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Ketoacidosis and otitis media as a potential cause of cerebral venous thrombosis in a 7-year-old boy

**Justyna Lipińska*¹, Maria Kowalczyk¹, Łukasz Lipiński¹, Izabela Kopec¹,
Joanna Mitek-Palusińska², Magdalena Woźniak²**

¹Student Scientific Society at the Department of Pediatric Radiology, Medical University of Lublin, Gębali 6, 20-093 Lublin, Poland

²Department of Pediatric Radiology, Medical University of Lublin, Gębali 6, 20-093 Lublin, Poland

Justyna Lipińska*¹, ORCID: 0000-0002-5712-0025, e-mail: lipinska.justyna98@gmail.com
Maria Kowalczyk¹, ORCID: 0000-0002-4319-5552, e-mail: marysia.kowalczyk@gmail.com
Łukasz Lipiński¹, ORCID: 0000-0002-0990-6269, e-mail: lipinski.lukasz00@gmail.com
Izabela Kopec¹, ORCID: 0000-0002-6724-6668, e-mail: izabela0kopec@gmail.com
Joanna Mitek-Palusińska², ORCID: 0000-0002-3971-1809, e-mail : joanna.mp@wp.pl
Magdalena Woźniak², ORCID : 0000-0001-7436-2432, e-mail : magdalena.wozniak@umlub.pl

* Corresponding author:

Justyna Lipińska,
ul. Radości 1/60
20-530 Lublin, Poland
Tel. : +48727687552
lipinska.justyna98@gmail.com

Abstract

Cerebral venous sinus thrombosis (CVST) in childhood is a rare disorder, occurring most often in the neonatal period, with mortality approaching 10%. This condition has multifactorial etiology including common childhood illnesses such as fever, infection, dehydration, and anemia, as well as acute and chronic medical conditions such as congenital heart disease, nephrotic syndrome, and malignancy. Thrombosis can also develop and propagate in response to local venous stasis. A large number of children have coincident local head or neck pathology, including head trauma, brain tumors, or recent intracranial surgery. Clinical symptoms are frequently nonspecific and include seizures, depressed level of consciousness, coma, lethargy, nausea, vomiting, headache, visual impairment, papilledema, and hemiparesis, which may often obscure the diagnosis and delay treatment. In the case of patients with neurological symptoms, imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) are invaluable in diagnostics of various pathologies of the nervous system, because of their non-invasiveness, high sensitivity, and specificity. Early diagnosis with management along with a plan for secondary prevention can save from catastrophic consequences.

Key words: cerebral venous sinus thrombosis, ketoacidosis, diabetes mellitus, otitis media

Introduction

Cerebral venous sinus thrombosis (CVST) is a blood flow disruption of local or diffuse character, secondary to obstruction of the venous vessels in the brain [1]. In adults, the incidence of CVST is estimated between 2-5 cases per million individuals per year. The annual incidence in children is higher and amounts to up to 7 cases per million per year, with mortality approaching 10% [2, 3, 4, 5]. More than 40% of pediatric CSVT involve neonates with an incidence of about 26 per million per year. The actual prevalence is probably higher, despite increasingly sensitive diagnostic methods [3,4]. In adults, cerebral venous sinus thrombosis the proportion of females is 75% and this predominance is restricted only to the fertile age, as it is not seen in the pediatric population, because of the absence of sex-specific risk factors [5, 6]. Same as in adults, the most frequently involved sinuses are superior sagittal and the transverse sinuses. It is also observed that transverse sinuses' involvement relates more often to children older than 2 years of age [5].

Thrombosis in the cerebral venous system leads to outflow obstruction and in consequence to an increase in the hydrostatic pressure in the veins and capillaries, which in absence of compensation from the anastomotic circuit of the cerebral venous system, results in driving fluid into the interstitium and producing edema. Furthermore, if the venous pressure exceeds the arterial pressure, a reduction of arterial flow and consequent arterial ischemia can occur [1, 3,5].

