PEDIATRICS

A CLINICAL CASE OF THROMBOSIS IN A TEENAGER IN THE POST COVID-19 PERIOD

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ABSTRACT

The article presents a case of a fatal outcome of a 15-year-old teenager with cerebral vascular thrombosis, which developed in the post COVID-19 period. The young man came in with complaints of headache, vomiting, photophobia, hyperacusis. It was known that at an early age he had been operated on for the Arnold – Chiari anomaly, had a subdural-peritoneal shunt. Two weeks before hospitalization, he suffered a new coronavirus infection of mild severity, which was confirmed by a positive analysis of a smear from the oropharynx by polymerase chain reaction.

Cephalgia was acute, stopped for a short time after the use of analgesics. During the examination, the patient laid with his eyes closed, asked for silence and blackout in the ward. Any movement of the head was accompanied by dizziness, headache, vomiting. During an objective examination, no pathological changes were found on the part of the internal organs.

The neurological status was determined by photophobia, double vision, asymmetric face, asymmetry of the eye slits S > D, drooping of the left corner of the mouth, nystagmus, hyperacusis. There was no rigidity of the occipital muscles. Meningeal signs were negative. There were no pelvic disorders.

According to the laboratory examination, lymphocytopenia, thrombocytosis, acceleration of ESR, moderate increase in ferritin, D-dimers were detected. Conducted neuroimaging methods (MSCT of the brain with intravenous contrast, brain MRI, ultrasound diagnostics of cerebral vessels) did not find any blood clots in intracranial and extracranial vessels. Low-positive values of IgM antibodies to cardiolipin were revealed. According to the results of polymerase chain reaction, polymorphism G20210A was detected in the prothrombin gene. The patient received high-dose glucocorticoids and heparin for treatment.

Despite the therapy, a month and a half after hospitalization, the teenager died from thrombosis of the central venous sinuses (cavernous sinus on the left, transverse sinuses, jugular veins), which were confirmed on autopsy.

This clinical case of venous sinus thrombosis in a teenager in the post COVID-19 period presented diagnostic difficulties, since accurate imaging methods did not detect the presence of a blood clot in the cerebral vessels.

Key words: *post COVID-19 syndrome, thrombosis, children, prothrombin gene mutation, antiphospholipid antibodies*

Received: 20.05.2022
Accepted: 09.03.2023
Published: 05.05.2023

For citation: Zhdanova L.V., Laperdina M.L. A clinical case of thrombosis in a teenager in the post COVID-19 period. *Acta biomedical scientifica*. 2023; 8(2): 179-183. doi: 10.29413/ABS.2023-8.2.17

КЛИНИЧЕСКИЙ СЛУЧАЙ ТРОМБОЗА У ПОДРОСТКА В ПОСТКОВИДНЫЙ ПЕРИОД

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РЕЗЮМЕ

В статье представлен случай летального исхода подростка 15 лет с тромбозом церебральных сосудов, развившимся в постковидном периоде. Юноша поступил с жалобами на головную боль, рвоту, светобоязнь, гиперакузию. Известно, что в раннем возрасте он был прооперирован по поводу аномалии Арнольда – Киари, имел субдурально-перитонеальный шунт. За две недели до госпитализации перенёс новую коронавирусную инфекцию в лёгкой степени тяжести, которая была подтверждена положительным анализом мазка из ротоглотки методом полимеразной цепной реакции.
Цефалгии носили острый характер, купировались кратковременно после применения анальгетиков. При осмотре лежал с закрытыми глазами, просил тишины и затемнения в палате. Любое движение головой сопровождалась головокружением, головной болью, рвотой. При объективном осмотре патологических изменений со стороны внутренних органов не обнаружено. В неврологическом статусе определялись светобоязнь, двоение в глазах, асимметричное лицо, асимметрия глазных щелей S > D, опущение левого угла рта, нистагм, гиперакузия. Ригидности затылочных мышц нет. Менингеальные знаки отрицательные. Тазовых нарушений нет.
По данным лабораторного обследования обнаружены лимфоцитопения, тромбоцитоз, ускорение скорости оседания эритроцитов, умеренное повышение ферритина, D-димеров. Проведённые методы нейровизуализации (мультиспиральная компьютерная томография головного мозга с внутривенным контрастированием, магнитно-резонансная томография головного мозга, ультразвуковая диагностика сосудов головного мозга) тромбов в интракраниальных и экстракраниальных сосудах не обнаружили. Выявлены низкопозитивные значения антител IgM к кардиолипину. По результатам полимеразной цепной реакции обнаружен полиморфизм G20210A в гене протромбина. В качестве лечения получал высокодозные глюкокортикоиды, гепарин.
Несмотря на проводимую терапию через полтора месяца от момента госпитализации подросток умер от тромбоза центральных венозных синусов (кавернозного синуса слева, поперечных синусов, яремных вен), которые подтверждены на аутопсии.
Данный клинический случай тромбоза венозного синуса у подростка в постковидном периоде представлял диагностические трудности, так как методы точной визуализации не обнаружили наличие тромба в церебральных сосудах.

