chest, macrocephaly, wide nose bridge, face with a large mouth, thick lips, skin folds, large forehead) were revealed.

On the examination, there was a disproportionate enlargement of hands and feet to the extremities. A right clavicle fracture, early neonatal hypoglycemia, and hepatosplenomegaly were diagnosed.

On the 2^{nd} day of life, a hyperbilirubinemia 249 μmol/L was detected (the direct fraction was 238 μmol/L); a differential diagnosis was made with mucopolysaccharidosis and Sotos syndrome (subsequently excluded). At the age of 1 month, a routine neurosonography revealed triventriculodilatation, enlargement of subarachnoid spaces, hypogenesis of the corpus callosum, hypoplasia of the cerebellar vermis, and enlargement of the cisterna magna.

The breastfeeding was until 2 months and then due to weakness of sucking and swallowing reflexes he was transferred to tube feeding. Then, pronounced psychomotor development delays were found. The child walks with help since 2 years of age. He had a delayed psycho-verbal development. He cannot be sitting or standing independently.

In the view of the suspicion of genetic disease, karyotyping and HRAS gene sequencing were performed. A karyotype 46XY and a partial *de novo* missense mutation in codon 12c.35G>A (*p.Gly12Ala*) in heterozygous state was detected. Thus, Costello syndrome was diagnosed.

During the first year he grew 3 cm (57 cm — 1 c.c., Z-score — –7.87), weight gain was 1.5 kg (6.25 kg, 1 c.c., Z-score — –3.82). A nocturnal alimentation via nasogastric tube was performed

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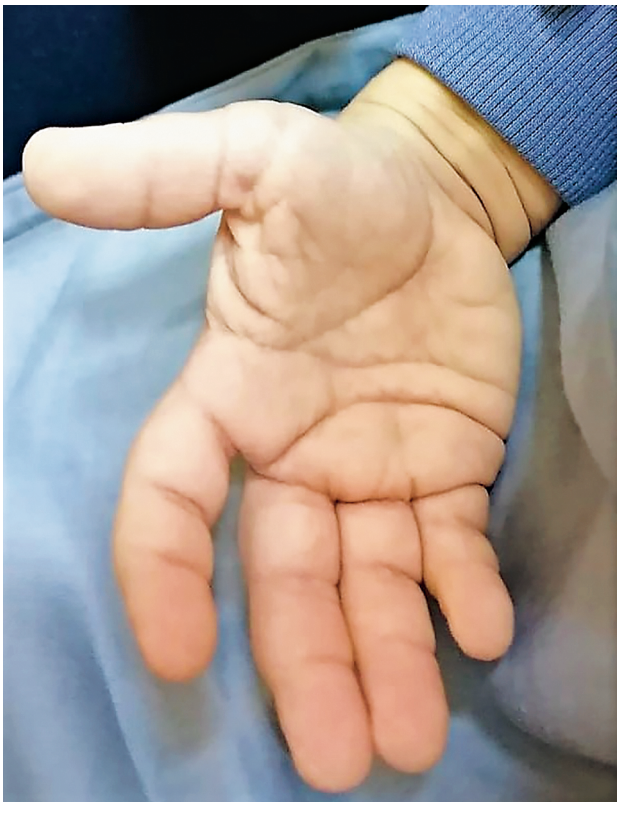


Fig. 1. Patient's palms (own observation)
Рис. 1. Ладони пациента (собственное наблюдение)

until 1.5 years of age on the recommendation of a nutritionist.

The allergoanamnesis is not aggravated. A prophylactic vaccination before the debut of the disease according to an individual calendar was with a delay. Past diseases: upper respiratory tract infections. Traumas were not noted. The main disease is not observed by a geneticist.