The etiology is often multifactorial and is similar in neonates and older children. A predisposing comorbid condition or disability is found in up to 95% of affected patients. Local or systemic infections, dehydration, fever, vascular trauma, cancer, acute lymphoblastic leukemia (ALL), asphyxia and maternal problems during the pregnancy and metabolic disorders have been reported as risk factors. Also, CVST can arise and extend in response to local venous stasis as a complication of brain injury or recent intracranial surgery [3]. Inherited thrombophilia such as protein C, S, anti-thrombin III deficiencies, factor V Leiden mutation, and other acquired prothrombotic states have been identified in children, who have suffered from CVST [2].

The symptoms are variable and nonspecific, because of that the diagnosis is frequently delayed to the median period of a week from the onset of clinical manifestation [5]. The most common presenting signs are the following: headache, seizures, depressed level of consciousness, lethargy, nausea, and vomiting, visual impairment, papilledema, hemiparesis, ataxia, cranial nerve palsies (VI), and acute psychiatric symptoms. Moreover, neonates may develop respiratory failure and jittery movements [3, 5].

A high index of suspicion in the acute phase of the disease is necessary for early confirmation of the CVST diagnosis. Unenhanced computed tomography (CT) is usually the first imaging investigation performed given the nonspecific clinical presentation, with a hyperdense thrombus in the occluded sinus being a typical, yet sometimes subtle imaging finding. Accompanying signs of venous infarction, hemorrhage or cerebral edema are not uncommon. CT venography (CTV) may confirm the diagnosis by revealing a filling defect in the place of occlusion. It is not recommended to perform routine contrast-enhanced CT as it can miss the diagnosis in up to 40% of patients with CVST.

Magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) can be a suitable alternative for CTV, especially concerning the children population, in which reducing radiation exposure is of particular significance [7].

In the treatment of cerebral venous sinus thrombosis, the most important is supportive care, rehydration, and in the case of infection, causal therapy. The most commonly used drugs are low molecular weight heparins (LMWH) and vitamin K antagonists (VKA) under INR control. Thrombolysis, thrombectomy, and surgical decompression are used in seriously ill patients, usually in a coma and with extensive thrombosis [3].

Case report

A 7-year-old boy was referred from a local hospital and admitted to the Department of Pediatric Endocrinology and Diabetology due to newly diagnosed diabetes mellitus. In medical history for 4 days, the child has been presenting the symptoms such as polydipsia, polyuria, nocturia, and weakness. For 2 days he has been vomiting 3-4 times per day and therefore the boy was initially admitted to the local hospital. On the basis of the laboratory tests (Table 1), diabetes mellitus was diagnosed and it was decided to transfer the child to the Department of Pediatric Endocrinology and Diabetology. Additionally, a week before the hospitalization, the patient had been treated for otitis media.

Tab. 1. Laboratory results of the patient in local hospital

Parameters	Diagnosis
Glycemia [mg/dl]	1650,5 (↑)
pH	7,212 (↓)
Base excess (BE) [mEq/l]	-17,4 (↓)
Na ⁺ [mmol/l]	149,70 (↑)
K ⁺ [mmol/l]	5,97 (↑)
C- reactive protein (CRP) [mg/l]	6,06 (↑)
Urea [mg/dl]	56,50 (↑)

On admission, the boy was in average general condition, sleepy with Kussmaul breathing. Physically he had tachypnoea 32/min, tachycardia 140/min, dry oral mucosa, and balanitis. Laboratory tests were performed repeatedly (Table 2) and based on the results, immediate intensive intravenous fluid and insulin therapy was implemented. Meanwhile, PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by oropharyngeal swab was done with a negative result.

