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Clinical Characteristics of Tuberous Sclerosis in Children

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ABSTRACT

This article is devoted to the question of rare hereditary disease from the phakomatoses group with autosomal dominant type of inheritance. It's Bourneville- Pringle`s disease. There are discussed the questions of this pathology prevalence, variable clinical picture, modern diagnosing procedure. The results of examination of children with tuberous sclerosis are presented.

Keywords: Bourneville-Pringle's disease, tuberous sclerosis, clinical manifestations.

INTRODUCTION

Bourneville-Pringle's disease (synonym: tuberous sclerosis, epiloyya, central neyronomatoz, neurocutaneous syndrome type of Bourneville, syndrome seborrheic adenoma, seizures and mental retardation) - a hereditary disease characterized by systemic lesions of visceral organs, bones, eyes, skin, nervous system (for by disrupting the proliferation, migration and differentiation of glial cells), pathologic substrate which is hamartomatous proliferation of various localization [1]. Frequency of pathologies in newborns varies from 1:6000 to 1:10000, among the adult population is 1:20,000 - 1:100,000 .

Disease affects all races, men and women are equally likely to get sick. Type of inheritance - autosomal dominant, with more than 75 % of cases are caused by new mutations, variable expressivity, incomplete penetrance gene. At the genetic level the disease is caused by mutations inactivating one of the genes TSC1 (34 - th portion of the long arm of chromosome 9 - 1/ 3 of the cases), or TSC2 (13th portion of the short arm of chromosome 16 - 2/ 3 of the cases) encoding hamartin protein synthesis (130kD) and tuberin (180kD), respectively. Hamartin - tuberin complex plays a key role in regulating of cell growth [6 - 9, 12].

Normally, TSC1 and TSC2 - natural genes tumor suppressors, their damage activates the signal transmission R13K/Akt/mTOR that underlies the pathogenesis of TS. MTOR inhibitors - pathogenetic basis targeted systemic therapy of TS [3, 10]. In 1999 E.S. Roach proposed diagnostic criteria for TS [11] (Table 1)

Table 1

Diagnostic criteria of tuberous sclerosis

Primary signs	Secondary signs
Facial angiofibroma or fibrous plaques on the forehead	Multiple grooves in tooth enamel
Nontraumatic periungual fibroma	Hamartomatous rectal polyps *
Hypopigmented spots (>3)	Bone cysts **
Area of "shagreen skin"	Migration paths in the white matter of the brain
Multiple hamartomas of the retina	Fibroids gums
Cortical tuber	Hamartomas of visceral organs
Subependymal nodes	Achromatic portion of the retina
Giant cell astrocytoma	Hypopigmented spots "confetti" on the skin
Cardiac rhabdomyomas multiple and single	Multiple renal cysts **
lungs Lymphangioleiomyomatosis	
Multiple renal angiomyolipoma	

Notes: * - requires histological confirmation ** - enough radiological confirmation

Criteria for the diagnosis of TS unquestioned - one / two primary and two secondary features. Criteria for the possible diagnosis - one primary and one secondary sign, presumptive diagnosis - one primary or two (or more) of the secondary [11].

The difficulties of diagnosis of tuberose sclerosis (TS) are associated with a marked of clinical polymorphism. Patients with TS are observed by doctors nearly all specialties during the life, so only informed about the nature and characteristics of the course of these diseases, as well as the consistency of their diagnostic and therapeutic measures can ensure the correct choice of tactics of treatment of patients. The clinical course of the disease was isolated 4 forms: classical, psycho-neurological, skin, and liquor. The classical form of the disease is manifested by an adenoma of the sebaceous glands, epilepsy, mental retardation (Vogt`s triad). At the predominance of general and focal neurological symptoms caused by the enlargement of neuroglia of various divisions of the brain, we are talking about neuropsychiatric disease form, with primary skin lesions - dermatological form. When there are symptoms of spinal fluid hypertension - liquor one [4, 8].

Bourneville-Pringle's disease has a tendency to progression. Prognosis in most cases unfavorable and depends on the severity of internal organ involvement. Almost 30% of patients do not survive to 5 years, and patients aged 6 years and over 75% of cases - up to 20 years [5].

All patients with any type of TS, as well as their relatives, especially first-degree relatives, are subject of multidisciplinary dynamic observation and inspection throughout life. Only such an approach can provide adequate therapy and will allow for genetic counseling in families with identified patients with this severe multisystem disease [2].

Purpose of the research: to analyze the clinical features of tuberous sclerosis in children.

