

CASE REPORT

Stroke in the vascularization area of Percheron artery during treatment of severe pneumonia in a patient with ulcerative colitis

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ABSTRACT

Stroke is an acute onset neurological event that is entirely vascular in origin. Patients with inflammatory bowel disease are at increased risk of thromboembolic events, and consideration of prophylactic anticoagulation in such patients with additional multiple risk factors seems justified.

The aim of this case report was to present a patient with severe ulcerative colitis undergoing biological therapy, who experienced a stroke in the vascularization area of Percheron artery during treatment of septic pneumonia. Due to severe course of ulcerative colitis, he was eligible for biological therapy. During hospitalization for pneumonia, patient developed neurological signs consistent with a stroke, confirmed by magnetic resonance imaging. Further investigations revealed factor von Leiden mutation and patent foramen ovale.

Given the rarity of stroke in the pediatric population, early and accurate diagnosis is important to start appropriate treatment as soon as possible.

KEY WORDS:

risk factors, stroke, pediatrics, ulcerative colitis.

INTRODUCTION

Stroke is an acute onset neurological deficit due to vascular causes only. In childhood, strokes occur between 29 days and 18 years, with 50% of events as hemorrhagic incidents and 50% ischemic. The classification of ischemic strokes distinguishes arterial ischemic stroke (AIS) from sinovenous thrombosis [1].

In 100,000 children, an estimated 3 to 13 cases suffer from pediatric AIS every year [2]. The incidence rate varies according to age and gender; it is the highest for infants and children under 5 years old and higher for boys than girls [3].

Clinical presentation of stroke depends on the etiology and age of the patient. The sudden onset of focal neurological deficits should suggest a stroke. The most common symptoms are hemiparesis, hemifacial weakness, speech or language disturbance, vision disturbance, ataxia, seizures, and headache [3].

Magnetic resonance imaging (MRI) is the preferred method for children with suspected stroke, as it is more sensitive than computed tomography (CT) for detecting ischemic changes in the acute phase. However, CT can be used if MRI is unavailable [2]. Echocardiography is also recommended for children with suspected AIS to identify potential risk factors of AIS, such as patent foramen ovale (PFO) [1].

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In the treatment of stroke, according to Summary of Product Characteristics in Poland, thrombolytic therapy may be considered in children aged 16 years and older after risk-benefit assessment, while in younger patients, it is off-label only. Mechanical thrombectomy may also be considered in older children. Patients with ischemic stroke should receive acetylsalicylic acid (ASA) in the absence of contraindications, and treatment should be continued for two years, as the recurrence risk is highest during this period [2].

The thalamus is part of the diencephalon, which is composed of gray matter clusters, also known as nuclei [4]. The thalamus receives blood supply from branches arising from the posterior cerebral artery and posterior communicating artery [5].

The medial thalamus and anterior midbrain are supplied by thalamic perforating arteries branching from the posterior cerebral artery, specifically P1 segments. There are several vascularization variants. The most common, type 1, has branches from each P1 segment. In type 2, the artery of Percheron (AOP) branches from P1 supply the bilateral thalamus and anterior midbrain, while type 3 features branching arteries forming an arch to vascularize the thalamus [6].

The frequency of AOP occurrence is 4–12% in the general population. Strokes involving vascularization of AOP are extremely rare, accounting for 0.1–2% of all strokes in the adult population. There are no epidemiological data for the pediatric population. Obstruction of the AOP vascular lumen leads to bilateral thalamic infarction, primarily caused by cardio-embolism [7].

Patients with inflammatory bowel disease (IBD) are at an increased risk of venous thromboembolism (VTE) compared with those without IBD [8]. Barclay *et al.* [9] observed a trend towards higher cerebral thromboembolic events in IBD patients.

Here, we present a case report of patient with severe ulcerative colitis, who experienced a stroke in the AOP vascularization area during treatment [10, 11].