Tab. 2. Laboratory results of the patient on admission to the Department of Pediatric Diabetology and Endocrinology

Parameters	Diagnosis
pH	7,168 (↓)
Base excess (BE) [mEq/l]	-21,70 (↓)
Na ⁺ [mmol/l]	159 (↑)
K ⁺ [mmol/l]	4,69 (N)
Glycated hemoglobin (HbA1c) [%]	12,84 (↑)
Urea [mg/dl]	56,50 (↑)
Creatinine [mg/dl]	1,02 (↑)
Fructosamine [μmol/l]	908,0 (↑)

On the first day of treatment the boy was sleepy, apathetic, vomited twice. Neurological examination revealed decreased muscle tone in the upper and lower limbs, positive Kernig's sign, and Brudzinski's neck sign. In the follow-up examination, a tendency for hypernatremia was observed (Na⁺ - 163 mmol/l). Because of suspected cerebral edema, a non-contrast head CT was performed, which showed a hyperdensity in the posterior part of the superior sagittal sinus, in the vein of Galen, left transverse sinus and in the distal parietal veins (Figure 1). The lesions raised suspicion of cerebral venous thrombosis.

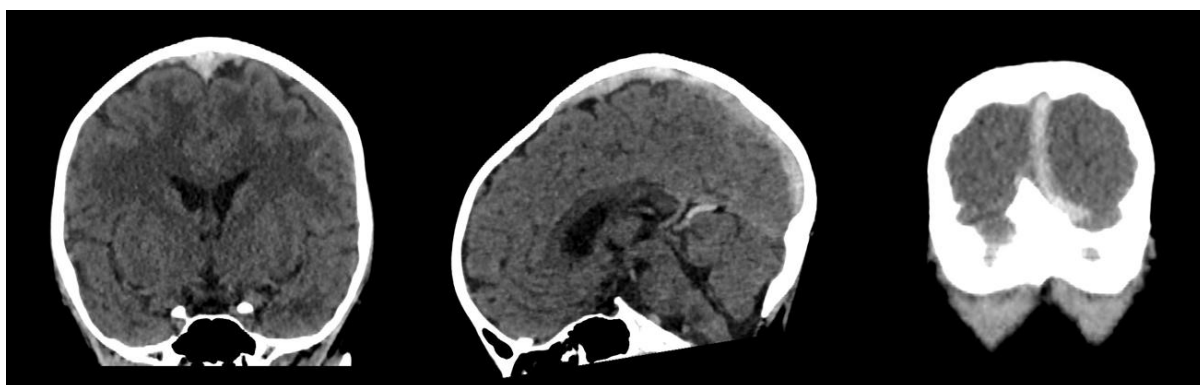


Fig. 1. Non-contrast computed tomography on the first day of treatment showing hyperdense great cerebral vein, superior sagittal sinus and left transverse sinus.

In the coagulation system, there were decreased activated partial thromboplastin time (APTT) – 18,3 s and elevated d-dimers level – 26 612 $\mu\text{g/l}$. After consultation with the transfusiologist 0,4 ml fraxiparin twice a day was ordered. During the next 3 days of hospitalization, the boy required intravenous hydration due to lack of appetite, had headaches, subfebrile condition, and vomited several times. On an urgent procedure, a contrast-enhanced MRI (Figure 2) and MRV in time-of-flight technique (Figure 3) were performed, which demonstrated a massive venous thrombosis of the superior sagittal sinus and left transverse sinus. There were also thrombotic lesions in the parietal veins and the cerebellar veins between the vein of Gallen and straight sinus.