MATERIALS AND METHODS

The study included patients with Bourneville-Pringle's disease, who were examined and treated in the Republican hospital №1 - National Center of Medicine, Pediatric center neuropsychiatric department number №1 (head of department Basova E.V.) and №2 (head of department Androsova Z.P.), clinical advisory office (neurologist Nikolaeva G.E.), office of children's epileptologist of City Children's Hospital (neurologist Vyuchin A.V.).

For each patient it is filled developed formalized questionnaire survey, which includes the anamneses of life, disease, somatic and neurological status, the nature and frequency of attacks, data of paraclinical examinations (EEG, MRI of the brain), social data, therapy.

Diagnosis of Bourneville-Pringle's disease is put due to International diagnostic criteria recommended by the International Committee of Experts on the tuberous sclerosis. Magnetic-resonance tomography of the brain is carried out in the Department of radiation diagnostics of Pediatric centre National Center of Medicine.

RESULTS AND DISCUSSION

In the course of the study, for the period 2008 - 2013 years, 7 children were diagnosed with tuberous sclerosis. In all cases of the disease it was male patients. Surveyed children were ranged in age from 8 months to 10 years. At the time of the study 1 child was at the age of 8 months, 1 patient - 2 years, 2 children - 3 years, 1 patient - 5 years, 2 boys - 10 years. Nationality of patients are: 5 children - Yakuts, 1 child - Russian, 1 patient - Uzbek.

Three mothers (43%) of the surveyed children had burdened obstetric and gynecological history: pregnancy proceeded against the background of the constant threat of interruption, chronic nicotine intoxication, toxicity, anemia, chronic pyelonephritis. Heredity, according to parents, was not burdened.

The onset of disease before the age of 1 year was in 5 children, 2 years in 1 child, 3 years in 1 patient. In all cases, the disease began with a seizure attack. At the onset of disease West

syndrome was diagnosed in 3 children, with attacks in the form of infantile spasms, in other cases, the attacks bore the focal character. At the time of the study in 5 (71%) children seizures were in the nature of the focal with secondary generalization, with frequency up to 5 times a day, 2 (29%) children attacks had the focal character, with frequency up to 2 times a day.

The first physician who has treated patients, in all cases was the neurologist. In the neurological status of all children showed symptoms pyramid insufficient: quickened tendon and periosteal reflexes with limbs; increased muscle tone 1 child. In one patient noted common hyperkinesis. All children were diagnosed with symptomatic epilepsy. Delayed psycho-speech development was revealed in 3 children with onset under 1 year.

On examination of the skin in the lumbar region areas of modified skin type «shagreen», and the areas of depigmentation various areas of the body were detected in 3 (43%) of the surveyed (Fig.1), facial angiofibroma (adenoma Pringle) - in 1 patient. When conducting neuroimaging research methods brain subependymal nodes was noted in all the examined children (Fig.2), subependymal giant cell astrocytomas - 1 child. Fundus examination revealed the presence of retinal hamartoma in 1 child (14%). Held other clinical methods of examination (sonography of abdominal organs, Echocardiography, CT chest) possible to diagnose polycystic kidney disease in 2 children, multiple renal cysts in 1 child, multiple rhabdomyomas heart in 2 children, lymphangioleiomyomatosis lungs in 1 child.

The children received symptomatic therapy. Treatment of epilepsy was conducted with anticonvulsant valproate monotherapy in 5 children, valproate polytherapy + oxcarbazepine in 1 child, valproate+topiramate + in 1 patient.

CONCLUSIONS

The Bourneville-Pringle's disease despite the low incidence of it has a severe course, a high percentage of disability and poorly amenable to correction. Timely diagnosis allows determining the future management of patients, and providing genetic counseling to family members, which should help reduce the incidence of this disease. To improve the diagnosis of tuberous sclerosis all doctors need to pay attention when inspecting children on cutaneous manifestations of the disease. There is also a need for the introduction of molecular genetic analysis to confirm the diagnosis and to prenatal diagnosis of the disease Bourneville-Pringle in Yakutia.

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Figure 1. Cutaneous manifestations of the Bourneville-Pringle's disease