CASE REPORT

A 17-year-old patient with severe ulcerative colitis, undergoing biological treatment with tofacitinib, was admitted to pediatric gastroenterology ward due to severe pneumonia. Ulcerative colitis was diagnosed in March 2022 based on endoscopic examination revealing an extensive form with moderate disease progression, with 40 points on the pediatric ulcerative colitis activity index (PUCAI). The patient initially received steroids and 5-ASA, but incomplete remission led to intensified treatment with rectal budesonide. In May 2022, the patient's steroid therapy was discontinued; however, in July the same year, a flare-up of the disease occurred, with a PUCAI score of 70 points. Steroid therapy was reinitiated, with azathioprine added to the treatment. Failing to achieve remission (cyclospo-

rine and infliximab treatment), the patient was referred to the Children's Health Center, a reference center, where he underwent other biologic therapies (ustekinumab, adalimumab, and vedolizumab); all were ineffective. Tofacitinib, started in December 2022, decreased the PUCAI score to 15 points. On April 2, 2023, the patient was transferred from the district hospital to pediatric gastroenterology ward of clinical hospital, due to pneumonia. On admission, his condition was severe; the patient was in a semi-sitting position, with fingers' cyanosis and facial skin pallor. On examination, the patient had the following initial vital signs: temperature 38°C, heart rate 145 beats/min, respiratory rate 44 breaths/min, blood pressure 74/37 mmHg, and oxygen saturation 86%. On the left side, at the basal area along the paravertebral line, bronchial breath sounds were heard, while in the mid-scapular and axillary lines, there was a reduction in vesicular breath sounds. Laboratory tests showed the following abnormalities: C-reactive protein level of 310 mg/l, procalcitonin level of 38 ng/ml, platelet count of $114 \times 10^9/l$, white blood cell count of $1.16 \times 10^3/\mu l$, creatinine clearance of 48 ml/min/1.73 m², prolonged international normalized ratio and prothrombin time, elevated fibrinogen and D-dimers, and CO₂ retention in the blood gas. Chest X-ray revealed bilateral, symmetric, patchy-linear consolidations in the middle and lower lung fields, and an arc-shaped shadow in the left lower lung field extending to the lateral contour of the fourth rib. Immediately, empirical therapy with vancomycin and meropenem was started and as a thromboprophylaxis, low molecular-weight heparin (LMWH) dalteparin was initiated. The choice of this antibiotic therapy was made on the hospitals' duty, and was not modified during the following days, although it was not according to any guidelines. Biological treatment was discontinued.

When *Streptococcus pyogenes* was cultured from the blood, clarithromycin was added to the treatment. According to the guidelines, the drug of choice for the treatment of *S. pyogenes* is penicillin, whereas severe invasive *S. pyogenes* infection can be treated with vancomycin or clindamycin. Also, clarithromycin can be used in case of immediate hypersensitivity to β -lactams. In our patient, clarithromycin was chosen due to the lack of penicillin in our hospital but according to the antibiogram. On the 10th day of hospitalization due to intensified coughing, sputum was collected for *Mycobacterium tuberculosis* culture, confirming its presence, and the patient was observed to have convergent strabismus in the left eye, oculomotor nerve paralysis in the right eye, visual acuity disturbances, and gradually developing consciousness disturbances. He exhibited reduced speech fluency, which gradually became slow and very unclear. Subsequently, the patient's condition deteriorated rapidly, leading to complete loss of consciousness and left-sided hemiparesis. The symptoms resolved completely within 15 minutes. An urgent contrast-enhanced CT ruled out acute hemor-