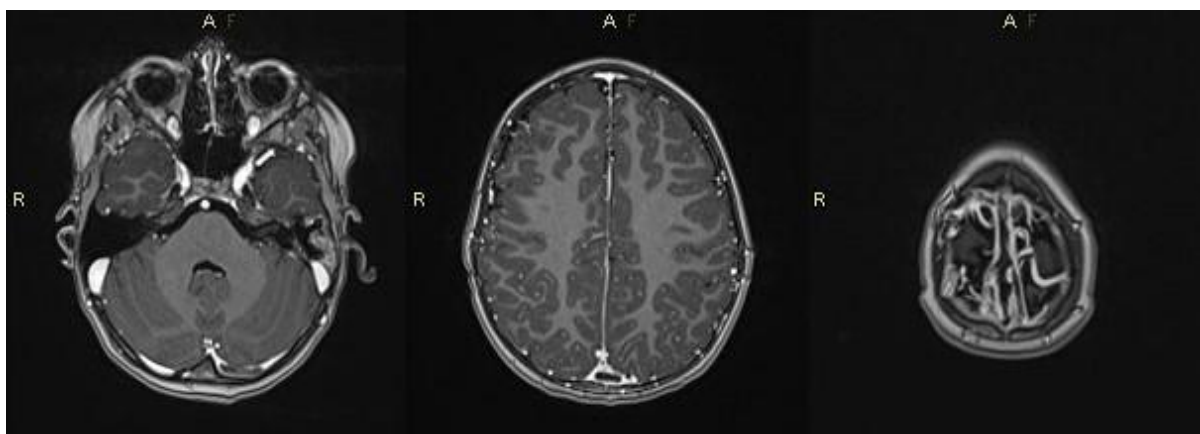


Fig. 2. Contrast-enhanced magnetic resonance imaging revealing filling defects at the sites of occlusion – left transverse sinus and superior sagittal sinus.

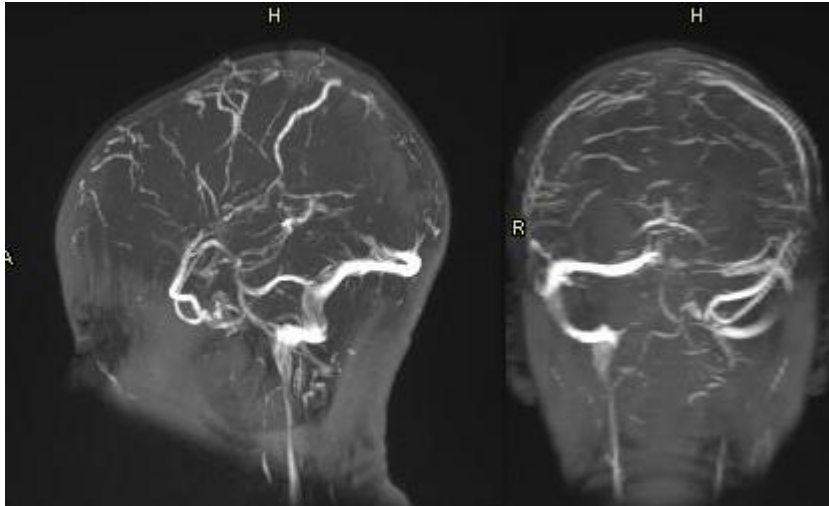


Fig. 3. Time-of-flight magnetic resonance venography showing a lack of flow in the occluded venous sinuses.

Based on neurological and neurosurgical consultation, the boy's condition did not qualify for endovascular or surgical treatment. The treatment was changed to neoparin 0.3 ml twice a day. Periodic headaches continued, but of lesser severity. The boy's condition improved and the results of coagulation tests were within the reference ranges. During hospitalization, hemostasis was repeatedly monitored, and low molecular weight heparin therapy was continued under the control of anti-Xa level. A follow-up MR scan of the head was scheduled. The parents along with the patient were trained to follow a diabetic diet based on a carbohydrate exchanges diet, taking blood glucose measurements, and administering insulin subcutaneously. Because of the difficulty in adaptation to the diagnosis, hospitalization, and treatment process, the patient remained under the care of a psychologist. After two weeks of hospitalization, the boy was discharged home in a good condition.

One month later a follow-up contrast-enhanced MRI and MRV scans were performed (Figure 4) proving regression of thrombotic lesions.