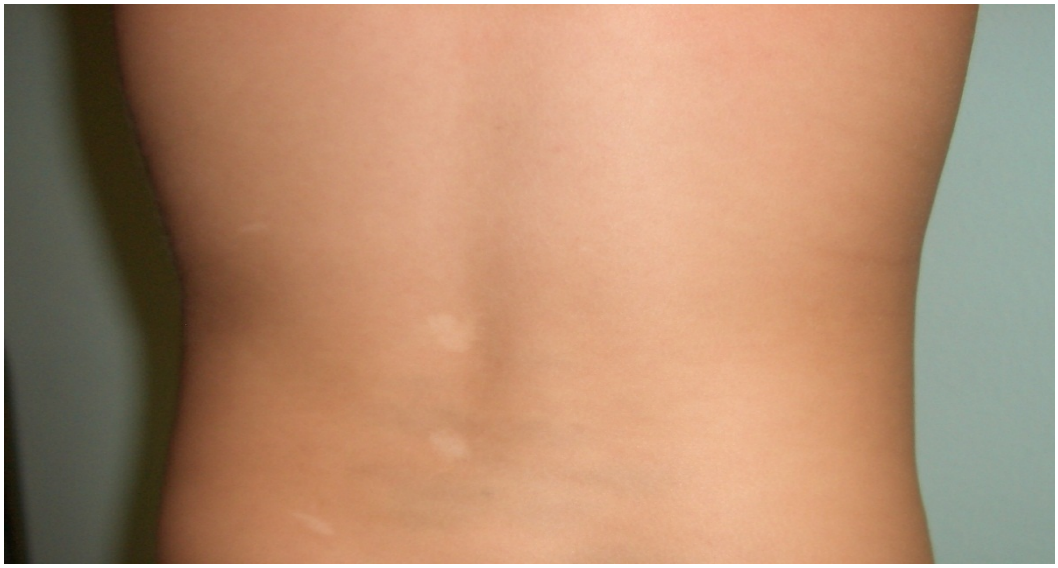
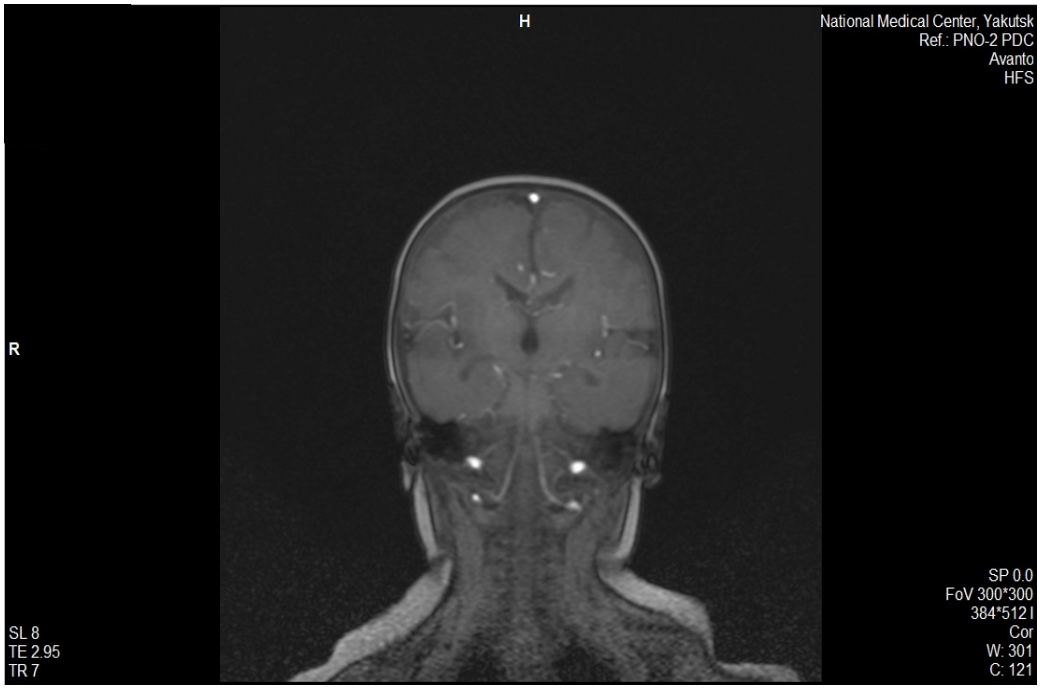
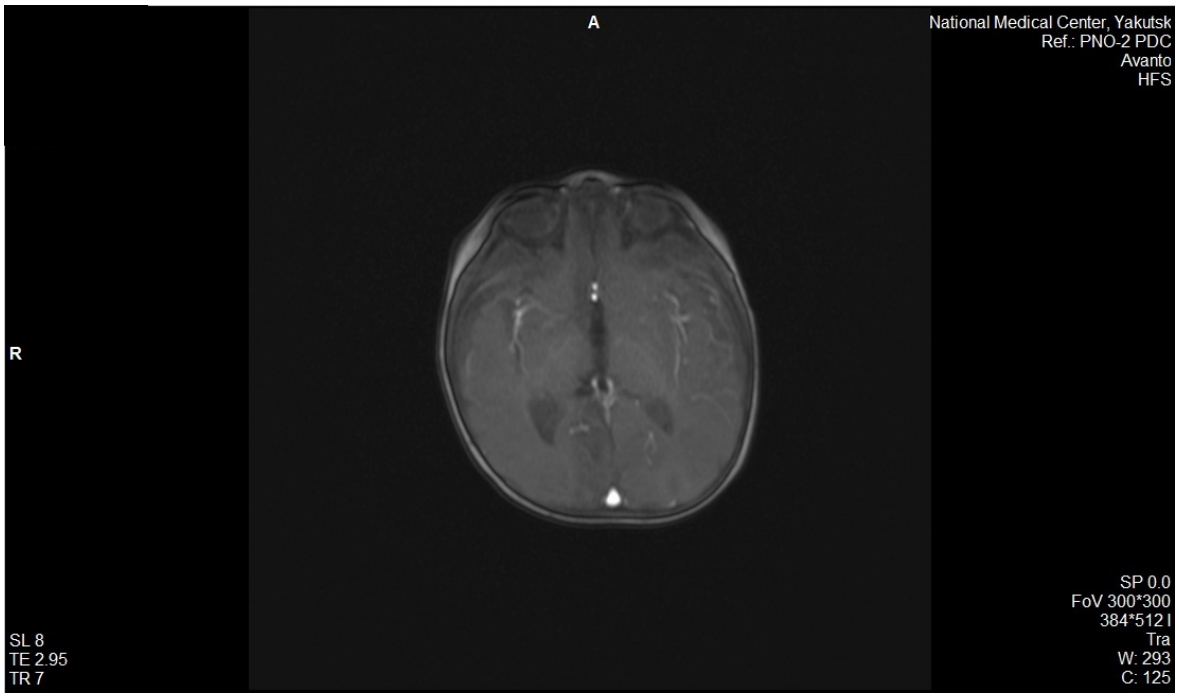