Anamnesis morbi

At the age of 3 years 11 months, the mother independently noticed a mass in the lower part of the abdomen, and because of that the child was taken to a children's specialized multidisciplinary hospital by an ambulance. During ultrasound examination of the abdominal cavity, kidneys and urinary tract organs (03.01.2018): a formation in the pelvis, pyelectasis on the left, enlargement of the ureter on the left were detected. In this way, the child underwent multispiral computed tomography of the abdominal cavity, retroperitoneum and pelvis. The results revealed a CT picture of space-occupying lesion with possible invasion of *m. psoas* on the left, pronounced volumetric impact, signs of hydronephrosis on the left against the background of compression of the left ureter. On 05.01.2019 laboratory determined the increase in the concentration of neuron-specific enolase (NSE) — 39.8 mcg/l (normal level is less than 18.3 mcg/l). The excretion of catecholamine metabolites in the urine on 05.01.2019 — the result was normal. On 09.01.2019, for the purpose of differential diagnosis, an incisional biopsy of pelvic mass, bone marrow aspiration from 4 points, bone marrow trepanobiopsy from 2 points were performed. Pathomorphologically, the embryonal rhabdomyosarcoma of the bladder was diagnosed. There were no pathologic changes in the bone marrow. In the view of the compression of the left ureter, its stenting was recommended. In January 2019, the child was admitted to the surgical department of the clinic for ureter stenting on the left.

Objectively on admission: the patient's condition was serious due to the disease, a consciousness was clear, intelligence was decreased, the patient was friendly, willingly made contact. In the neurological picture there were not any focal neurological signs, severe delay in psychomotor and verbal development, nystagmus.

Multiple developmental anomalies of the musculoskeletal apparatus were revealed: deformation of the thorax and limbs, hydrocephalic form of the skull. The subcutaneous fat was sharply reduced; the patient has a muscle hypotonia. A nasal breathing was difficult. Heart tones were rhythmic, loud. The patient had a tendency to constipations. Phenotypic changes of the palms, characteristic for CS patients and shown in the literature, were also noted in the patient (Fig. 1) [14]. Perianal papillomas were detected.

During the preoperative check-up in 2019, the results of ultrasound examination revealed a mass in pelvic and abdominal cavity, the kidney's size was in accordance with the age norm (the right was 73.9×29.1 mm, parenchyma — 11.7 mm, pelvicalyceal system is not dilated; the left kidney — 81.2×33.7 mm, an anteroposterior diameter of the pelvic — 28.2×28.3 mm, parenchyma — 9 mm), dilation of the left ureter in the distal 1/3 was 7.2 mm. NSE values (15.01.2019) were 369.5 ng/mL. On 17.01.2019, surgical ureter stenting on the left was performed. The control ultrasound detected, that the left kidney pelvic was 18×18 mm, parenchyma — 8 mm, the left ureter in the distal 1/3 dilated to 7 mm. Then, the child was transferred to the urological department of the Children's Oncology Center for treatment of oncological disease.

After 9 courses of targeted polychemotherapy, on 24.02.2019, the child underwent radical surgery: laparotomy, cystotomy, bladder tumor removal with resection of the distal 1/3 of the left ureter, ureterocystoneoanastomosis, cystostomy; a biopsy of the subcapsular formation of the left kidney, drainage of the abdominal cavity was done. In the early postoperative period, a course of polychemotherapy (PCT) was started according to the CWS-2009 protocol. The histologic conclusion was: embryonal rhabdomyosarcoma with signs of maturation, post-therapeutic changes, first degree.

On the next hospitalization on 11.09.2019, the removal of the internal ureteral stent on the left was performed. Urodynamic disorders and recurrent urinary tract infections were not detected.

