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КЛИНИКО-ЭПИДЕМИОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ТУБЕРОЗНОГО СКЛЕРОЗА В РЕСПУБЛИКЕ БАШКОРТОСТАН

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Clinical and Epidemiological Characteristics of Tuberous Sclerosis in The Republic of Bashkortostan

Резюме

Актуальность. Туберозный склероз (ТС) — это наследственный опухолевый синдром с аутосомно-доминантным типом наследования, встречающийся с частотой 1:6000 — 10000 новорожденных в мире. Болезнь характеризуется тяжелыми клиническими проявлениями в виде астроцитом головного мозга, рабдомиом сердца, ангиомиолипом почек, лимфангиолеомиоматоза легких и ангиофибром кожи. Поскольку для лечения болезни разработан эффективный метод лечения ингибиторами mTOR, актуально своевременное выявление пациентов с ТС. **Цель исследования.** Определение клинико-эпидемиологических особенностей ТС в Республике Башкортостан. Материалы и методы. Проведен ретроспективный анализ данных и исследование пациентов ТС в Республике Башкортостан. **Результаты.** В Республике Башкортостан зарегистрировано 86 пациентов ТС из 82 семей, частота встречаемости составила 1:47048 человек. Средний возраст пациентов составил 18,5 лет (от 1 года до 61 лет). Характерные для ТС пятна депигментации определены у 90 % пациентов, ангиофибромы лица — у 56 %, фиброзные бляшки головы — у 33 %, шагреневые бляшки — у 36 %, субэпендимальные узлы головного мозга — у 66 %, субэпендимальная гигантоклеточная астроцитома — у 19 %, ангиомиолипомы почек — у 43 %, лимфангиомиоматоз легких — у 1,2 %. Когнитивный дефицит выявлен у 47 %, эпилепсия — у 67 %, аутизм — у 1 % пациентов ТС. **Обсуждение.** Сравнительный анализ особенностей клинических проявлений ТС у пациентов из Республики Башкортостан с мировыми данными показал значимо более редкое выявление ангиофибром лица, опухолей легких, почек и головного мозга, когнитивных нарушений и аутизма. В Республике Башкортостан 8 пациентов с идентифицированными мутациями в генах TSC1/TSC2 получают лечение ингибитором mTOR. **Заключение**. Полученные результаты свидетельствуют о низкой частоте зарегистрированных случаев ТС в республике по сравнению с мировыми данными, в связи с чем необходимо ознакомление врачей всех специальностей о необходимости направления пациентов с симптомами, характерными для ТС, на медико-генетическую консультацию. Для достоверного выявления опухолей головного мозга и внутренних органов необходимы инструментальные исследования в динамике, оценка психологических нарушений у пациентов ТС с консультацией психотерапевтов, неврологов и психологов.

Ключевые слова: *ангиомиолипомы почек, астроцитомы, ген TSC1, ген TSC2, лимфангиолеомиоматоза легких, пятна депигментации, рабдомиомы сердца, туберозный склероз, частота встречаемости.*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Relevance. Tuberous sclerosis (TS) is a hereditary tumor syndrome with autosomal dominant type of inheritance, occurring with frequency of 1:6000 — 10000 newborns worldwide. The disease is characterized by severe clinical manifestations in the form of astrocytomas of the brain, rhabdomyomas of the heart, angiomyolipomas of the kidneys, pulmonary lymphangioleomyomatosis and angiofibromas of the skin. Since effective treatment with mTOR inhibitors has been developed for TS, timely detection of patients with TS is important. **The aim of the study.** To determine the frequency and clinical features of TS in the Republic of Bashkortostan to improve organizational and therapeutic and diagnostic approaches in providing medical care to patients with TS. **Material and methods.** Determination of clinical and epidemiological features of TS in the Republic of Bashkortostan. **Results.** In the Republic of Bashkortostan, 86 patients with TS from 82 families were registered, the frequency of occurrence was 1:47048 people. The average age of patients was 18.5 years (from 1 year to 61 years). Depigmentation spots were found in 90 % of patients, facial angiofibromas in 56 %, head fibrous plaques in 33 %, shagreen plaques in 36 %, subependymal nodules of the brain in 66 %, and subependymal giant cell astrocytoma in 19 %, renal angiomyolipomas in 43 %, pulmonary lymphangioleiomyomatosis in 1.2 % of patients. Cognitive deficit was found in 47 %, epilepsy in 67 %, and autism in 1 % of patients with TS. **Discussion.** Comparative analysis of TS clinical manifestations in patients from the Republic of Bashkortostan with global data showed a significantly lower incidence of facial angiofibromas, lungs, kidneys and brain tumors, cognitive impairment and autism. 8 patients with identified mutations in the TSC1/TSC2 genes are treated with an mTOR inhibitor. **Conclusion**. The obtained results indicate a low frequency of registered cases of TS in the republic compared to world data. Therefore it is necessary to familiarize doctors of all specialties with the need to refer patients with symptoms characteristic of TS for medical genetic consultation. For reliable detection of tumors of the brain and internal organs, dynamic instrumental studies are necessary; assessment of psychological disorders in TS patients is necessary with consultation of psychotherapists, neurologists and psychologists.