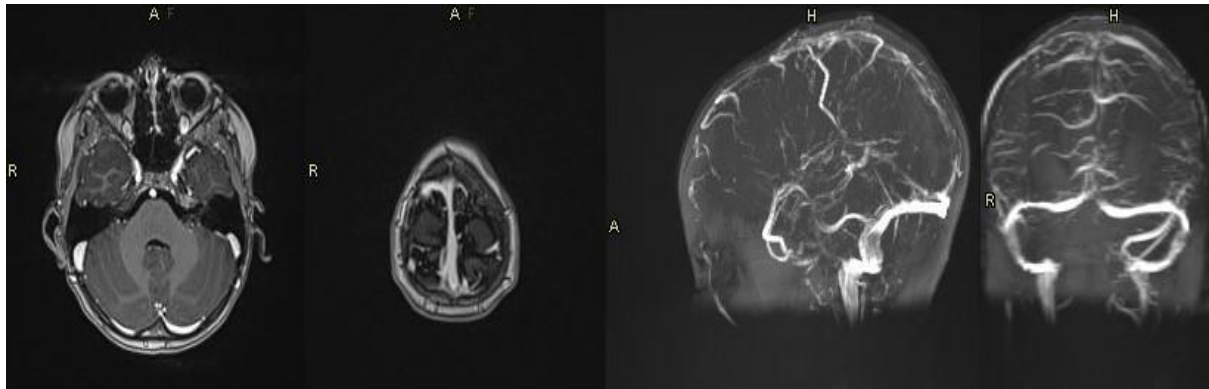


Fig.4. Follow-up MRI and MRV time-of-flight scans showing recanalization of venous sinuses.

Discussion

Although cerebral venous sinus thrombosis is uncommon, it is considered a severe problem because of the potential for associated fatality in children. Wasay et al in 2008 reported that the mortality rate among 70 patients amounted to 13% - 6 neonates and 3 children to 12 years. Factors that increase the risk of death include coma at presentation, presence of intracranial hemorrhage and age less than 12 months [8]. Lower mortality was found by Monagle and Newall (2018) of ~3%, with ~16% of children with CVST dying from their underlying illness [9]. Of that group, 28% have parenchymal hemorrhage [10]. The prevalence of CVST in children at the population level is very low, ranging from 7 to 14 per 1 million per year [9]. This incidence is an underestimate for several reasons: many clinicians are unaware of the condition, some factors make the radiological diagnosis more difficult in the neonate than in the adult, and above all, the clinical presentation is not specific [1]. A pediatric multicenter study in the US showed that CVST affects predominantly children < 6 months old [11].

The disease occurs when at least one component of Virchow's triad is activated: stasis of blood flow, injury to the endothelial lining, and hypercoagulability of blood components. More than 90% of pediatric CVST patients have > 1 risk factor [9]. Based on Philip Connor et. al. (2020) study, commonly reported risk factors for CVST in childhood include birth complications, infection of the head or neck, cancer, traumatic head injury and acquired or inherited thrombophilia [12]. The frequency of discovered prothrombotic disorders, acquired and congenital, can reach 50% of the population, often with presence of Factor V Leiden and G20210A prothrombin gene mutation as the most common hereditary disorders, and the

antiphospholipid syndrome as the most common acquired disorder [1]. Recently SARS-CoV-2 infection has been associated with a hypercoagulable state and potential thrombogenic risk. It is believed that the viral infection triggers an inflammatory response from the endothelium, resulting in its dysfunction and tissue factor expression, leading to massive coagulation activation [13, 14]. Historically, CVST ranked second to meningitis in the preantibiotic areas the most common fatal complication of acute otitis media (AOM) [15]. AOM is a popular infection in children, its incidence is estimated at 256 cases per 1000. However, intracranial complications can be seen in up to 3%, with an incidence rate of 0-2,7% of CVST observed in some of the case series [16]. Acute emergencies can be also a cause of thrombosis in the cerebral venous system. Sasiadek et al (2010) and Keyzer et al reported CVST as the first clinical presentation of diabetic ketoacidosis, this condition in the course of diabetic hyperglycemia seems to be extremely rare, because of the small number of reports of such cases. In diabetic hyperglycemia/ketoacidosis, the diagnosis of cerebral venous thrombosis is even more difficult, because neurologic symptoms are almost always referred as cerebral edema, the most common neurologic complication in diabetic children [17, 18].