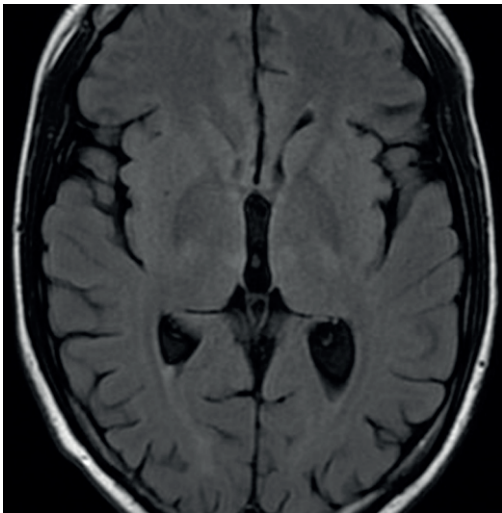


FIGURE 1. Brain MRI – hyperintense lesion with mild diffusion restriction in the left thalamus

rhage or other abnormality, while brain MRI revealed a small area of increased signal in T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, with features of mildly expressed diffusion restriction in the left thalamus (Figure 1). Electrocardiogram (ECG) showed deeply negative T waves in II, III, and aVF leads. In the afternoon of the same day, the patient experienced two short episodes of impaired eye movement, and troponin level escalated from 323 to 380 ng/l. The dose of LMWH was increased to a therapeutic dose of 1 mg/kg of body weight every 12 hours, with ASA included in the treatment.

Two days later, a follow-up MRI revealed bilateral areas of elevated signal intensity in the medial parts of the thalami on T2-weighted and FLAIR images, exhibiting clear features of water molecule diffusion restriction, indicating progression when compared with previous examination. The findings corresponded to ischemic changes within the vascular territory of anatomical variant of AOP in the subacute phase (Figure 2). After cardiological consultation, the patient was not eligible for urgent coronary

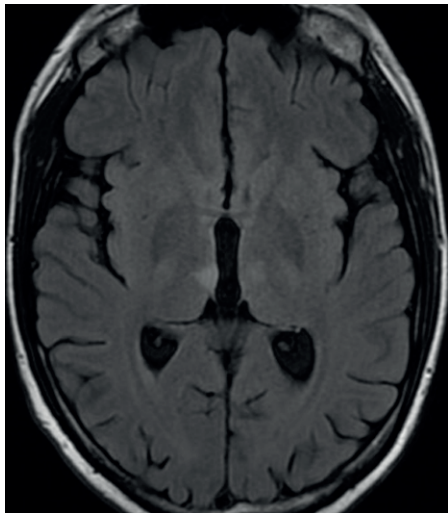


FIGURE 2. Follow-up brain MRI – bilateral medial thalamic ischemia in AOP territory

angiography. Two days after, a follow-up brain MRI revealed a partial regression of the previously described changes within the thalami.

During hospitalization, a thrombophilia screening was performed using polymerase chain reaction method, which confirmed the presence of the factor V Leiden mutation and genetic predisposition to thrombophilia. Following antibiotic therapy and chest X-ray improvement, the patient was discharged with a recommendation for planned PFO evaluation in cardiology department.

In May 2022, the patient was admitted to cardiology department. An echocardiogram showed no abnormalities, with normal heart function. A transcranial Doppler (c-TCD) detected one high-intensity transient signal (HITS) at rest, and around 20 microembolic signals during the Valsalva maneuver, indicating a moderate right-to-left shunt. The patient was qualified for a PFO closure surgery, and underwent this procedure in May 2023. During further observation, the patient did not show any neurological deficit. The course of events is summarized in Figure 3.

