COVID 19 in a family with rare genetic disease of the nervous system

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We present familial tuberous sclerosis (TS) case complicated by COVID-19. COVID-19 aggravates the course of TS and may lead to a fatal outcome. We review the role of mTORC1 (mechanistic/mammalian Target of Rapamycin Complex 1) in the development and functions of the nervous system and the pathogenesis of TS and COVID-19 with emphasis on the involvement of the brain and lungs. We observed that COVID-19 worsens the course of epilepsy in patients with TS. In TS patients, lymphangioleiomyomatosis may predispose to SARS-CoV-2 invasion into the respiratory system because of the increased expression of ACE2 and TMPRSS2 in type II pneumocytes and thus may worsen the prognosis. We also review the current data on the continuation/termination of everolimus administration in patients with TS associated with COVID-19.

Keywords: *tuberous sclerosis; brain; epilepsy; lymphangioleiomyomatosis; COVID-19; SARS-CoV-2; mTORC1; rapamycin; everolimus.*
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The novel coronavirus infection pandemic poses one of the most serious health threats which has been observed for the past several decades due to its continuous spreading, multiorgan systemic involvement and complications, and significant mortality.

Recent studies have demonstrated an interaction between the patientys immune response and comorbidities, and COVID-19 severity [1, 2]. Less is known about the course of COVID-19 in patients with rare genetic diseases. Malle L. at el. [3] report that patients with Down syndrome (DS) suffered from more severe COVID-19 than controls and were more likely to develop acute respiratory distress syndrome and sepsis. It is proposed that increased susceptibility to severe COVID- 19 in individuals with DS is the consequence of an altered immune response [4, 5]. In another genetic disease п Gaucher disease, Fierro L. et al. [6] did not observe a significant difference in the risk of infection or severity of COVID-19 in the patients compared with controls. Moreover, the evaluation of production of IgG to SARS-CoV-2 virus showed an active immune response in patients with Gaucher disease and COVID-19.

One of rare genetic diseases for which immunosuppressive treatment is administered is tuberous sclerosis (TS). According to Henske EP. et al. [7], there are approximately 50 000 patients with TS in the United States and up to 2й000й000 TS patients in the world. The estimated number of TS patients in Russia is approximately 7000 [8].

Tuberous sclerosis belongs to a phacomatosis group and is manifested by development and progression of hamartromas in the brain, skin, kidneys, heart, lungs, and other organs and tissues. The disease is inherited in an autosomal-dominant mode with mutations in the *TSC1* (9q34, hamartrin) or *TSC2* (16p13.3, tuberin) genes. Normally, *TSC1* or *TSC2* prevent cell proliferation and tumor growth. Hamartin and tuberin form a protein complex that inactivates mTORC1 (mechanistic/mammalian target of rapamycin complex 1) [9], which regulates cell metabolism and proliferation (Fig. 1). Mutations in *TSC1* or *TSC2* result in a failure to form hamartin-tuberin complex and lead to a chronic activation of mTORC1 and cell proliferation [1, 12]. Up to 80–85% of TS cases are caused by mutations in the *TSC2* gene, leading to

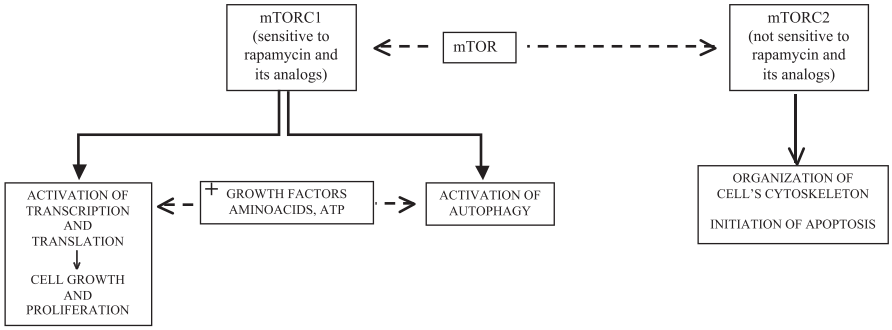

Fig. 1. *mTOR kinase and mTORC1 and mTORC2 complexes*
mTOR (mechanistic/mammalian target of rapamycin) – a highly conservative serine/threonine protein kinase is a subunit of mTORC1 and mTORC2 complexes, which regulate various cell cycle processes. mTOR was discovered during the studying of rapamycin. ATP – adenosine triphosphate

multiorgan systemic involvement and a more severe clinical course [12, 13].