Ключевые слова: *постковидный синдром, тромбоз, дети, мутация гена протромбина, антифосфолипидные антитела*

Статья получена: 20.05.2022
Статья принята: 09.03.2023
Статья опубликована: 05.05.2023

Для цитирования: Жданова Л.В., Лапердина М.Л. Клинический случай тромбоза у подростка в постковидный период. *Acta biomedica scientifica*. 2023; 8(2): 179-183. doi: 10.29413/ABS.2023-8.2.17

RELEVANCE

For the past two years, the entire world has been focused on the infection caused by SARS-CoV-2. To date, the pathogenetic mechanisms that determine the severity of the course of this infection have been studied. Understanding of the main pathogenesis links led to the revision of therapeutic treatment, which is aimed at suppressing the synthesis of proinflammatory cytokines that cause the hyperinflammation syndrome, to stop hypercoagulability, which also affects the severity of the course of SARS-CoV-2 infection.

To a lesser extent, the mechanisms of the development of the so-called post COVID-19 syndrome have been studied. Post COVID-19 syndrome is characterized by various clinical manifestations that occur after SARS-CoV-2 infection and can last up to 6 months. Hyperproduction of cytokines, fibrosis, autoantibody production, and direct tissue damage by the virus are considered as the main pathogenetic links of this pathological condition. No less frequent manifestation of post COVID-19 syndrome is thrombosis in vessels of various caliber and localizations, which are due to vasculopathy and impaired hemostasis.

This article presents a death case of a teenager with venous sinus thrombosis that developed in the post COVID-19 period.

INTRODUCTION

Thrombosis in pediatric practice is quite rare. There are recognized risk factors for thrombosis: surgical treatment; presence of a central venous catheter; nephrotic syndrome; oncopathology; carrying mutations and polymorphisms of genes associated with a high risk of thrombosis; antibodies to phospholipids; and infections. The pathogenesis of SARS-CoV-2 infection includes hemostasis disorders that affect all its links: activation of vascular hemostasis, suppression of fibrinolysis, increased thrombin formation, which determines the risk of thrombosis [1–3]. To date, there are insufficient data on the incidence of thrombosis in children with SARS-CoV-2 infection, and there are no recommendations for the prevention of thrombosis in the post COVID-19 period. Nevertheless, hemostasis studies in children with SARS-CoV-2 infection show the presence of hypercoagulability [4]. In a systematic review of the literature [5], the authors presented data on 19 children with clinical thrombosis. The most frequent localization of thrombosis was pulmonary vessels (21 %); thromboses of various localizations (cerebral, intestinal, renal, and deep veins of the extremities) were also described. A more recent publication on the results of a multicenter retrospective study [6] determined that thrombosis is more likely to occur in children older than 12 years of age, and risk factors include the presence of multisystem inflammatory syndrome and a central venous catheter. These findings are supported by a literature review of 16 publications on the high incidence of thrombosis in children with multisystem inflammatory disease [7]. The authors showed that the incidence of thromboembolism in multisystem inflammatory syndrome is 1.4–6.5 %. One third of thrombosis cases are localized in cerebral vessels, which is accompanied by a high mortality rate. So of the three children with cerebral infarctions, all of them died. All publications on the presence of thrombosis in children refer to the acute period of SARS-CoV infection.

A search for publications in the scientific electronic libraries PubMed, e-Library yielded no data on the development of thrombosis in children in the post COVID-19 period.

THE AIM OF THE PUBLICATION

To present a case of venous sinus thrombosis in a post COVID-19 teenager.