Key words: *renal angiomyolipomas, astrocytomas, TSC1 gene, TSC2 gene, pulmonary lymphangioleomyomatosis, depigmentation spots, cardiac rhabdomyomas, tuberous sclerosis, frequency of occurrence*

Conflict of interests

The authors state that this work, its theme, subject and content do not affect competing interests

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Conformity with the principles of ethics

The study was approved by the local ethics committee of UFRC RAS (protocol no. 5 dated December 7, 2009)

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RB — Republic of Bashkortostan, PLAM — pulmonary lymphangioleiomyomatosis, MGSC — Medical Genetics Scientific Center, RMGC — Republican Medical Genetics Center, SEGA — subependymal giant-cell astrocytoma, SEN — subependymal node, TS — tuberous sclerosis.

Introduction

Tuberous sclerosis (TS) is an autosomal dominant multisystemic disease [1] from the group of hereditary neoplastic syndromes, with an average global incidence within the range from 1:6,000 to 1:10,000 of newborns [2]. TS is caused by inactivating mutations in *TSC1* and *TSC2* (abbr. Tuberous SClerosis) tumor suppressor genes. Most common mutations are detected in the *TSC2* gene (in 70–90 % cases) [3]. Mutations in *TSC1* and *TSC2* genes causing TS are characterized by significant variability and absence of mutagenesis hot points. The meta-analysis of molecular-genetic test results in various countries did not demonstrate significant differences in the types of mutations and genophenotypical correlations [4]. TS is characterized by variable clinical manifestations in different organs and systems, including the emergence of hamartomas (benign neoplasms) on the skin, in the lungs, brain, heart, kidneys, and liver [3].

Depigmentation spots are detected since birth in patients with TS; their amount and sizes gradually increase [5]. Depigmentation spots are detected in 90 % patients [2, 5]. Specific facial angiofibromata start emerging from the age of 3–4 years; the number of lesions increases in adolescence, stabilizing in the adult age. Angiofibromata are determined in 83 % patients with TS. These manifest with violaceous or normally colored (depending on the blood vessel predominance) papules in zygomatic regions, the back of the nose, nasolabial fold, forehead, and chin. Periungual fibromata are detected in patients with TS over 20 years of age, most commonly — in female toes. Gingival fibromata develop in 20–50 % patients (mainly adults) [5]. “Shagreen” plaques emerge during the first 10 years of life and are detected in 50 % patients with TS, while fibrous cranial plaques (mainly on the forehead) are detected in 25 % patients [2].

Besides external manifestations, patients with TS suffer from the systemic neoplastic lesions of various organs and tissues. Brain lesions, including subependymal nodules (90 %), cortical tubers (80–90 %), subependymal giant-cell astrocytoma (5–20 %), are detected in the majority of patients with TS. Renal angiolipomata (benign neoplasms consisting of blood vessels, smooth muscles, and fatty tissue) are diagnosed in 75 % patients with TS [6]. Cardiac rhabdomyomata (benign mesenchymal neoplasms consisting of cardiomyocytes) are detected in 90 % children with TS aged under 2 years. Cardiac rhabdomyomata usually spontaneously regress during the first year of life in patients with TS, thus this tumor incidence decreases to 20 %, starting from the second year of life [3]. Pulmonary lymphangioleiomyomatosis is detected in 40 % patients with TS [5, 6]. A specific category of renal neoplasms has been defined for TS, i.e. "TS-associated renal cell carcinoma" (eosinophilic solid cystic renal cell carcinoma) [7].