In neonates and older children with CVST, the use of anticoagulant therapy, with the potential for intracranial hemorrhage, is more controversial because of the absence of clinical trials and the infectious nature of CVST in many children [12]. According to Monagle et al (2018) there are no anticoagulant drugs approved for use in children, with very little specific research on children. Methods of treatment in children were applied from the practice and recommendations of adults, despite the major differences between adults and children in the epidemiology and pathophysiology of thrombosis, the physiology of the coagulation system, and the impact of this on the pharmacology of antithrombotic agents [9]. Although, Dlamini et al (2010) reported that in the case of cerebral venous sinus thrombosis with infectious etiology many children receive parenteral antibiotic therapy, including second- or third-generation of cephalosporins. The anticoagulation treatment in neonates and older children in the acute setting includes parenteral unfractionated heparin, subcutaneous low molecular weight heparin (LMWH), or oral warfarin. Anticoagulation should be carefully monitored, with APTT for unfractionated heparin, anti-Xa for LMWH, or INR for warfarin, to achieve adequate levels for efficacy while preventing overdose, which may be a cause of intracranial hemorrhage [3].

Conclusions

In conclusion, cerebral venous thrombosis is a rare condition. It can be a complication of both acute otitis media and severe uncompensated hyperglycemia. In the case of children with non-specific neurological symptoms and with the risk factors for thrombosis such as those presented by the patient, it is necessary to keep a special vigilance. Imaging studies such as CT and MRI are invaluable in diagnostics of various pathologies of the nervous system, because of their non-invasiveness, high sensitivity, and specificity. Early diagnosis with management along with a plan for secondary prevention can save from catastrophic consequences.

Literature:

1. Ramenghi LA, Cardiello V, Rossi A. Neonatal cerebral sinovenous thrombosis. *Handb Clin Neurol.* 2019;162:267-280. doi: 10.1016/B978-0-444-64029-1.00012-6.
2. Moiz B, Ukrani RD, Arif A, Akbar I, Sadiq MW, Altaf S. Case Study of Pediatric Cerebral Sinus Venous Thrombosis Center of a Low Middle-Income Country. *Clin Appl Thromb Hemost.* 2021 Jan-Dec;27:10760296211022847. doi: 10.1177/10760296211022847.
3. Dlamini N, Billingham L, Kirkham FJ. Cerebral venous sinus (sinovenous) thrombosis in children. *Neurosurg Clin N Am.* 2010 Jul;21(3):511-27. doi: 10.1016/j.nec.2010.03.006. PMID: 20561500; PMCID: PMC2892748.
4. Heller C, Heinecke A, Junker R, Knöfler R, Kosch A, Kurnik K, Schobess R, von Eckardstein A, Sträter R, Zieger B, Nowak-Göttl U; Childhood Stroke Study Group. Cerebral venous thrombosis in children: a multifactorial origin. *Circulation.* 2003 Sep 16;108(11):1362-7. doi: 10.1161/01.CIR.0000087598.05977.45.
5. Capecchi M, Abbattista M, Martinelli I. Cerebral venous sinus thrombosis. *Journal of thrombosis and hemostasis.* 2018 Jun, 16 : 1918-1931. doi : 10.1111/jth.14210
6. Aguiar de Sousa D. Cerebral Venous Thrombosis: What's New? *Hamostaseologie.* 2021 Feb;41(1):25-30. doi: 10.1055/a-1332-3042.