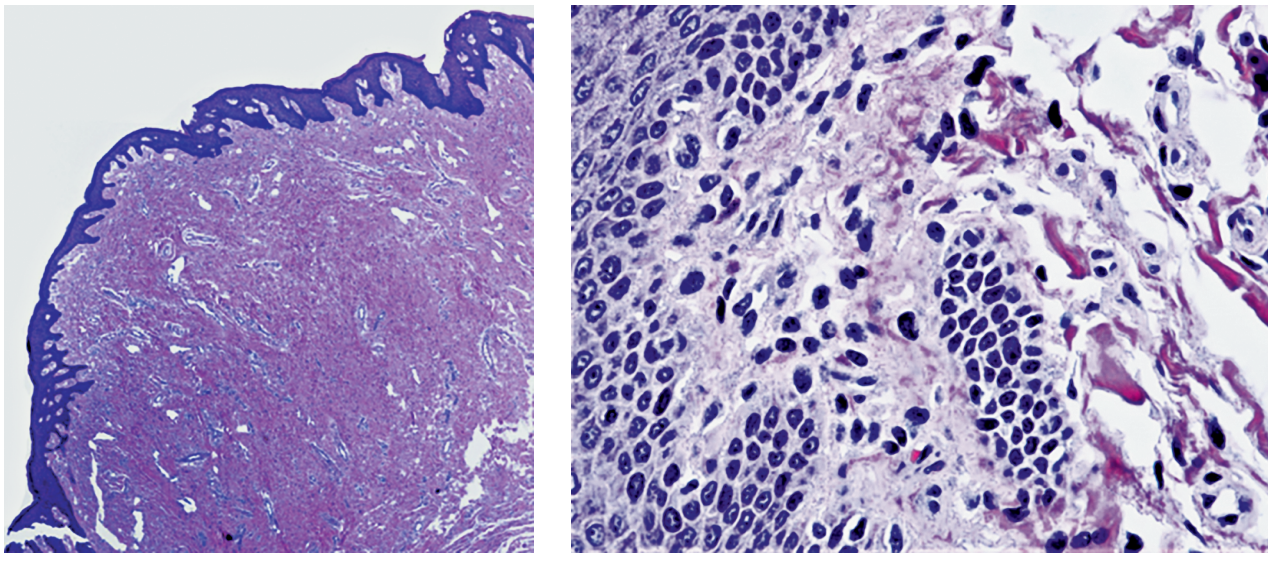
In the period from 17.10.2019 to 26.11.2019, a course of proton radiation therapy was performed on the area of the original tumor and the postoperative pelvic tumor place with a margin for micro-proliferation followed by local boost on the area of residual tissue of the formation.

According to the results of control cystography on 07.06.2020, vesico-uretero reflux (VUR) on the left (III degree) was still presented. Because of that endoscopic treatment of left VUR (endoscopic gel injection of the left ureterovesical junction) was performed on 19.06.2020. According to the results of a control cystography, the left VUR of III degree was detected, the control ultrasound of kidneys and bladder showed a decrease in the size of the left kidney with enlargement of the renal pelvis 19.60×37.9 mm. In this regard, on 23.03.2021, the next endoscopic treatment of left VUR was performed. The laser removal of perianal papillomas was performed (according to the results of histologic study — keratin masses and strata of multilayer squamous epithelium without vacuolar degeneration, with artificial changes without underlying stroma) (Fig. 2).

Immunohistochemical examination for human papillomaviruses did not show expression in the multilayer squamous epithelium. The postoperative period proceeded without complications. There were no signs of acute disturbance of urodynamics at ultrasound control. On 27.10.2021 a control cystography was performed: VRU of III degree on the left side was revealed. An endoscopic treatment of the left VRU was repeatedly performed.

At age of 5 years, his height was 71 cm (Z-score — -8.55), weight — 7.9 kg (Z-score — –5.63), BMI — 15.7 (27.4th percentile).

On 25.11.2021 MRI of abdominal cavity organs, retroperitoneal organs with contrasting was performed to determine further tactics: the condition after surgical treatment of embryonal radbomyosarcoma of the bladder, PCT was noted without significant dynamics, no active accumulation of contrast agent. The interpretation of changes in the left kidney was the same. The deformation of the bladder was detected.



А/A В/Б

Fig. 2: Histologic study of skin biopsy: A — magnification ×40; B — magnification ×400. Hematoxylin and eosin staining

Рис. 2. Гистологическое исследование биоптата кожи: А — увеличение ×40; Б — увеличение ×400. Окраска гематоксилином и эозином

The patient was re-examined by nutritionists and pediatricians during routine hospitalization at the age of 7 years. Body weight was 16 kg (1 c.c.). Objectively, there were also signs of severe malnutrition (sharp decrease in the development of the subcutaneous fat, decreased tissue turgor), multiple developmental anomalies, limb deformities, dysmorphic facial features, changes in palms, soles of feet and fingers with hyperkeratosis.

During the hospitalizations, no abnormalities were detected according to the data of control electrocardiographic and echocardiographic studies.