Epilepsy is detected in 63–93 % patients with TS with the onset during the first year of life; it is closely associated with the impaired neurocognitive development. Neuropsychiatric disorders develop in 90 % patients with TS [3]. Meta-analysis conducted in 2020 demonstrated that 30 % patients with TS suffered from the autistic spectrum disorder (ASD), with 90 % showing signs of intellectual deficit [8]. A significant association was detected between seizures and ASD in patients with TS — this was not affected by the genotype, number and location of neoplasms [9]. Based on the 2012 Diagnostic Criteria adopted by the International Consensus Group on the Tuberous Sclerosis Complex, 2 major or 1 major and 2 minor diagnostic criteria are required to establish the diagnosis of TS (Table 1). Major criteria include over 3 hypopigmentation spots (with the minimum diameter of 5 mm), facial angiofibromata (over 3) or fibrous plaques on the head, periungual fibromas (over 2), "shagreen" plaques, multiple renal hamartomata, cortical dysplasias, subependymal nodes, subependymal giant-cell astrocytoma, cardiac rhabdomyomas, lymphangioleiomyomatosis, angiomyolipomata (over 2). Minor criteria include polycystic renal disease, extrarenal hamartomata, achromatic retinal areas, oral cavity fibromata (over 2), foveae on the dental enamel (over 3), cutaneous "confetti"-type lesions [2]. 202 patients with TS were reported in the Russian study conducted in the N.P. Bochkov Medical Genetics Scientific Center, with mutations detected in 96.5 % patients (with 6.7 % represented by prolonged deletions) [10]. Clinical features of 71 patients with TS were described by the State Autonomous Healthcare Institution of Sverdlovsk Region "Regional Pediatric Clinical Hospital" in Ekaterinburg [11].

As mutations in *TSC1* and *TSC2* genes [3] eliminate the inhibition of mTOR (mammalian target of rapamycin), this leads to the uncontrollable proliferation of normal resting cells [1]. Thus, mTOR inhibitors are used in the TS treatment. According to the meta-analyses arranged, rapamycin (sirolimus) and its analogues decrease the sizes of cerebral astrocytomas, renal angiolipomata [6], with a significantly decreased rate of seizures [12], including in children over 1 year of age concerning astrocytomas, facial angiofibromata, optic nerve tumors [13]. Moreover, mTOR inhibitors used by females pregnant with fetuses with TS decreased the sizes of cardiac rhabdomyomata [14]. Meta-analysis conducted in 2024 confirmed the data on rapamycin efficacy in TS [1]. Various topical sirolimus levels were tested for the treatment of facial angiofibromata. Based on the meta-analysis, after the application of various topical sirolimus levels, the hazard ratio was 3.34 for the 1 % drug, 4.43 for the 0.2 % drug, 2.7 for the 0.1 % drug, 3.87 for the 0.005 % drug. The rank analysis demonstrated that the best result belonged to the 0.2 % topical sirolimus [1]. Everolimus (sirolimus derivative), which is another mTOR inhibitor, is the most efficient anticonvulsant in TS [15].

Table 1. *Diagnostic criteria for tuberous sclerosis and their frequency*

Criterion	Frequency	Author
Depigmentation spots on the skin	90 %	[5]
Faces angiofibromas	83 %	[5]
Heads fibrous plaques	25 %	[2]
Skin shagreens plaques	50 %	[2]
Pulmonary lymphangioleiomyomatosis	40 %	[5, 6]
Heart rhabdomyomas	90 % in children under 2 years of age, 20 % over 2 years of age	[3]
Subependymal giant cell astrocytoma	5–20 %	[6]
Subependymal nodes	90 %	[6]
Brain cortical dysplasia	80–90 %	[6]
Multiple renal hamartomas	75 %	[6]
Gingival fibromas	20–50 %	[5]
Multiple renal cysts	30 %	[3]

Study objective

Determining clinical & epidemiological features of tuberous sclerosis in the Republic of Bashkortostan (RB).