Several recent studies highlighted a functional interaction between the immune system and mTORC1. mTORC1 complex regulates the metabolism of quiescent and activated macrophages, dendritic and T-cells [14, 15], and interferon type I production [16]. Viruses [17], including SARS-CoV-2 [18, 19], may modulate mTORC1 to alter the host immune response.

Presently, everolimus (E) п a rapamycin analog, which belongs to the family of mTOR inhibitors, is the first line medication for treatment of TS. Everolimus administration leads to a significant reduction in the volume of subependymal giant cell astrocytomas (SEGA), kidney angiolipomas and skin angiofibromas, and also decreases the frequency of epileptic seizures [20–22]. The dose of E is calculated with respect to the body surface area (3п5 mg/m^2) and in most cases ranges from 4.5 to 6.5 mg/day [20, 23]. The dosage modification or discontinuation of E is required in patients with infectious complications or in patients taking CYP3A4/PgP inhibitors.

The prognosis of TS is primarily dependent on the involvement of the brain, lungs, and kidneys [24, 25]. Since the lungs, brain, and kidneys are also frequent target organs in COVID-19 patients [2], TS patients may have an increased risk of developing target organ complications, if infected with COVID-19. However, at present the relationship between TS, risk of being infected with COVID-19, and its severity in TS patients is unknown, and the regimen of E administration in patients with TS infected with COVID-19 is not elucidated. In clinical practice [26] patients with TS or patients with lymphangioleiomyomatosis (LAM) and probable clinical diagnosis of COVID but negative polymerase chain reaction (PCR) continued to receive E at a dose of 3п5 mg/daily. Discontinuation of E administration was recommended only in cases with pneumonia and/or other lung complications.

Thus, in the setting of COVID-19 pandemic, patients with TS as well as clinical practitioners face some questions. In particular, does TS increase the risk of being infected with COVID-19, and does COVID-19 alter the course of TS? How may the preexisting pathology of the brain and internal organs in TS patients affect COVID-19 severity? What should the regimen for E administration be in patients with TS and COVID-19, and can E administration alter the course of COVID-19?

Presently, there are only few publications on this issue and answers to the questions formulated above are provisional.

We report a clinical case of a family in which father and children suffered from TS (Pringle-Burneville's disease), and father and daughter died from COVID-19 confirmed by repeated PCR.

The family consisted of parents and two children (brother, born in 1998, and sister, born in 2000) and lived in a remote village in the Voronezh region. TS in father and both siblings was diagnosed in 2014, when the boy was 16 years old, and the girl n 14 years old. In the siblings TS debuted with generalized tonic-clonic seizures, in brother at the age of 1.5 years, and in sister - at the age of 2 months. Both children were diagnosed with retardation of psychomotor development complicated by epileptic seizures syndrome, were registered at the local psychoneurological dispensary, and repeatedly hospitalized to Voronezh Regional Pediatric Hospital. In 2014 during a check-up the boy was diagnosed with a kidney neoplasm, and his brain MRI revealed foci typical of TS patients. These findings served as the basis for an extended check-up of all members of the family. After genetic, clinical and instrumental examination (Table 1) father and both children were diagnosed with TS with TSC2 mutation. No information was available about the family history of TS in fatherys parents. For continuous treatment father and siblings were administered E 10 mg/day. For treatment of epileptic seizures brother and sister were prescribed Encorate Chrono at a dose of 500 mg 2 times/day. The father suffered from stroke in 2019, and in the fall of 2020 he was diagnosed with esophagus cancer. In November of 2020 he was infected with COVID-19, and died from complications on December 20, 2020.