On 01.11.2022, the micturition cystography revealed VRU of III-IV degree on the left, rounded bladder with smooth contours. According to the results of ultrasound of kidneys and bladder, there were nephrosclerosis of the left kidney (57.1×26.9 mm), thinning of parenchyma — 9.3 mm; the right kidney has a normal size.

During dynamic renal scintigraphy (RSG): morphologicaly the parenchyma of the right kidney had a normal function, the left kidney had not any function activity. According to MRI of the abdominal cavity and retroperitoneum performed in November 2022, the left kidney was reduced (27×27×59 mm), represented by multicystic structures, the contours are uneven, corticomedullar differentiation was not traced, the left renal pelvis was moderately dilated, the ureter had a different diameter, multiple small cystic inclusions ~1–3 mm in diameter were traced in the distal part of the ureter wall. No zones of active pathologic accumulation were noted during contrasting. Lymph nodes were visualized in the pararenal space on the left side with the size 3.5 mm. In the retroperitoneal space on the left, paravertebrally at the level of Th XI-L I, there are nodular areas along the course of renal vessels on the left with clear contours, shape and size ~22×10×44 mm, which enveloped the renal vessels in a "muff-like" way. No evidence for restriction of diffusion was obtained. After contrast agent injection no zones of active accumulation in the foci were noted. The bladder was deformed in the bottom area, pulled to the left in the projection of the deformed left ureter, no zones of pathologic contrasting were noted. The right kidney was located normally, its size was ~42×42×80 mm, corticomedullar differentiation was not disturbed. The kidney contours were smooth. There was no evidence of the right kidney pelvicalyceal system enlargement. The pararenal space was not compacted. The adrenal glands were traced on both sides. Their shape and size were preserved. No pathologic formations in their structure were revealed.

DISCUSSION

This article presents a rare case of long-term observation of Costello syndrome caused by partial *de novo* missense mutation in codon 12 c.35G>A (*p.Gly12Ala*). The leading phenotypic manifestations of the syndrome were mental retardation, delayed psychomotor development, biphasic growth (large fetal size for gestational age followed by postnatal reduction of development), pronounced malnutrition with dysphagia, macrocephaly, development of neoplasms, dysmorphic signs on the face, typical skin signs and papillomas. Child's physical and neuropsychiatric development was delayed.

The CS of p.G12A phenotype is the second most common missense mutation with a high malignancy rate [12]. In the case, the patient had embryonal rhabdomyosarcoma of the bladder in the period of the second childhood. Surgical treatment of oncologic disease with partial resection of the left ureter and anastomosis resulted in the vesicoureteral reflux of III-IV degree, which was resistant to surgical treatment, with subsequent nephrosclerosis and multicystic transformation of the left kidney. Early oncologic disease may indicate the degree of HRAS proto-oncogene activity.

In addition to malignant neoplasms, the patient was also found to have benign papillomas unrelated to human papillomavirus, which is the result of a mutation in the HRAS proto-oncogene [17, 33, 47]. Their features were perianal localization (rarer than nasal papillomas) and later manifestation — at the age of 4 years (previously encountered from birth to 2–3 years) [8].

The long-term survival of the patient was due to normalization of nutrition and elemination of the malnutrition. A dysphagia in the structure of pseudobulbar syndrome was noted early. It required not only transfer to artificial feeding, but also the use of a nocturnal alimentation regimen. At the age of 4-5 years, the clinical picture of dysphagia regressed, which allowed to normalize an enteral nutrition.

CONCLUSION

The case report of a 4-year follow-up of Costello syndrome of the boy with embryonal rhabdomyosarcoma of the bladder shows the need for

caution in cancer in children with diagnosed CS. The lack of reliable criteria for prenatal ultrasound diagnosis determines the difficulties in making the diagnosis before birth. An elimination of malnutrition, which develops in children with CS and associated with pathology both digestive and nervous systems, is an important therapeutic goal.

ADDITIONAL INFORMATION

Author contribution. Thereby, 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, fi nal approval of the version to be published and agree to be accountable for all aspects of the study.

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

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Informed consent. The informed consent on publication of patient's data from patient's parents was not received. All the provided information in this article is impersonal, any identifying information has been deleted.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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