Figure 2. MRI data of patients with tuberous sclerosis.

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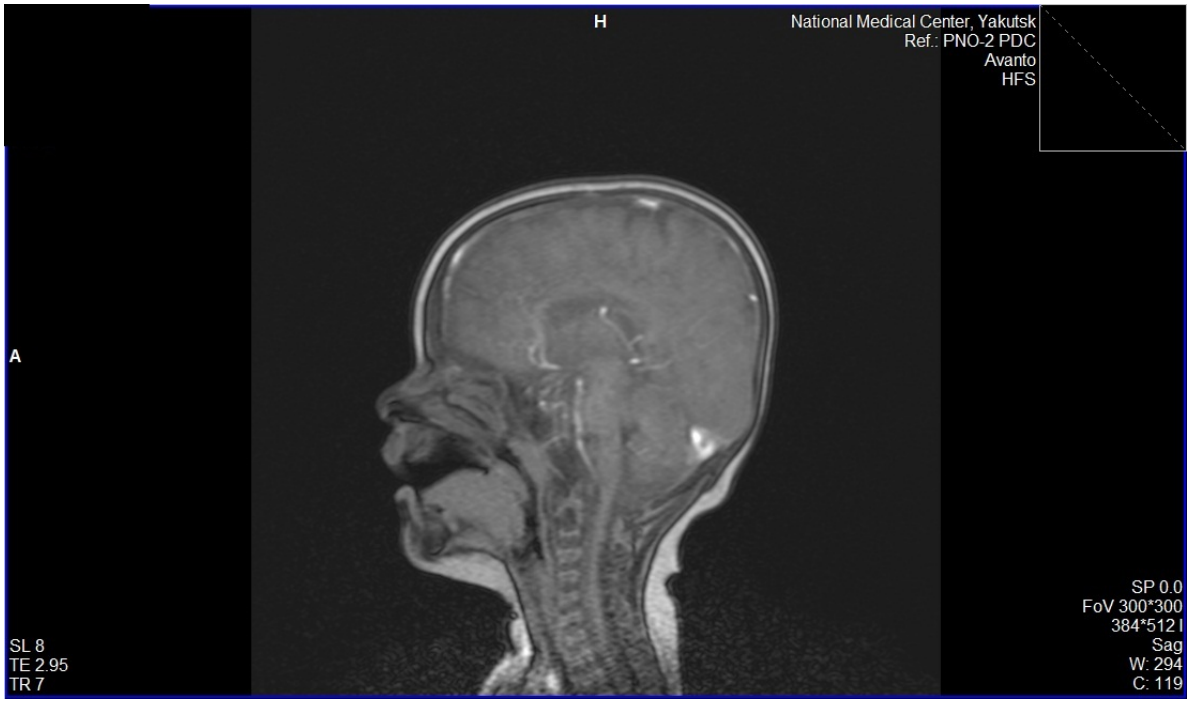
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