According to motherys words and medical documentation, the daughter fell ill on October 27, 2020, when she had fever up to 38 °C, general weakness and cough. On October 29, 2020, she was consulted by a physician, who prescribed paracetamol, ceftriaxone 2.0 g/day (5 days), azithromycin 500 mg/day (5 days), and flemoxin 500 mg 3 times/day for outpatient treatment. Because of the infection and azithromycin administration (moderate CYP3A4/PgP inhibitor), E was discontinued. Despite the treatment, the patient continued to have a high temperature and symptoms of the upper respiratory tract infection. On 16.11.2020 a PCR test for SARS-CoV-2 infection was done, but it was negative. Despite the continuing treatment, the patientys condition deteriorated due to the progression of respiratory failure. On 22.11.2020 a chest CT scan showed a left-sided abscess pneumonia and a left-sided hydrothorax were diag-

Table 1. **Genetic and clinical manifestations of TS in the father and children**

Patient	Gene	Clinical symptoms				
		Skin	Heart	Kidneys	Lungs	Brain
Father	*TSC2*	Areas of hypopigmentation, a patch of depigmented scalp hair, angiofibromas on the body	No information	Polycystic disease	No information	No information
Sister	*TSC2*	Areas of hypopigmentation, angiofibromas on the face and body	Rhabdomyoma	Multiple angiolipomas	LAM	Calcified tubers, SEN (brain CT, Fig. 2)
Brother	*TSC2*	Areas of hypopigmentation, angiofibromas on the face and body	No information	Multiple angiolipomas	No information	Tubers, migration tracts, SEGS and SEN (brain MRI)

nosed. On 24.11.2020 the patient was hospitalized to Voronezh Emergency Hospital э 1 (VEH э 1).

In VEH № 1 she was again examined for COVID 19: PCR test for SARS-CoV-2 was negative, IgM and IgG for SARS-CoV-2 were within the normal range. The patient was consulted by a pulmonologist, internist, neurologist, and cardiologist. Based on the results of the chest CT (26.11.2020), sputum culture (E. coli +10×4), normal results of the analyses of the urine and cerebrospinal fluid (CSF – colorless, transparent, protein n 0.33g/L, neutrophil n 0, lymphocytes n 1, glucose n 4.1 mmol/L, no culture growth) the severity of the disease was attributed to abscess pneumonia and a combination of amikacin 1 g/day and meropenem 3 g/day was administered. Despite the antibiotic treatment the respiratory failure progressed. The PCR test for SARS-CoV-2 which was done on 30.11.2020 was positive. On 02.12.2020, the patient was transferred to Voronezh Regional Clinical Hospital № 1 (VRCL № 1) for specialized treatment.

On admission to VRCL э 1, PCR test for SARS-CoV-2 was again positive. During the physical examination the patientys condition was assessed as severe, the level of consciousness corresponded to somnolence. Her height was 162 cm, body mass n 60 kg, body surface area n 1.64 m^2. The temperature was 36.7 °C. She had pale and dry skin with acrocyanosis. On her face there were multiple angiofibromas each approximately 2 mm in diameter, on the gluteal muscles and on the anterior surface of the body there were areas of hypopigmentation. Peripheral lymph nodes were normal and there was no edema. Her chest configuration was normal, respiratory rate was 21 breaths per minute, and SpO2 was 96% with room air respiration. A bandbox sound on percussion of the left side of the chest was registered, and on the right side of the chest a percussion sound was shortened. Breath sounds were decreased, and coarse moist rales were heard on the left side. Her heart tones were clear and rhythmic and pulse was 115 beats per minute, rhythmic, satisfactory in volume and tension. Blood pressure was 120/70 mm Hg. There was no abdominal wall tenderness on palpitation, and the abdominal muscles were soft. The liver was along the coastal margin and the spleen was not palpable. Murphyys percussion test was negative on both sides. Physiological excretions were normal, urination was through the catheter.

On neurological examination: verbal contact with the patient was difficult because of the reduced state of consciousness to the level of somnolence and pronounced intellectual decline. Meningeal signs were absent. Her palpebral fissures and pupils were of equal size. Reactions of pupils to light were normal and symmetrical. Her eyeballys movements were in full range. Nasolabial folds were symmetrical. Spontaneous nystagmus was absent. Pharyngeal reflexes were preserved and symmetrical. The tongue in the mouth was in the proper position and along the midline. She had a severe spastic tetraparesis with symmetrically increased deep tendon reflexes, muscular hypo- and atrophies, and positive Babinski sign on both sides. Flexion contractures in joints were present. Coordination probes and sensory assessment were not possible as a result of the difficulties in the contact with the patient.