Materials and methods

Data were analyzed for patients with TS from RB that were followed up by the genetic specialist in SBHI "Republican Medical Genetics Center" (RMGC) with the confirmed TS diagnosis. A total of 86 patients (48 males, 37 females) aged 1 to 61 years (25 [21; 33] years) with the diagnosis of tuberous sclerosis established by genetic specialists in RMGC of RB were enrolled in the study. All patients had their history collected, they underwent the clinical examination, including the ultrasound (US) of the abdominal cavity, echocardiography, magnetic resonance imaging (MRI) or computed tomography (CT) of the brain. *Inclusion criteria:* confirmed clinical diagnosis of tuberous sclerosis with at least 2 major or 1 major and 2 minor diagnostic criteria based on the 2012 Diagnostic Criteria adopted by the International Consensus Group on the Tuberous Sclerosis Complex [2]. The study protocol was approved at the meeting of the Local Ethics Committee (Protocol No. 5 dated December 7, 2009). Each TS patient was analyzed concerning the data about specific signs, including subependymal giant-cell astrocytoma (SEGA), subependymal nodes (SEN), pulmonary lymphangioleiomyomatosis (PLAM) according to the Russian clinical guidelines on the diagnosis and treatment of tuberous sclerosis in children [16]. The results of the US of internal organs were also accounted for when determining the presence of cardiac rhabdomyomata, renal angiolipomata; features of cognitive functions were described to detect the mental retardation and cognitive defects. See the Table 2 for baseline patient characteristics.

Features of clinical TS manifestations in patients from RB were compared to the global ones. All patients signed the informed consent. Checklists and schemes developed by international healthcare organizations (EQATOR, Enhancing the Quality and Transparency of Health Research) were used [17, 18].

Data were statistically processed and presented based on Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Ann Intern Med 1997, 126: 36–47) [19]. When preparing the Statistics section, special guidelines were used ("Quality Editorial Practice Charter", https://scardio.ru/content/publication/Buklet_150x150_v3.pdf; European Heart Journal Guidelines. Calculator link: https://medstatistic.ru/calculators/calchi.html [20]. Quality binary data were statistically processed using the 2x2 interactive contingency table calculating the link statistics (Pearson's χ^2 test) with the Yates' adjustment for continuity developed by V.P. Leonov, as well using quadrupole contingency tables. Differences were considered statistically significant with $p < 0.05$.

Table 2. Initial characteristics of patients with tuberous sclerosis from the Republic of Bashkortostan

Criterion	Frequency in patients from RB n (%)
Depigmentation spots	78 (90 %)
Face angiofibromas	48 (56 %)
Heads fibrous plaques	28 (33 %)
Skin shagreen plaques	36 (42 %)
Pulmonary lymphangioleiomyomatosis	1 (1,2 %)
Heart rhabdomyomas in pateints under 2 years	6 (75 %)
Heart rhabdomyomas in patients over 2 years	30 (38 %)
Subependymal giant cell astrocytoma	16 (19 %)
Subependymal nodes	57 (66 %)
Cortical dysplasia	37 (43 %)
Renal angiomyolipomas	37 (43 %)
Gingival fibromas	4 (5 %)
Multiple renal cysts	19 (22 %)

