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Thromboembolic complications associated with COVID-19 infection in children

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Introduction

With increasing knowledge of the course of coronavirus disease 2019 (COVID-19) in children, it is possible to detect complications associated with the disease more frequently, such as thromboembolic complications, with the most frequently observed being venous thromboembolisms, covering the spectrum of deep vein thrombosis and pulmonary embolism [1–3]. The prothrombotic and proinflammatory state accompanying COVID-19 infection can lead to ischemic stroke in children [4]. One parameter that closely correlates with thromboembolic incidents is elevated D-dimer level [5]. Moreover, thrombotic events occur in some patients despite thromboprophylaxis [3].

The objective of the work was to present two cases of pediatric patients who developed thromboembolic complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

We here describe two patients hospitalized in the Department of Pediatrics, Hematology and Oncology (PHO) between December 2021 and March 2022.

Case series

Patient 1

The first presented case associated with thromboembolic complications was a 4-month-old boy admitted to the PHO because of coagulation disorders. The patient was born at 40 weeks' gestation by emergency cesarean section due to maternal COVID-19 infection. He scored 7/10 on the Apgar scale due to respiratory failure and moderate birth asphyxia. On the first day of life, the patient developed convulsive seizures with breathlessness, and these were resistant to treatment with phenobarbital, diazepam, clonazepam and pyridoxine. Hence, he was transferred to the Neonatal Intensive Care Unit. Due to suspected early onset sepsis, combined empiric broad-spectrum antibiotic therapy was applied. On the second day of life, polymerase chain reaction (PCR) test for SARS-CoV-2 was found to be positive. Based on cerebrospinal fluid examination, neuroinfection was excluded. Blood and stool cultures were also negative. On the following days, the neonate's condition deteriorated, including cough, fever, increasing inflammatory markers and coagulation disturbances tending towards hypercoagulopathy (high D-dimers, high fibrinogen, and decreased antithrombin III level). A chest X-ray confirmed pneumonia in the newborn. Improvement occurred after antibacterial treatment. At the first screening of D-dimers, the measured value reached 1,537 ng/mL (norm <500 ng/mL), gradually decreasing over the following days. In the course of further diagnostics, a computed tomography (CT) scan of the head was performed, which described an edematous-ischemic area in the left frontoparietal region 25 × 68 mm in dimension. An initial magnetic resonance imaging (MRI) scan confirmed an ischemic stroke, describing a 55 × 22 × 33 mm ischemic lesion in the left temporal lobe and a 14 × 10 × 6 mm small hemorrhagic area in the left occipital region.

At the age of 4 months, the patient was admitted to the PHO. The only abnormality was slight muscle weakness in the right upper limb. Laboratory results showed normal blood count parameters, as well as slightly elevated

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D-dimers (686 ng/mL) and decreased fibrinogen levels (154 mg/dL; normal 200–393 mg/dL). Moreover, laboratory tests for thrombophilia were performed. Factor VIII and protein S concentrations were normal. Genetic testing excluded factor V Leiden mutation and prothrombin gene mutation. A follow-up MRI scan showed no ischemic changes in the acute phase within the brain, and some changes corresponding to a post-stroke scar.

During the hospitalization, the patient received enoxaparin 1.5 mg/kg 1 × daily subcutaneously, valproic acid 2 × 7.5 mg/kg, as well as iron, cyanocobalamin, folic acid and pyridoxine supplementation. From the overall clinical presentation, and by excluding other possible causes of coagulopathy, it was established that the possible cause of the thromboembolic incident was SARS-CoV-2 infection.

Patient 2

A 13-year-old girl was admitted to hospital because of deep vein thrombosis of the left lower limb. A week before admission, sudden pain in the left lower limb had appeared. The patient denied chronic diseases, trauma, prolonged immobilization, and taking medication, including contraceptives. Two months before hospitalization, she had an upper respiratory infection (no swabbing for SARS-CoV-2). On admission to the PHO, physical examination revealed: forced positioning, edema, redness and positive Homans' sign in the left lower limb. Dyspnea, chest pain and hemoptysis were not observed. Laboratory tests showed elevated D-dimers (6,610 ng/mL), prolonged prothrombin time (15.9 s; normal 10.2–12.9 s), and elevated C-reactive protein (CRP) (50 mg/L; normal <5 mg/L).

Doppler ultrasound showed no flow in the left external iliac and common iliac veins. Also, inferior vena cava with visible thrombus in the central part and marginal flow: the thrombus reached the level of the right renal vein outlet. Enoxaparin 2 × 1 mg/kg was started, with clinical improvement. Lupus anticoagulant, p-cardiolipin antibodies and anti-beta$_2$-glycoprotein antibodies were not found, thus antiphospholipid syndrome was excluded. Congenital thrombophilia was excluded by genetic testing. Positive IgG anti-SARS-CoV-2 antibodies were found in the examined sample.