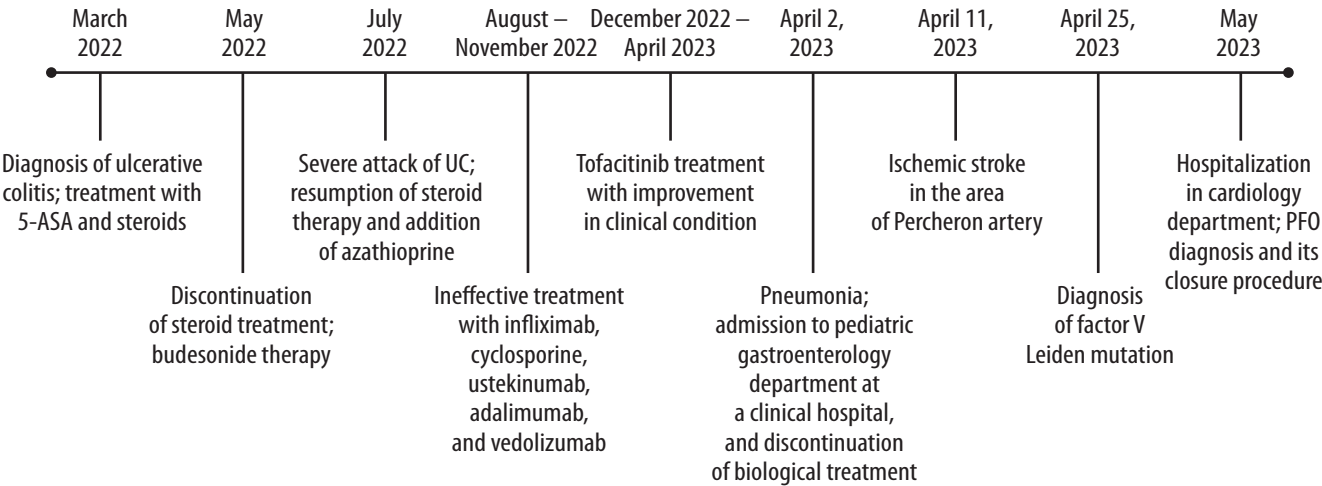


FIGURE 3. Timeline of events

DISCUSSION

Patients with IBD have a significantly increased risk of venous thromboembolism (VTE), with ulcerative colitis (UC) as a contributing factor. VTE development is further influenced by disease pathogenesis as well as activity, age, hospitalization, medications, such as glucocorticoids and tofacitinib, genetics, surgery, and pregnancy [10, 12–14]. Factors stimulating inflammatory and thrombotic processes during the active phase of the disease include inflammatory cytokines, acute-phase reactants, procoagulants, and platelets, accompanied by a reduction in anticoagulant level. Moreover, during an exacerbation of IBD, a decrease in protein S and antithrombin, which are anticoagulants, is observed [10]; therefore, it is not only the disease itself but also disease activity, which increases the risk of VTE in IBD patients. In a retrospective cohort study by Grainge *et al.* (2010) [8], the adult population of patients with IBD flares had the highest risk of VTE compared with patients with active disease or remission. In another single-center retrospective study on IBD patients with thromboembolic complications, 71% of VTE events were diagnosed during the active phase of IBD [10].

The high-risk of thromboembolic events in our patient was indicated by the elevated D-dimer and fibrinogen levels, and his young age. It has been demonstrated that younger IBD patients have a four-fold higher risk of VTE compared with older patients, although the incidence of VTE in this group is rare [10].

In a recent meta-analysis, Mahajerin *et al.* [15] reported that another risk factor for VTE was recent hospitalization associated with reduced mobility. Other factors, such as central catheters, prolonged hospital stay, intubation, and intensive care unit (ICU) admission, significantly increased the risk of hospital-acquired venous thromboembolism (HA-VTE). Furthermore, hospitalized patients with IBD have higher rates of VTE and VTE-related mortality than hospitalized patients without IBD [13]. In our patient, right before the VTE incident, he underwent a prolonged hospitalization due to pneumonia.

Medications used in the treatment of UC may also increase the risk of thromboembolism. After the diagnosis, our patient was treated with steroids. In a meta-analysis by Sarlos *et al.* [14], the use of corticosteroids was shown associated with a higher risk of VTE events in IBD patients.

In the case of our patient, tofacitinib was introduced into the treatment regimen following the failure of numerous alternative therapies. Tofacitinib is a pharmacological agent that belongs to the class of drugs known as Janus kinase (JAK) inhibitors, showing activity against both JAK1 and JAK3. Consequently, it impedes the signal transduction of cytokines, including IL-2, IL-4, IL-6, IL-7, IL-9, IL-15, IL-21, and interferon- γ [16, 17]. Upadacitinib is another JAK inhibitor, which specifically targets JAK1, and reduces inflammation by limiting immune cell migration, adhesion, and cytokine release. Although

upadacitinib has been approved for adult use in Crohn's disease and UC, and tofacitinib is currently the only approved drug for adult UC, their utility in pediatric populations is largely unexplored. Several case series and case reports on pediatric patients have demonstrated the effectiveness of these JAK inhibitors in helping patients achieving clinical remission [18].