Notes: RB — Republic of Bashkortostan, TS — tuberous sclerosis

Results

86 patients (48 males, 37 females) aged 1 to 61 years (25 [21; 33] years) from 82 families were reported in RB (Fig. 1). Patients were distributed irregularly in the different Republic of Bashkortostan districts: 28 patients with TS were rural dwellers (33 %), while 58 patients lived in cities (67 %). Patient ethnicities corresponded to distribution features in the region. Accounting for the RB population in 2025 (4,046,094 people), the incidence of TS is 1:47,048 people, which is 5.9-fold lower than the global average [2]. The maternal disease inheritance was 13 cases (15 %), while the other 73 were sporadic (85 %). The analysis of clinical TS manifestations corresponding to the established diagnostic criteria of the disease [2] demonstrated that their incidence among patients from RB differed from those collected from the global TS statistics (Table 3). Cutaneous depigmentation spots were detected in 78 patients with TS (90 %), facial angiofibromata — in 48 (56 %), fibrous plaques on the forehead — in 28 (33 %), "shagreen" plaques on the skin of the torso — in 36 (42 %), pulmonary lymphangioleiomyomatosis — in 1 (1.2 %), subependymal nodes — in 57 (66 %), cortical tubers — in 37 (43 %), subependymal giant-cell astrocytoma — in 16 (19 %), renal angiolipomata — in 37 (43 %), gingival fibromata — in 4 (5 %), renal cysts — y 19 (22 %). The incidence of cardiac rhabdomyomata significantly differed depending on the age of patients with TS, accounting for the fact that many of those anomalies tended to regress spontaneously after 2 years of age [3]. The current article calculated the incidence of cardiac rhabdomyomata in various age groups: they were detected in 6 (75 %) of 8 children with TS aged under 2 year, while in patients over 2 years (n=78) this parameter reached 30 (38 %).

The analysis of data presented in Table 1 demonstrated that the incidence of polycystic kidney disease, subependymal giant-cell ependymoma, cardiac rhabdomyomata, "shagreen" plaques on the skin, fibrous plaques on the forehead, and depigmentation spots did not differ statistically from global data. At the same time, gingival fibromata, renal angiomyolipomas, cortical dysplasias, subependymal nodes, pulmonary lymphangioleiomyomatosis, and facial angiofibromata in patients with TS from RB were detected less frequently.

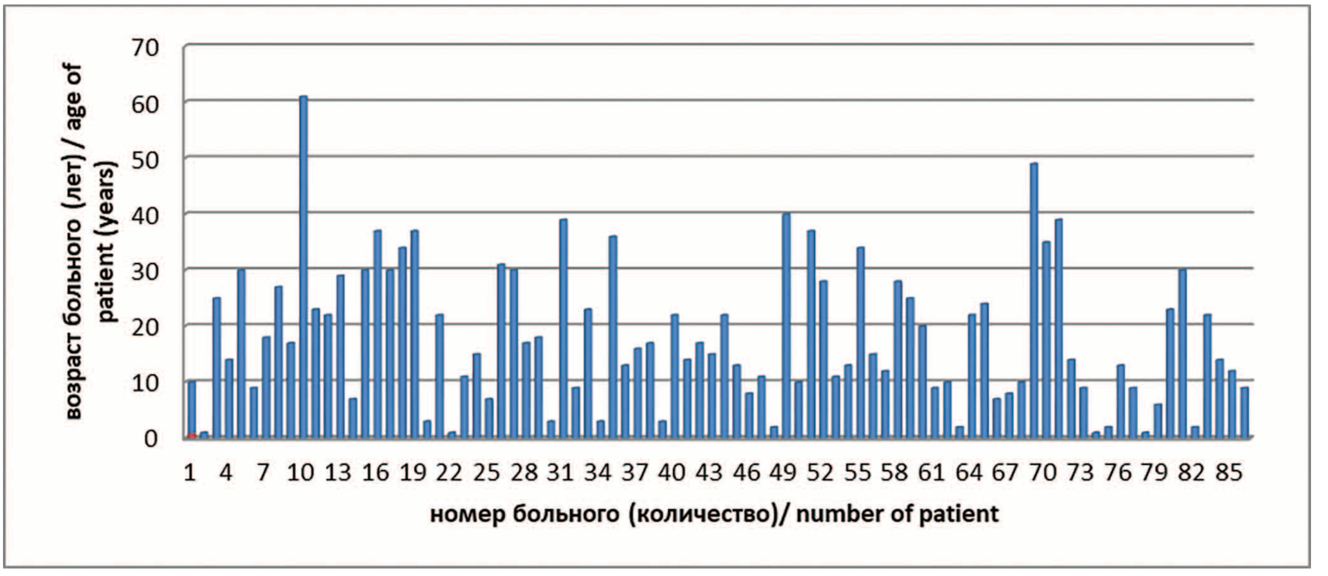

Figure 1. *Age range of patients with tuberous sclerosis in the Republic of Bashkortostan*

Table 3. *Comparative characteristics of diagnostic criteria for tuberous sclerosis in patients from RB with world data [2, 3, 5, 6]*