7. Portanguen S, Tournayre P, Sicard J, Astruc T, Mirade PS. Toward the design of functional foods and biobased products by 3D printing: A review. *Trends in Food Science & Technology*. 2019 Feb; 86 :188-198. doi : 10.1016/j.tifs.2019.02.023
8. Wasay M, Dai AI, Ansari M, Shaikh Z, Roach ES. Cerebral venous sinus thrombosis in children: a multicenter cohort from the United States. *J Child Neurol*. 2008 Jan;23(1):26-31. doi: 10.1177/0883073807307976.
9. Monagle P, Newall F. Management of thrombosis in children and neonates: practical use of anticoagulants in children. *Hematology Am Soc Hematol Educ Program*, 2018 Nov 30;2018(1):399-404.
10. Beslow LA, Abend NS, Smith SE. Cerebral sinus venous thrombosis complicated by cerebellar hemorrhage in a child with acute promyelocytic leukemia. *J Child Neurol*. 2009 Jan;24(1):110-4. doi: 10.1177/0883073808321057.
11. Filippidis A, Kapsalaki E, Patramani G, Fountas KN. Cerebral venous sinus thrombosis: review of the demographics, pathophysiology, current diagnosis, and treatment. *Neurosurg Focus*. 2009 Nov;27(5):E3. doi: 10.3171/2009.8.FOCUS09167.
12. Connor P, Sánchez van Kammen M, Lensing AWA, Chalmers E, Kállay K, Hege K, Simioni P, Biss T, Bajolle F, Bonnet D, Grunt S, Kumar R, Lvova O, Bhat R, Van Damme A, Palumbo J, Santamaria A, Saracco P, Payne J, Baird S, Godder K, Labarque V, Male C, Martinelli I, Morales Soto M, Motwani J, Shah S, Hooimeijer HL, Prins MH, Kubitza D, Smith WT, Berkowitz SD, Pap AF, Majumder M, Monagle P, Coutinho JM. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). *Blood Adv*. 2020 Dec 22;4(24):6250-6258. doi: 10.1182/bloodadvances.2020003244.
13. Ippolito Bastidas H, Márquez-Pérez T, García-Salido A, Luglietto D, García Moreno R, Martínez de Azagra-Garde A, Nieto-Moro M, Leoz-Gordillo I, Budke M, Rivero-Martín B. Cerebral Venous Sinus Thrombosis in a Pediatric Patient With COVID-19. *Neurol Clin Pract*. 2021 Apr;11(2):e208-e210. doi: 10.1212/CPJ.0000000000000899.
14. Dakay K, Cooper J, Bloomfield J, Overby P, Mayer SA, Nuoman R, Sahni R, Gulko E, Kaur G, Santarelli J, Gandhi CD, Al-Mufti F. Cerebral Venous Sinus Thrombosis in COVID-19 Infection: A Case Series and Review of The Literature. *J Stroke Cerebrovasc*

Dis. 2021 Jan;30(1):105434. doi: 10.1016/j.jstrokecerebrovasdis.2020.105434. Epub 2020 Nov 6. PMID: 33190109; PMCID: PMC7833244.

15. Hutz MJ, Moore DM, Hotaling AJ. Neurological Complications of Acute and Chronic Otitis Media. *Curr Neurol Neurosci Rep.* 2018 Feb 14;18(3):11. doi: 10.1007/s11910-018-0817-7.
16. Wong BY, Hickman S, Richards M, Jassar P, Wilson T. Management of paediatric otogenic cerebral venous sinus thrombosis: a systematic review. *Clin Otolaryngol.* 2015 Dec;40(6):704-14. doi: 10.1111/coa.12504.
17. Sasiadek MJ, Sosnowska-Pacuszko D, Zielinska M, Turek T. Cerebral venous thrombosis as a first presentation of diabetes. *Pediatr Neurol.* 2006 Aug;35(2):135-8. doi: 10.1016/j.pediatrneurol.2006.01.010.
18. De Keyzer K, Paemeleire K, De Clerck M, Peeters D, De Reuck JL. Diabetic ketoacidosis presenting as a cerebral venous sinus thrombosis. *Acta Neurol Belg.* 2004 Sep;104(3):117-20.