An angio-CT of the chest described a thrombosed, obstructed superior lobe artery together with segmental arteries to the upper part of the upper lobe of the right lung. In addition, in the right pulmonary artery and segmental arteries there were present small defects in contrasting which could correspond to thrombi. Moreover, a thrombus within the inferior vena cava at the level of the hepatic vein outflow was suspected — the flow at this level was mainly peripheral. Therefore, abdominal angio-CT was performed, which described venous thrombosis of the left iliac axis in the inferior vena cava from the junction of the iliac veins to the segment just below the renal veins. Hepatic vein thrombosis was excluded. The girl was consulted by a cardiologist — cardiac markers were negative, electrocardiogram (ECG) showed sinus rhythm, regular heart rate 80/min, corrected QT interval (QTc) 0.43 s, no ST-T disturbances, and no hypertrophy. In echocardiogram, no abnormalities were found, despite weak low velocity flow in right pulmonary artery.

During hospitalization, pain and swelling of the left lower limb decreased. Based on the whole clinical picture, the thromboembolic changes were most probably due to the COVID-19 infection.

Discussion

In both presented cases, SARS-CoV-2 infection possibly increased the risk of a thromboembolic complication. Recent studies have described a spectrum of thromboembolic incidents in children as a consequence of COVID-19, including acute ischemic stroke involving one or more vessels and deep vein thrombosis with pains in an extremity, edema and pruritus [6, 7].

It has been proven that complications can occur in children of different ages, particularly affecting those over 12 years of age, but cases of thrombotic incidents have also been reported in infants [3]. A feature uniting our patients was elevated D-dimers. The first patient, during COVID-19 infection and after the incident of ischemic stroke, showed increased D-dimers. The result was slightly reduced but was still above the norm even after several months. In the second patient, D-dimers were the highest with accompanying CRP elevation and signs of extensive venous thrombosis. In addition, the laboratory test of both patients indicated hypercoagulopathy. Elevated levels of fibrinogen, ferritin, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), increased platelet count and prolonged prothrombin time (PT) were also observed in pediatric patients after COVID-19 infection in a 2020 US study [8]. Each patient was diagnosed for thrombophilia, protein C and S and coagulation factor VIII levels, as well as genetic tests for factor V Leiden mutation and prothrombin gene mutation. Antiphospholipid syndrome was also excluded. Low-molecular-weight heparin had been used in the treatment of patients.

Current works report a low percentage of possible COVID-19 intrauterine infection. The factor in determining the moment of infection (i.e. *in utero*, intrapartum or postpartum) is the timing of the sample collection and contact with the infected mother [9].

It is difficult to assess the moment of infection in patient 1. The boy remained asymptomatic for the first few days, which supports a possible postnatal exposure. In addition, seizures were the symptom of stroke, but possibly also of SARS-CoV-2 infection, which may suggest that the symptoms of infection appeared as early as day 1 of life and the neonate could have been infected in an intrauterine

manner. Studies are needed to determine which route of infection induces thromboembolic complications most frequently in newborns.

In the 13-year-old girl, the detection of IgG antibodies to SARS-CoV-2 raised the suspicion that the patient could developed pediatric inflammatory multi-organ syndrome temporally associated with SARS-CoV-2 (PIMS-TS). Several research studies have also demonstrated an increased prevalence of coagulopathy in patients with PIMS-TS [5, 10]. The diagnosis of PIMS-TS requires the fulfilment of six criteria, based on definitions according to the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) [11, 12], plus Polish guidelines such as: age (0–18 years); fever >38.0°C for ≥3 days; high inflammatory markers (elevated values of: CRP; procalcytonin; fibrinogen; D-dimers; ferritin); multi-organ damage (symptoms from at least two organs); exclusion of other causes; and COVID-19-association. Our 13-year-old patient did not meet the fever criterion and presented symptoms only from the cardiovascular system. Therefore, her symptoms and disease manifestation were not a manifestation of PIMS-TS and were probably related to recent COVID-19.

To conclude, coronavirus-infected children, as well as adults, can develop thromboembolic complications after SARS-CoV-2 infection. Pediatric patients with COVID-19 present coagulation abnormalities and a predisposition to thrombosis [8, 13, 14], indicated mostly by elevated D-dimers. Further exploration of the mechanisms and predisposition to thromboembolism in children following SARS-CoV-2 infection would be advisable.

Authors' contributions

AJ, MC, NC, KC, MRP — design of the study. MRP — provision of clinical data. AJ, MC, NC, MRP — literature search and analysis of data. AJ, MC, NC, MRP — manuscript writing. AJ, MC, NC, KC, MRP — critical revision and final approval.

Conflicts of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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