Criterion	Frequency in patients from RB, n (%)	World frequency in patients with TS, n (%)	χ2 test; p-value at 1 degree of freedom
Depigmentation spots	90 %	90 %	$\chi^2 = 0$; $p=1$
Face angiofibromas	56 %	83 %	$\chi^2 = 17{,}195$; $p<0{,}001$
Heads fibrous plaques	33 %	25 %	$\chi^2 = 1{,}554$; $p=0{,}213$
Skin shagreen plaques	42 %	50 %	$\chi^2 = 3{,}998$; $p=0{,}046$
Pulmonary lymphangioleiomyomatosis	1,2 %	40 %	$\chi^2 = 46{,}664$; $p<0{,}001$
Heart rhabdomyomas in pateints under 2 years	75 %	90 %	$\chi^2 = 7{,}792$; $p=0{,}006$
Heart rhabdomyomas in patients over 2 years	38 %	20 %	$\chi^2 = 7{,}868$; $p=0{,}006$
Subependymal giant cell astrocytoma	19 %	13 %	$\chi^2 = 1{,}339$; $p=0{,}248$
Subependymal nodes	66 %	90 %	$\chi^2 = 16{,}783$; $p<0{,}001$
Cortical dysplasia	43 %	85 %	$\chi^2 = 38{,}281$; $p<0{,}001$
Renal angiomyolipomas	43 %	75 %	$\chi^2 = 21{,}166$; $p<0{,}001$
Gingival fibromas	5 %	35 %	$\chi^2 = 28{,}125$; $p<0{,}001$
Multiple renal cysts	22 %	30 %	$\chi^2 = 1{,}663$; $p=0{,}198$

Notes: RB — Republic of Bashkortostan, TS — tuberous sclerosis

Table 4. *Characteristics of tuberous sclerosis clinical manifestations (not included in the criteria for diagnosis) in patients from RB compared with world data*

Criterion	Frequency in patients from RB, n (%)	World frequency in patients with TS, n (%)	χ2 test; p-value at 1 degree of freedom
Epilepsy	67 %	78 % [3]	$\chi^2 = 3{,}034$; $p=0{,}082$
Cognitive impairment	47 %	75 % [5]	$\chi^2 = 16{,}478$; $p<0{,}001$
Autism spectrum disorder	1 %	30 % [8]	$\chi^2 = 32{,}105$; $p<0{,}001$

Notes: RB — Republic of Bashkortostan, TS — tuberous sclerosis

Besides the aforementioned TS manifestations (diagnostic criteria), other clinical signs were also detected in patients from RB: epilepsy was detected in 58 (67 %), cognitive disorders — in 40 (47 %), while ASD — only in 1 (1.16 %) TS patient. Compared to global data (Table 4), the incidence of epilepsy in patients with TS from RB did not differ statistically, while cognitive disorders and ASDs occurred significantly less frequently compared to global data.

The analysis of Table 4 confirms that patients with TS need to be examined by psychiatrists and psychologists to describe the cognitive disorders and ASDs in them.

8 (9 %) people with the genetically confirmed diagnosis of TS from 86 followed up by the RMGC are administered everolimus 10 mg/day. 2 of these patients had a prolonged *TSC2* gene deletion, 1 had a binucleotide deletion in the *TSC1* gene (exon 7:c.530_531delTC (p.Leu177fs*40)), and 5 had intragene TSC2 mutations: exon 12:TSC2:c.1225G>T; exon 30:c.3610+6G>A; exon30:c.3610+1G>A; exon17:c.1840-1G>A; exon17c.1831C>T(p.R611W). All 8 patients using everolimus had neoplastic and brain lesions typical for TS: 6 (75 %) — cardiac rhabdomyomata, 5 (63 %) — renal angiolipomata, 4 (50 %) — epilepsy, 4 (50 %) — cognitive disorders in various combinations. Compared to global data, the incidence of cardiac rhabdomyomata, renal angiolipomata, cognitive disorders, and epilepsy did not differ statistically from 8 patients administered everolimus, accounting for the small sample size (using the φ test and Pearson's contingency ratio).