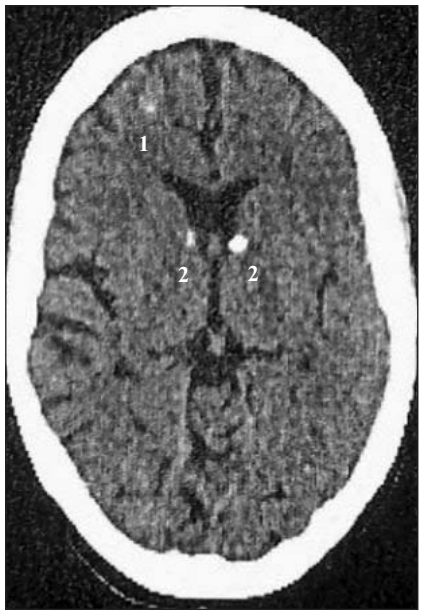

Fig. 2. *Calcified tuber (1) and subependymal nodules (2) in patient M.*

Total blood count showed anemia (Hb n 55 g/L, erythrocytes n 3.09×10^{12}/L), leukocytosis with neutrophilic shift and lymphopenia (leukocytes n 21.0×10^9/L, neutrophils n 74%, band cells n 9%, lymphocytes n 8%), elevated number of platelets n 514×10^9/L, hypoproteinemia (total protein n 48 g/L). On electrocardiography the patientys heart rate was 128 beats per minute with supraventricular pacemaker migration, and disturbances of repolarization processes. On brain CT calcified subependymal nodes (SEN) and tubers in both hemispheres were observed (Fig. 2). Chest CT scans showed double-sided polysegmental pneumonia, left-sided pneumo- and hydrothorax, encysted hydrothorax, and disk-like atelectasis.

Consultation of a pulmonologist: TS with the involvement of the brain, skin, heart and kidneys, LAM, COVID-19 (second positive PCR on the 02.12.2020). Double-sided polysegmental pneumonia of mixed origin, complicated by the left sided pyopneumothorax. Recommendations: consultation of a thoracic surgeon, laboratory control of homeostasis, continuation of combined antibacterial therapy.

Consultation of a thoracic surgeon: COVID-19, TS, LAM. Discoid cavity in the lower lobe of the left lung with adequate drainage through the bronchus. Left-sided small encapsulated hydrothorax. There were no indications for surgical treatment. Recommendations: combined antibacterial therapy, postural drainage, mucolytics, and chest CT in dynamics.

Consultation of a neurologist: COVID-19, TS with pronounced intellectual decline, severe spastic tetraparesis, symptomatic epilepsy.

In the intensive care unit of VRCL э 1 combined antibiotic therapy with meropenem 1.0g 3 times/day and linezolid 600 mg 2 times/day was continued, and an intensive care support was also started. For correction of pulmonary failure oxygen support was administered. On 02.12.2020 the noninvasive mechanical ventilation with oxygen flow of 5–10 L/min was started, but since the respiratory failure progressed she was put on artificial mechanical ventilation on 05.12.2020. On 06.12.2020 inotropic medications were started. Convulex (2000 mg a day intravenously through an infusion pump) and sibazone (0.5% 2 ml intravenously) were added to her basic antiepileptic regimen since generalized sporadic and repeated epileptic seizures resumed from the day of admission to VRCL № 1. Despite the treatment, respiratory and cardiovascular failure progressed. The patientys level of consciousness also decreased from somnolence on 02.12.2020 to stupor on 03.12.2020 and to coma two days later. She died on 08.12.2020 at 23:30 as a result of respiratory and cardiovascular failure.

The postmortem conclusion: Patient M., born in 2000, suffered from TS with the involvement of the brain, lungs, heart, skin, and kidneys. The cause of death was COVID-19 complicated by double-sided polysegmental pneumonia, abscess of the lower lobe of the left lung, and left-sided empyema.