CASE HISTORY

A 15-year-old boy was hospitalized at the Children's Republican Clinical Hospital in Ulan-Ude with complaints of headache, vomiting, photophobia, hyperacusis. From the patient's life history it is known that he was born from the first normal pregnancy. The delivery was physiological, on time, birth weight 3,076 g, height 52 cm. In physical and neuro-psychological development did not lag behind. No chronic illnesses. At the age of 11 months of life, he was operated for Arnold – Chiari malformation and had a subdural-peritoneal shunt. Monitored by a neurologist and neurosurgeon on an irregular basis.

Two weeks prior to hospitalization, he had a new mild form of coronavirus infection after family contact. In clinic there was subfebrile temperature for 2 days, weakness, sore throat, runny nose. SARS-CoV-2 infection was confirmed by positive analysis of an oropharyngeal swab by polymerase chain reaction.

As treatment he received Grippferon, throat gargle with antiseptics, decongestants. Recovery was recorded one week after the onset of the disease by a negative nasopharyngeal swab by polymerase chain reaction.

From the history of the disease it is known that 2 weeks after recovery from SARS-CoV-2 infection he began to complain of headaches with predominant localization in the occipital region. Cephalgia was acute, stopped for a short time after the use of analgesics. When seeking medical help at the place of residence, no focal neurological symptoms were detected. Continued symptomatic treatment was recommended. Subsequently, the headaches became continuous, accompanied by vomiting. Started noting that bright lights and loud noises increased the intensity of the cephalgias. In 5 days from the onset of the disease he was hospitalized at the Children's Republican Clinical Hospital in Ulan-Ude. On admission, the patient's condition was considered moderately severe. On examination: forced position due to intense cephalgias. The patient tried to lie still, as any movement of the head caused dizziness, headache, vomiting. Preferred to lie with his eyes closed, asked for silence and blackout in the room. On physical examination:

the skin is clean, pink, no pathologic changes in the pharynx. Lungs are vesicular. Heart tones are rhythmic, audible. The abdomen is soft, painless, liver and spleen are not enlarged.

Neurological status on admission

Cranial nerves: 1st pair – olfaction is not affected; 2nd pair – follows objects for a short time, photophobia; 3rd pair, 4th pair, 6th pair – pupils D = S, photoreaction is alive, eye movements in full volume, convergence, accommodation are normal, the patient noted double vision in extreme leads; 5th pair – sensitivity on the face is preserved, pain at palpation of the 1st branch on both sides; 7th pair – face asymmetrical, eye slits S > D, left corner of the mouth was lowered; 8th pair – nystagmus at the extremes of gaze, hearing preserved, hyperacusis; 9th pair, 10th pair, 12th pair – no bulbar disorders, tongue along the midline; 11th pair – movements in the cervical spine preserved, not limited. There are no sensory disturbances, active and passive movements in the limbs are not limited. Muscle tone in all muscle groups is satisfactory. Symmetrical and brisk tendon reflexes from the arms and legs. Doesn't walk, doesn't sit up, rolls over in bed. There was no rigidity of the occipital muscles. Meningeal signs were negative. There were no pelvic disorders.

Additional health examination results

A complete blood count (CBC) on admission: hemoglobin – 166 g/L, erythrocytes – 5.97 million/L**,** leukocytes – 16.6 thousand/μL, neutrophils – 80 %, lymphocytes – 7 %, monocytes – 12 %, platelets – 482 thousand/μL, an erythrocyte sedimentation rate (ESR) – 23 mm/h. There are no pathologic changes in the biochemical blood analysis. Coagulogram results: decreased thrombin time – 15.5 sec, a high d-dimer test – 2 mg/mL (norm – 0.5 mg/mL). Highly positive IgG values to SARS-CoV-2 were detected with a KP of up to 10.3. According to electroencephalogram: diffuse changes in electrobiological activity. No pathologic changes were found in the cerebrospinal fluid (CSF). Doppler ultrasound revealed decreased blood flow in the left vertebral artery, poor visualization of the left internal carotid artery. According to the data of duplex scanning of extracranial sections of brachiocephalic arteries, the conclusion about the increased level of peripheral resistance in the left internal carotid artery was given. Blood flow through the vertebral arteries without signs of extravascular compression, reduced velocity indices at the level of V1-, V2-segments.