Discussion

The comparative analysis of TS incidence in RB (1:47,048) and global data (1:6,000 — 1:10,000) demonstrate that the incidence of reported cases is 5.9-fold lower than the expected one. This can be explained by the fact that not all patients with TS are referred for counseling to the RMGC. Thus, this issue has to be widely discussed among pediatricians, general practitioners, dermatologists, diagnostic specialists (determining typical TS manifestations on US, EchoCG, MRI); it also has to be included into educational programs for junior and postgraduate medical students, young physicians. The regional issue is also associated with the possibility of using everolimus treatment (currently in 8 patients).

The comparative analysis of clinical TS features in RB and the global statistics data demonstrates a significantly less frequent detection of facial angiofibromata. If the age effect is assumed (i.e. angiofibromata in TS emerge at the age of 3–4 years [5]), this factor cannot be used, as the mean age of examined patients was 18.5 years, while the number of patients under the age of 3 years was 7 (8 %). Subependymal nodes, cortical dysplasias, renal angiolipomata, gingival fibromata, and pulmonary lymphangioleiomyomatosis (important diagnostic criteria in TS) were also detected less frequently [2]. The results obtained may reflect the features of clinical TS manifestations in RB, however repeated imaging of internal organs and the brain is required for a more accurate evaluation. Insufficient patient examination may be the possible cause of a lower tumor diagnosis. Thus, brain neoplasms were detected in 65 (76 %) patients with TS from RB. However, only in 2 (2.3 %) patients the MRI was not abnormal, while the brain MRI was not arranged in 19 (22 %) patients.

Concerning other TS manifestations, the rate of epilepsy in patients with RB is not statistically different from the global data. However, cognitive disorders and ASDs were reported significantly less frequently, which requires counseling of neurologists, psychotherapists, psychologists to be arranged in all patients with TS with the purpose of determining the character of psychoneurological disorders and recommendations on their treatment. Although neoplastic lesions of internal organs (in various combinations) were detected in all 86 patients with TS, only 8 of those (9 %) are currently treated with everolimus. This is related to the fact that the genetic disease confirmation is required to obtain the drug via the Krug Dobra fund. This organization was created on January 5, 2021 by the Order of the President of the Russian Federation "On Creating the Fund for Supporting Children with Severe Life-Threatening and Chronic Diseases, Including Rare (Orphan) Diseases (Krug Dobra)". The procedure of obtaining drug products in the Krug Dobra Fund is presented in the Decree of the RF Government dated April 6, 2021 No. 545 according to the List of Children Categories (Krug Dobra). Criteria for everolimus administration include children with the clinical symptom complex of tuberous sclerosis; children with the symptom complex of tuberous sclerosis, but no detected TSC1 or TSC2 mutation, confirmed by the mutual statement of two Federal Medical Centers concerning the drug product administration; children with the detected TSC1 or TSC2 gene mutation; children with dysphagia under 18 years of age; children with cognitive disorders under 18 years of age [21].

To provide the drug coverage of patients with TS, mutations in *TSC1*/*TSC2* genes have to be identified in all patients with further referral for everolimus treatment and regular follow-up. It should be noted that when encountering pulmonary lesions in young females and children, physicians often establish the diagnosis of lymphangioleiomyomatosis without differential diagnosis with TS. It is important to accentuate the attention of general practitioners, pediatricians, and other specialists about the hereditary disease and possible lesions of other organs (mainly the heart, kidneys, and brain).

As stated in our article, in RB 24 patients (28 %) underwent the genetic testing, which differs from global data, according to which the mutation detection rate in different countries varies from 13 % in the Netherlands [22] to 72 % in the USA [23], 76 % in Taiwan [24], 78 % in Germany [25], 80 % in the UK [26], 83 % in the USA [27], 89 % in Brazil [28], and 94 % patients with TS in Mexico [29]. This situation is due to the fact that patients from RB have to apply to the N.P. Bochkov Medical Genetics Scientific Center (MGSC) for mutation testing, and this is not available to everyone due to the required trip to Moscow. One possible solution is to conduct the tests in the Republican Medical Genetics Center or to develop a scientific diagnostic program with the possibility of collecting blood in RMGC (Ufa) and sending it for free testing to N.P. Bochkov MGSC without visiting Moscow.