Discussion

Factors contributing to the severe course of COVID-19. Systemic multiorgan and brain pathology, which is more charac-

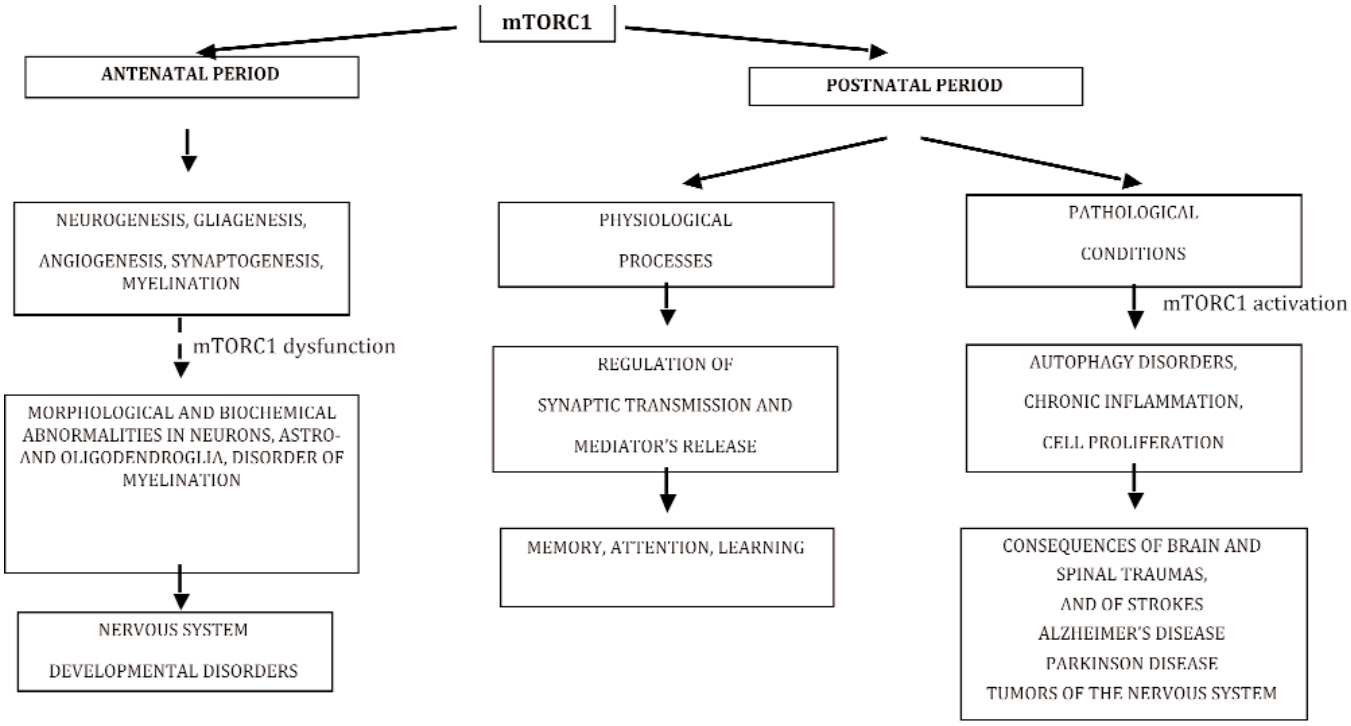

Fig. 3. *mTORC1 regulation of brain development and functioning in the ante- and postnatal periods*

teristic of type 2 TS, aggravated the course of COVID-19 and contributed to the fatal outcome.

According to clinical and radiological data, LAM was the main contributing factor to the fatal outcome of the disease. In TS patients LAM is diagnosed in approximately 1/3 of cases, almost always in women of childbearing age, and severely aggravates the course of the disease, being the third cause of death after kidney and brain pathology [24]. In this clinical case LAM was the possible predisposing factor for SARS-CoV-2 entry into the respiratory tract and further dissemination. According to Tang Y. et al. [27], chronic activation of mTORC1 may contribute to the upregulation of the *ACE2* and *TMPRSS2* genes expression in type II pneumocytes and make them more vulnerable to SARS-CoV-2 entry. On the other hand, mTORC1 inhibitors may independently contribute to the entry of SARS-CoV-2 into epithelial cells of the upper respiratory tract and lungs by downregulating type I interferon activated transmembrane proteins [28]. Besides, women with TSC2 mutations are characterized by the upregulation of proinflammatory cytokines production in the lungs, which predisposes to proinflammatory phenotype [29].