Studies conducted on patients with rheumatoid arthritis treated with tofacitinib have revealed an elevated risk of VTE. This risk was particularly pronounced in patients with a history of other cardiovascular risk factors, who were treated with a 10 mg dose of tofacitinib [16, 17]. Pediatric data on the efficacy and safety of this drug are poor. In one of the largest retrospective observational studies of 101 children aged 2–18 years with UC from 16 centers in Europe, North America, and the Middle East, no thromboembolic events were reported [19]. This study highlights the need for further research on the association between thrombotic complications and using JAK inhibitors in treating children with UC. JAK inhibitors have the potential to reduce the need for prolonged steroid use in this population, and may significantly eliminate the necessity for eventual colectomy due to refractory disease.

The underlying disease and condition being treated are independent factors, which contribute to stroke. However, it is not uncommon for multiple coexisting factors to be identified in a single patient. This served as the basis for expanding the diagnostic process of our patient, which ultimately led to the diagnosis of PFO and factor V Leiden mutation.

Stroke symptoms depend on various factors, such as age, location, and size of brain ischemia [2]. The AOP symptom triad includes consciousness disturbances, cognitive decline, and vertical eye movement paralysis [20]. Our patient displayed speech disorders with reduced verbal fluency and gradual loss of consciousness, leading to complete unconsciousness. Additional symptoms were right oculomotor nerve paralysis, left eye convergent strabismus, and visual acuity disturbances. The first episode lasted a few minutes, with a subsequent episode occurring several hours later.

Another potential risk factor for ischemic strokes is congenital thrombophilia, such as a deficiency of antithrombin, protein C or S, or factor V Leiden and prothrombin mutations. In our patient, the factor V Leiden mutation in one copy of the gene (heterozygote) was diagnosed, which is associated with a moderate risk of thromboembolism. The presence of thrombophilia has been used in risk-assessment models in adult and pediatric acute leukemia patients. However, its utility for predicting healthcare-associated VTE in a pediatric population has not yet been demonstrated [12].

Research on the frequency of genetic mutations, such as factor V Leiden or prothrombin G20210A, has shown similar rates in patients with and without IBD as well as for IBD patients with and without VTE [10].

In cases with a history of cryptogenic stroke diagnosed with PFO and thrombophilia, PFO surgical closure is the recommended course of treatment [21]. Following the prevailing guidelines, surgical closure of the obstructed PFO was undertaken in our patient.

Given the VTE risk factors in IBD patients, the need for preventive measures arises. According to the European Crohn's and Colitis Organization and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition, prophylactic anticoagulation is recommended when one or more risk factors are present during disease activity due to the increased VTE risk. These factors include smoking, oral contraceptives, immobilization, central venous catheters, obesity, significant infection, prothrombotic disorders, previous VTE occurrence, and family history of VTE. In adults with acute severe colitis (ASC), LMWH is considered if risk factors are present, while in children, further research investigating LMWH's safety and effectiveness is needed. LMWH may be used if two or more risk factors are present, with minor bleeding episodes being rare. During ASC, mobilization, hydration, and removal of unnecessary central catheters are crucial. The risk of VTE is higher in UC than in Crohn's disease [22]. Our patient received prophylactic anticoagulation with LMWH during pneumonia hospitalization.

CONCLUSIONS

Patients with UC have many risk factors for thromboembolic events. Although stroke is rare in the pediatric population, it is important to consider these risk factors during the diagnostic process, and to recognize early warning signs of a stroke in order to start the necessary treatment without delay. Prophylactic anticoagulation is recommended for patients with multiple risk factors. In addition, the relationship between IBD and VTE is not fully understood and requires further studies.

DISCLOSURES

1. Institutional review board statement: Not applicable.
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4. Conflicts of interest: None.

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