Case Report

Tuberous Sclerosis Complex in a 7-Year-Old Child

Complejo de esclerosis tuberosa en una niña de siete años

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ABSTRACT

Introduction: Tuberous sclerosis complex is a genetically determined orphan disease that has a progressive course and leads to irreversible morphological changes in various organs and systems due to the formation of multiple benign tumors (hamartomas), including the brain, eyes, skin, heart, kidneys, liver, lungs, gastrointestinal tract, endocrine and skeletal systems.

Objective: To present the clinical course and treatment of tuberous sclerosis in a 7-year-old child.

Case Report: A girl born in 2018 from the 3rd pregnancy with a birth weight of 3500 g. At the age of 11 days, she was transferred to the neonatal pathology department with a diagnosis of: Space-occupying lesion of the brain. Venous sinus thrombosis. At the age of 1 month, during a magnetic resonance imaging: signs of tuberous sclerosis. Based on the results of the genetic examination, a variant of the nucleotide sequence of exon 6 of the TSC2 gene was detected. Sabril was introduced at 1 month 24 days of age. A brain magnetic resonance imaging (MRI) scan at 4 months showed tuberous sclerosis. Everolimus 4 mg/day was introduced at 8 months. MRI scan at 6 years showed tuberous sclerosis with numerous tubercles and white matter changes along the migration pathways of the cerebral hemispheres, including a small tuber in the left cerebellar hemisphere.

Conclusions: The above clinical case of tuberous sclerosis makes it possible to focus the attention of doctors of various specialties on the features of the clinic, diagnosis and treatment of this pathology.

Keywords: children; tuberous sclerosis complex; hamartoma.

RESUMEN

Introducción: El complejo de esclerosis tuberosa es una enfermedad rara, genéticamente determinada, que presenta un curso progresivo y provoca cambios morfológicos irreversibles en diversos órganos y sistemas debido a la formación de múltiples tumores benignos (hamartomas), incluyendo en el cerebro, los ojos, la piel, el corazón, los riñones, el hígado, los pulmones, el tracto gastrointestinal, el sistemas endocrino y esquelético.

Objetivo: Presentar la evolución clínica y el tratamiento de la esclerosis tuberosa en una niña de siete años.

Presentación del caso: Niña nacida en 2018, fruto del tercer embarazo de su madre, con un peso al nacer de 3500 g. A los 11 días de vida fue trasladada al Departamento de Patología Neonatal con diagnóstico de lesión cerebral ocupante de espacio. Trombosis de senos venosos. Al mes de edad se observaron signos de esclerosis tuberosa en una resonancia magnética. Según los resultados del examen genético, se detectó una variante de la secuencia de nucleótidos del exón 6 del gen TSC2. Se inició el tratamiento con Sabril al mes y 24 días de edad. Una resonancia magnética cerebral realizada a los cuatro meses reveló esclerosis tuberosa. A los ocho meses se inició el tratamiento con everolimus (4 mg/día). Una resonancia magnética realizada a los seis años mostró esclerosis tuberosa con numerosos tubérculos y alteraciones de la sustancia blanca a lo largo de las vías de migración de los hemisferios cerebrales, incluyendo un pequeño tubérculo en el hemisferio cerebeloso izquierdo.

Conclusiones: El caso clínico de esclerosis tuberosa presentado permite concentrar la atención de los médicos de diversas especialidades en las características clínicas, el diagnóstico y el tratamiento de esta enfermedad.

Palabras clave: niños; complejo de esclerosis tuberosa, hamartoma.

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Introduction

Tuberous sclerosis complex (TSC) is a genetically determined disease from the group of neurocutaneous, with a wide range of clinical manifestations, accompanied by the development of multiple benign tumors (hamartomas) in various organs, including the brain, eyes, skin, heart, kidneys, liver, lungs, gastrointestinal tract, endocrine and skeletal systems. The incidence of tuberous sclerosis among newborns varies from 1:6000 to 1:10000, inherited in an autosomal dominant type.