The other cause that aggravated the course of COVID-19, was the preexisting TS pathology of the brain. mTORC1 is expressed in all compartments of the nervous system and plays a key role in its ante- and postnatal development and activity (Fig. 3) [30]. In TS patients, chronic activation of mTORC1 which begins at the antenatal period results in various morphological and biochemical abnormalities in the central nervous system. The most frequent morphological abnormalities include focal cortical dysplasia (tubers) and radial migration tracts, as well as SEN and SEGA. These abnormalities were observed on brain CT/MRI in both siblings. On the biochemical level, mTORC1 dysfunction leads to the disruption of cell membranes transport and synapse signal transduction, and also to chronic activation of angiogenesis and inflammation [31п33].

In patients with COVID-19 the brain is also one of frequent target organs. According to Chen R. et al. [34], neurons, astrocytes, oligodendrocytes and endothelial cells in various brain compartments express ACE2 receptors. More active expression of ACE2 receptors is registered in choroid plexuses and gray matter of the brain hemispheres, which makes them particularly vulnerable to SARS-CoV-2 entry. Presently, endothelial dysfunction, increased blood-brain barrier permeability, reactive astroglia and microglia and secondary neuronal involvement are reported as the main cause of neurological disorders in patients with COVID-19 [35]. These changes add up to the baseline neurotransmitter disorders and proinflammatory state that exist in TS patients and contribute to the worsening of neurological symptoms.

Epileptic seizures are one of the most frequent clinical presentations of the brain involvement in TS patients. This clinical feature was observed in both siblings. Clinical presentations of TS epilepsy largely depend on the number, size, and distribution of tubers, migration tracts and other structural abnormalities [36]. Besides that, in experimental [37] and clinical [38] studies a correlation between epilepsy severity and mutations in TSC2 was observed. Generally, infectious complications aggravate the course of epilepsy and result in the need for correction of the antiepileptic therapy. In the presented clinical case COVID-19 infection increased the frequency and severity of epileptic seizures and necessitated the intensification of antiepileptic therapy. This finding is consistent with Sun M. et al. [39] who also reported the increased frequency and severity of epileptic seizures in patients with epilepsy infected with COVID-19, which required intensification or changing the regimen of antiepileptic treatment.

mTORC1 inhibitors administration in COVID-19. In the case of infection, TS patients are recommended to decrease E dose if the infection is mild or discontinue the drug if the infection is severe.

mTORC1, which is blocked by its inhibitors, plays a key role in response to infection agents by regulating interferon activation and expression of interferon pathway genes [40], differentiation and activity of antigen-presenting cells, T and B cells, as well as other features of innate and acquired immunity [14, 15]. Rapamycin *in vitro* downregulates interferon-induced genes expression [41], induces preferential macrophages polarization to M1 proinflammatory phenotype [42], downregulates anti-inflammatory cytokine IL-10 expression, and stimulates tissue factor and tumor necrosis factor activation (TNFα) [43]. mTORC1 inhibitors may facilitate SARS-CoV-2 entry into epithelial cells of the upper respiratory tract and lungs by down-regulating interferon type I activated transmembrane proteins [28]. It should be also noted that, besides mTORC1 inhibitors, infectious agents can independently modify the hostys immune response. Viruses may modulate and pretunec hostys mTORC1 to gain entry into cells and replicate [17]. This feature is also true for SARS-CoV-2, whose structural and nonstructural segments of RNA downregulate interferon type I expression as well as activation of interferon-induced genes pathway [18, 19], and impair dendritic cell and T cell responses [44]. Resulting interferon type I deficiency in combination with the upregulation of TNFα and IL-6 in COVID-19 promotes proinflammatory responses and may result in the development of cytokine storm [45].

Therefore, COVID-19 infection may seriously aggravate the course of TS up to the fatal outcome. The key factors that influence the prognosis in TS patients infected with COVID-19 include the preexisting systemic multiorgan (primarily lungs) and brain pathology as well as a possibility of an altered immune response in TS patients combined with the direct effect of SARS-CoV-2 on the immune response through the mTORC1 pathway.

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