Multispiral computed tomography of the brain was performed, and data were obtained on the presence of signs of the condition after subdural-peritoneal shunt, excision of a cyst of the left frontal and temporal region, Arnold – Chiari malformation, borderline ventriculomegaly, and arachnoid cyst of the left temporal region. Contrast-enhanced magnetic resonance imaging of the brain showed signs of Arnold – Chiari malformation, tonsillar herniation, asymmetric ventriculomegaly, deformation of the lateral ventricles, periventricular leukoareosis, and temporal lobe pole cyst on the left side. No pathologic selective accumulation of contrast agent was noted. No abnormalities in the cerebral vascular bed were found according to the results of neuroimaging methods.

Differential diagnostics was carried out with liquorodynamic disorders on the background of Arnold **–** Chiari malformation, hemorrhagic stroke, brain neoplasms.

The severity of the patient's condition was presumed to be due to post COVID-19 encephalitis. Pulse therapy with methylprednisolone at a dose of 10 mg/kg/injection, for a total dose of 2,500 mg followed by oral prednisolone 35 mg/day for 2 weeks was performed. During the whole period of hospitalization, the patient received anticoagulants – enoxiparin 40 mg/day, then heparin 20 units/kg/hour.

The patient's condition progressively deteriorated. The cerebral syndrome in the form of dizziness, headache persisted, and focal symptoms – complete ophthalmoplegia on the left, flaccid tetraparesis, facial nerve paresis on the left, bulbar paresis – were added. According to the data of blood tests, thrombocytosis remained within 400 thousand/μL, acceleration of ESR – 30–50 mm/h. A moderate increase in ferritin – 268.8 μg/L (reference values – 140 μg/L), IL-6 level – 4.1 pg/mL, which is not out of the norm, progressive increase in D-dimers up to 9 mg/L were revealed. The results of repeated magnetic resonance imaging of the brain with visualization of arterial vessels and venogram showed the absence of focal and diffuse changes in the brain substance, asymmetry of blood flow along the P1 segments of the posterior cerebral artery (D > S). Minimal asymmetry of blood flow along the intracranial section of vertebral arteries (D > S).

The search for prothrombogenic risk factors continued. There was a decrease in antithrombin III – 79.46 % (norm – 96–126 %), low level of homocysteine – 7.61 μm/l. To exclude antiphospholipid syndrome, antibodies to phospholipids were investigated; positive values of IgM antibodies to cardiolipin – 27 units/mL and negative IgG values were determined. No antibodies to β-2 glycoprotein-1, lupus anticoagulant were detected. A genetic study was performed to determine polymorphisms of genes responsible for hereditary thrombophilias. Polymerase chain reaction results revealed a G20210A mutation in the prothrombin gene.

Despite anticoagulant therapy, a month and a half after hospitalization, the teenager died of thrombosis of intracranial central venous sinuses (cavernous sinus on the left, transverse sinuses, jugular veins), which was confirmed on autopsy.

CONCLUSION

Venous sinus thrombosis in children is rare, with an average of 0.5 per 100,000 pediatric population [8]. There is a multifactorial nature of thrombogenic risks in its etiology, and 32 % of cases are hereditary thrombophilias [9]. This case once again confirms that thrombosis in pediatric practice occurs against the background of combined prothrombotic factors. Thus, the following risks of increased thrombosis were found in the teenager: the presence of subdural-peritoneal shunt, G20210A mutation in the prothrombin gene, hypohomocysteinemia, low level of antithrombin III. Low-positive antibodies to cardiolipin class IgM could not be an independent cause of thrombosis. They were more likely to be

produced by SARS-CoV-2 infection, which is also an independent risk for increased thrombosis.

The presented clinical case demonstrates the difficulty in the diagnostic search for cerebral venous thrombosis in a post COVID-19 teenager. The examinations performed with the inclusion of highly sensitive neuroimaging methods did not reveal thrombi in intracranial and extracranial vessels. But the presence of signs of hypercoagulability in a patient with neurologic focal symptoms allowed us to think about the possibility of cerebral vascular thrombosis. And despite the results of magnetic resonance imaging and multispiral computed tomography of the brain, the search for prothrombogenic factors continued.

Thus, we want to draw attention to the possibility of the development of hemostasis disorders in children not only during the acute course of SARS-CoV-2 infection, but also in the post COVID-19 period. Diagnosis of the thrombosis causes should include investigation of inherited thrombophilias as the most significant risk factor for increased thrombosis.

Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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