The polysystemic nature of the disorders suggests a diverse clinical picture of TSC, which varies significantly depending on age at onset, severity, and rate of progression. Currently, the TSC clinic distinguishes the main (large, primary) and additional (small, secondary) signs. The main signs include convulsive paroxysms, skin lesions, impaired intelligence, and the presence of tumor-like formations in various organs.[1,2]

The diagnosis of TSC is based on clinical criteria, with genetic testing providing confirmatory support by identifying a pathogenic mutation in TSC1 or TSC2.[3] The role of these genes is to regulate cell growth through the phosphatidylinositol-3 kinase signaling pathway, which inhibits the mammalian target rapamycin (mTOR). The gamartin/tuberin complex is an important inhibitor of tumor growth. These proteins inhibit the activity of the mTOR signaling pathway responsible for cell proliferation and inhibition of cellular apoptosis. In patients with TSC, changes in these proteins lead to constant activation of the mTOR signaling pathway and, consequently, to the formation of hamartomas in various organs. Despite the fact that hamartomas are benign in nature, gradually increasing in size, they disrupt the functions of organs, which leads to the development of life-threatening conditions, disability and shortening of life. Treatment for TSC was unavailable until 2012, and before that, only symptomatic therapy was used. In 2012, the drug everolimus, an inhibitor of proliferative signal transmission, was registered. The drug has an effect on reducing the growth of tumors in the central nervous system and in the kidneys.[4]

The objective of this article is to present the clinical course and treatment of tuberous sclerosis complex in a 6-year-old child.

Case Report

Patient E., born in 2018. A girl from third pregnancies, delivered at 38 weeks by cesarean section. Body weight at birth is 3500 g., body length is 51 cm. The Apgar score is 1/2/3 points. Neonatal seizures on the first day of life. At the age of 11 days of life, she was transferred to the Moscow Regional Perinatal Center, a state budgetary healthcare institution in the Department of Pathology of Newborns and Premature Infants, Balashikha, with a diagnosis of bulky brain formation. Magnetic resonance imaging (MRI) of the brain at 14 days showed extensive accumulation of protein substrate (blood?) along the transverse venous sinuses on both sides.

MRI of the brain at 1 month 10 days - tuberous sclerosis with the presence of a large number of immature heterotopions in the cortical and subcortical tubers, the presence of subependymal heterotopions, giant cell astrocytoma in the area of both foramina of Monro. At the age of 1.5 months, video monitoring of the electroencephalogram (EEG) – epileptiform activity independently in the occipital

regions during sleep. Vigabatrin 500 mg/day was introduced into therapy. Hypopigmentation spots appeared from the age of two months.

In two months, a genetic examination was conducted at the N. P. Bochkov Medical and Genetic Research Center in Moscow. A variant of the nucleotide sequence of exon 6 of the TSC2 gene was identified, which confirms the diagnosis of TSC.

Regional epileptiform activity was recorded on EEG at 3 months. In therapy, the dose of Vigabatrin was increased to 1000 mg/day.

At four months of age, an ultrasound examination of the abdominal organs and kidneys was performed at the Veltischev Moscow Research Institute of Pediatrics and Pediatric Surgery. An enlarged gallbladder and its abnormal shape were revealed. Diffuse changes in the pancreas. Kidney changes characteristic of TSC.

On an MRI scan of the brain: a picture of TS with the presence of calcified cortical and subcortical tubers, calcified subependymal nodes, and changes in white matter. A clinical diagnosis was made: TS (multiple calcified cortical and subcortical tubers in the cerebral hemispheres). Vigabatrin 1500 mg/day is prescribed for therapy.

At 8 months, the EEG revealed epileptiform activity in the waking state and the appearance of new regional discharges during sleep, and therefore therapy was adjusted: Vigabatrin 1500 mg/day, Levetiracetam 600 mg/day. From 8 months of age, the drug Everolimus is prescribed at a dose of 4 mg/day.