Only 9.3 % patients with TS from RB are administered targeted therapy, while based on global data the treatment is recommended for all patients [22–29]. This regional limitation is associated both with the incomplete genetic testing coverage of all patients from RB (as detection of mutations in *TSC1* or *TSC2* genes is required for everolimus administration) and the required informed consent of patients for treatment (not all patients consent for therapy, especially those with mild clinical disease manifestations). It should be noted that thanks to the molecular-genetic testing, 5 patients had mutations in the *TSC1* gene detected, with 3 mutations (c.530_531delTC:p.Leu177fs, c.587C>T:p.Pro196Leu, c.936C>G:p.Tyr312X) not described priorly in the scientific literature, while 2 were observed by other researchers: c.682C>T:p.Arg228X in Germany [25], c.2287C>T(p.Gln763Ter) in the Netherlands [22], the USA [23], and Brazil [27]. In our study, 19 patients had mutations in the *TSC2* gene detected, with 11 pathogenic variants (c.43delT:p.Phe15fs, c.707T>C:p.Leu236Pro, c.767G>T:p.Cys256Phe, c.931_932del:p.Ser311fs, c.973C>T:p.Gln325X, c.1225G>T:p.Glu409X, c.1840-1G>A, c.2380C>T:p.Gln794X, c.2707dupC:p.Leu902fs, c.3610+6G>A, c.4161_4162del:p.Ser1387fs) not described earlier in the scientific literature. 8 mutations detected in RMGC among patients from RB were described priorly in patients with TS in other countries: c.268C>T(p.Gln90X) in the USA [23, 27] and Taiwan [24], c.976-15G>A in Germany [30] and the USA [27], c.1831C>T(p.Arg611Trp) in India [31], the USA [23], China [32], and Mexico [29]; c.2083C>T(p.Gln695X) in the UK [26], China [33], and the USA [23]; c.3095G>C(p.Arg1032Pro) in the Netherlands [34], c.3610+1G>A in the UK [26] and the USA [27], c.4174C>T(p.Gln1392X) in China [35] and Mexico [29], c.4242dupT(p.Lys1415fs) in the USA [23].

RB has accumulated the experience of administering and using everolimus in 8 patients with mutations detected in the *TSC1* (exon 7:c.530_531delTC (p.Leu177fs*40)) and *TSC2* genes (exon 12:TSC2:c.1225G>T; exon 30:c.3610+6G>A; exon30:c.3610+1G>A; exon17:c.1840-1G>A; exon17c.1831C>T, and prolonged gene deletions in 2 patients). The treatment administered resulted in the reduction of several clinical TS manifestations, including seizures. The follow-up also confirmed the improvement of cognitive functions in patients with TS administered targeted therapy (everolimus). This confirms its efficacy and cost-effectiveness of drug administrations to a larger pool of patients with TS, which requires the molecular-genetic testing with the detection of mutations in *TSC1* and *TSC2* genes.

Conclusion

The results obtained confirm the lower (5.9-fold) rate of reported TS cases in RB compared to global data. This may be associated with the low alertness of physicians about typical TS symptoms and diagnostic criteria. When finding such signs as depigmentation spots, facial angiofibromata, fibromata on the forehead, “shagreen” plaques on the skin, renal angiolipomata, cardiac rhabdomyomata, pulmonary lymphangioleiomyomatosis, nodular cerebral lesions, clinicians should suspect TS and refer the patient to the medical genetics counseling. The detected statistically significant differences in the incidence of specific TS manifestations may be associated with the insufficient examination — thus, all patients with TS should undergo regular brain MRI, US of internal organs, EchoCG. Psychotherapist, neurologist, and psychologist counseling is required to detect and treat psychoneurological disorders. Considering the treatment of neoplastic disease manifestations, all patients in need have to be provided mTOR inhibitors, which requires the molecular-genetic confirmation of the diagnosis by detecting mutations in *TSC1* and *TSC2 genes*. Physicians in different Russian regions should know that patients with suspected TS should be referred to the genetics specialist counseling in interregional medical genetics centers or directly in Moscow MGSC (if the former ones are absent) in order to detect the disease timely and administer targeted therapy.

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