An ultrasound examination of the abdominal cavity and kidneys at 1 year 3 months revealed echo signs of reactive changes in the liver and pancreas. Splenomegaly. Diffuse changes in the renal parenchyma characteristic of tuberous sclerosis. Multiple angiomyolipomas and kidney cysts were found. MRI of the brain at 1 year 3 months: picture of Tourette syndrome with the presence of calcified cortical and subcortical tubercles, calcified subependymal nodes, and changes in white matter. Formations near the Monro holes (astrocytomas) on the right and left, large sizes on the right. In relation to brain atrophy, compared to the study at 4 months 10 days, a moderate positive trend is observed: a decrease in the volume of the astrocytoma on the right (Fig. 1).

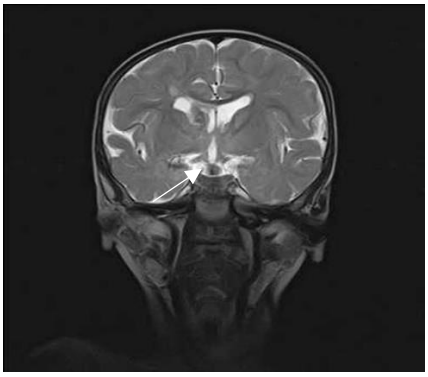

Fig. 1 - MRI of the brain at 1 year 3 months.

At the age of 3 years 10 months she was examined by a neurologist-epileptologist, clinical diagnosis: TS. Sub-perpendicular giant-cell astrocytomas of the lateral ventricles of the brain. Multiple angiomyolipomas of the kidneys, few kidney cysts. Structural focal epilepsy. Delayed speech development. Autism spectrum disorder. Bilateral sensorineural hearing loss 2 art. Vigabatrin 3000 mg per day, Levetiracetam 800 mg per day, Everolimus at a dose of 4 mg per day.

At the age of 4 she was examined by a neurosurgeon, but surgical treatment was not indicated. At the age of 5, she was examined by a psychiatrist. Disinhibited, restless, unable to sit still. Emotionally unstable. Eye contact is uncertain. Speech is absent, mainly sound complexes.

MRI of the brain at 6 years old: a picture of TS with the presence of numerous tubers and changes in the white matter of the major hemispheres along the migration pathways, a small tuber in the left hemisphere of the cerebellum, multiple subependymal hamartomas along the walls of the lateral ventricles, as well as giant cell astrocytoma in the area of the right foramen magnum and small nodular formations in the area of the left foramen magnum (Fig. 2).

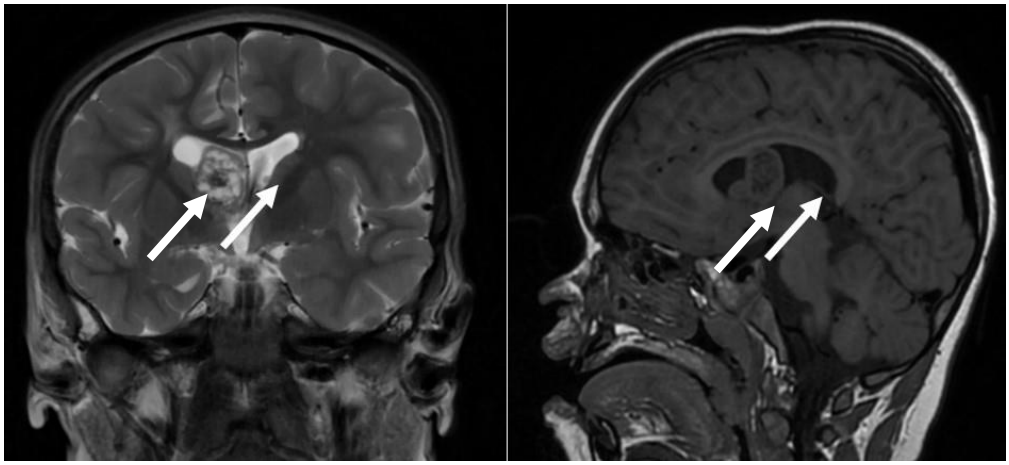

Fig. 2 - MRI scan of the brain at 6 years old.

Ultrasound examination of the abdomen and kidneys at 7 years old: in the parenchyma of both kidneys: Multiple angiomyolipomas on the right up to 0.9 x 0.35 cm, on the left up to 0.6 x 0.2 cm, Single cysts measuring 0.4 cm. Therapy is in the same volume; dynamic monitoring is underway (Fig. 3).

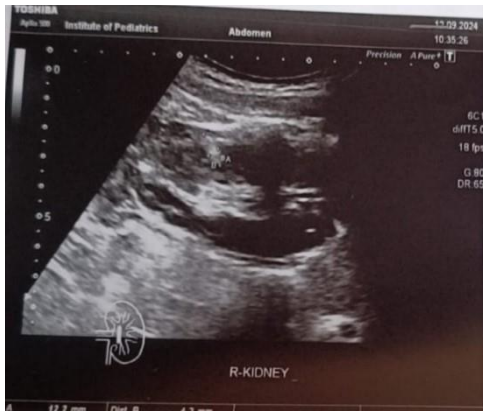

Fig. 3 - Ultrasound of the kidneys at 7 years old.

Discussion

The manifestations of TSC vary significantly and depend on many factors, such as the number, location and size of hamartomas, the clinical picture differs in different age periods, starting from the intrauterine period of development from the 20th week, which creates difficulties in timely diagnosis of the disease. Many patients with TSC do not have a full set of typical clinical symptoms, and in such cases the diagnosis is confirmed by genetic studies, pathological mutations in which are identified in 80% of patients.(5)

The clinical case presented in this paper demonstrates the importance of early diagnosis and timely treatment of TSC in children. In children at risk for the development of TSC, a high-quality diagnostic search, comprehensive echocardiography, neurosonography, ultrasound examination of internal organs, kidneys, eyes, and MRI of the brain should be performed.(6)

Everolimus is an inhibitor for mTORC1 and is currently used to treat TSC for its main role in rapidly reducing subependymal giant cell astrocytoma volume and seizure burden, although mainly studied in the adult population. Recent literature data indicate, that 42% of patients taking everolimus experienced at least a 50% reduction in renal angiomyolipoma size compared with 0% in the placebo group. Banerjee S. et al. (2024) found similar results in their study. All three patients were also found to have an improvement in kidney function, normalization of creatinine levels, and improvement in their eGFR after everolimus therapy. These findings support the positive implications of everolimus on cystic kidney disease.(7)

In the reported case by Li Y. et al (2023), the patient presented with symmetrical, reddish, firm, and waxy papules that protruded from the skin surface and ranged in size from needle-shaped to horse-bean-shaped on both cheeks. There were two hypopigmented macules (approximately 4 cm long) on the patient's left arm and

back. In addition, the patient's cranial computed tomography (CT) scan showed insular and subependymal calcifications, while cranial MRI showed cortical tubers, senile endothelial neoplasia, and white myelomas. By CT, the authors observed multifocal micronodular pulmonary histiocytosis and multiple renal cysts. The results of whole exome genetic testing revealed that the patient has a copy number variation with a deletion of a fragment of approximately 27 kb in the 16p13.3 region, indicating a pathogenic mutation. Notably, the TSC2 gene, associated with TSC type 2, was localized in this region, further confirming the diagnosis of TSC.[8]

The life expectancy of patients with TSC depends on the nature of the manifestations and the rate of their progression. In some cases, only symptomatic therapy is performed, without the need for surgical intervention. The average life expectancy in patients with TSC is approximately 25 years.[9,10,11]

Conclusions

Given the diversity of clinical manifestations of tuberous sclerosis, physicians of virtually all specialties must monitor patients throughout their lives. It is important for specialists to be aware of the nature and characteristics of the course of this disease.

TSC is a rare disease characterized by a variety of clinical manifestations from different organs and systems. Early administration of everolimus may improve the prognosis of the disease. The low incidence of TS in the population and severe disability give this problem exceptional relevance.

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Conflict of interest

The authors stated that there was no conflict of interest.