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PRACA POGLĄDOWA
REVIEW

Cerebral venous sinus thrombosis in pediatric population – a literature review

Zakrzepica zatok żylnych mózgowia w populacji pediatrycznej – przegląd literatury

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ABSTRACT

Cerebral venous sinus thrombosis (CVST) is a rare neurological disorder in the pediatric population. It occurs in children of all ages; nevertheless, newborns and infants younger than three months represent up to 43% of cases. The etiology is multifactorial, often encompassing various predisposing conditions. An early and accurate diagnosis and well-chosen treatment are crucial for better outcomes. The process of diagnosis might cause several difficulties as the symptoms tend to be non-specific. In different age groups the neurological signs may vary, and thus elongate the time between the first contact with the doctor and the initiation of treatment. What is more, there is no marker that is suitable in this diagnostic course. Due to such difficulties, different neuroimaging techniques such as cranial ultrasound, magnetic resonance imaging, and magnetic resonance venography should be used. CVST might lead to severe neurological and cognitive complications. Fortunately, appropriate treatment can help lower the mortality rate and prevent those complications. In this paper, we summarize the current knowledge of CVST in children.

KEYWORDS

stroke, pediatrics, anticoagulants, cognitive impairment

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STRESZCZENIE

Zakrzepica zatok żylnych mózgowia (*cerebral venous sinus thrombosis* – CVST) to rzadkie, ale poważne schorzenie neurologiczne w populacji pediatrycznej. Występuje u dzieci w każdym wieku, ale noworodki i niemowlęta poniżej trzeciego miesiąca życia stanowią nawet do 43% przypadków. Etiologia tego schorzenia jest wieloczynnikowa, obejmuje wiele różnych predysponujących stanów i chorób. Wczesna i dokładna diagnoza oraz dobrze poprowadzona terapia są kluczowe dla uzyskania lepszych wyników leczenia. Proces diagnostyki może być utrudniony z powodu niespecyficznych objawów. W różnych grupach wiekowych objawy mogą się różnić, co może się przyczyniać do wydłużenia czasu pomiędzy pierwszym kontaktem z lekarzem a zainicjowaniem leczenia. Ponadto nie ma aktualnie żadnego markera, który mógłby zostać użyty w celu postawienia diagnozy. Z powodu tych trudności w diagnostyce zakrzepicy u dzieci w zależności od wieku pacjenta stosuje się odmienne techniki neuroobrazowania, takie jak ultrasonografia przezczaszkowa, rezonans magnetyczny lub wenografia rezonansu magnetycznego. CVST może powodować poważne neurologiczne i kognitywne powikłania. Na szczęście odpowiednio poprowadzone leczenie może obniżyć wskaźnik śmiertelności, a także zapobiec tym powikłaniom. W niniejszej pracy podsumowano aktualną wiedzę na temat CVST u dzieci.

SŁOWA KLUCZOWE

udar, pediatria, antykoagulanty, upośledzenie funkcji poznawczych

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is an uncommon but potentially serious condition in the pediatric population. It accounts for less than 1% of strokes in children [1]. CVST is characterized by thrombus formation in the intercranial venous system. Blood clots can form in different sinuses. Therefore, the symptoms and disease presentation vary between individual patients, without any specific clinical signs. According to the study by deVeber et al. [2], the estimated annual incidence rate of CVST is 0.67 per 100 children. They stated that neonates account for nearly half of the CVST cases. There are indeed more recent studies where the proportion of neonates is lower. However, there is a high possibility that their prevalence is underestimated. Because of the oligosymptomatic course of the disease, lacking neurological signs, the diagnosis of CVST is often not raised in this age group [3].

CVST is a multifactorial disease arising from various medical conditions, such as infections, metabolic causes, thrombophilia and neoplasm [4]. Often more than one factor leads to the development of the disease. The diagnosis of the disease is based on neuroimaging studies. Imaging techniques used in CVST include computed tomography scan, magnetic resonance imaging, venography and cranial ultrasound. The imaging modalities are chosen based on the patient's age [5]. The management strategies involve anticoagulation therapy, whose purpose is to stop the thrombus enlargement and dissolve it. Anticoagulation therapy can be administered at any age, with special caution in the youngest patients. A multidisciplinary approach involving pediatricians, neurologists, and hematologists is crucial for optimal outcomes. Further research is needed to enhance our understanding of this condition and improve therapeutic strategies for affected children.

MATERIAL AND METHODS

For the search of articles, PubMed and EMBASE databases were used, as well as references from relevant articles and internet sources. The search terms included "CVST children", "CVST pediatric", "cerebral venous sinus thrombosis children", "CVST diagnosis children", and "CVST treatment children". We excluded articles older than 2001, and regarding the diagnosis and treatment, stricter inclusion criteria were used – only studies from 2019 to July 2024 were included.

DISCUSSION

Risk factors

The conditions associated with an increased risk for CVST differ between pediatric and adult patients. The most common risk factors in children are dehydration, infections, such as mastoiditis or meningitis, and head trauma. Other less common, but equally significant causes are malignancies, especially acute lymphoblastic leukemia, systemic lupus erythematosus, and inherited thrombophilia.

Nonetheless, in the neonate subgroup, the most frequent factors were maternal thrombophilia, respiratory distress, mechanical ventilation, perinatal asphyxia, and meconium aspiration [6]. What is more, there are studies suggesting that anemia or inflammatory bowel disease are linked to CVST development [7,8,9].

Diagnosis

CVST is a serious clinical condition that might be found in patients of every age. Regarding a recent pediatric health information system database study, more than 17% of the hospitalizations concerned

neonates. It is crucial to have a better understanding of CVST in neonatal patients as they often present fewer symptoms and thus the diagnosis is hindered. Some of the newborns might present encephalopathic symptoms and seizures, however, predominantly the symptoms are non-specific. When compared to older children, congenital heart disease and sepsis are more common in CVST patients, which might contribute to higher mortality rates in this population [3]. What is more, usually, contrary to older children, no signs of increased intracranial pressure are found in newborns [1,3]. On the other hand, regarding some recent studies, the most commonly reported symptoms in older children are drowsiness (87.5% of the patients), seizures followed by headache (50%), headaches (62.5%), fever (46%) and vomiting (43%) [10,11]. Furthermore, decreased consciousness and headache without another apparent cause in young patients might indicate a need for further examination to confirm or exclude CVST [11]. What is more, head trauma may pose another diagnostic difficulty owing to a similar presentation of symptoms. Notably, headaches related to isolated CVST tend to be more diffuse and to progress over days, while a change in the characteristics of the pain suggests another underlying cause or complication. Thus, it is crucial to stay alert, especially in pediatric patients after head injury [12].

There is a study suggesting that low hemoglobin and anemia might be used as a biomarker in pediatric CVST as a positive association of anemia with multiple sinus involvement was revealed in a retrospective study. Unfortunately, there is not enough research to assess whether those laboratory findings might be commonly used in the diagnosing process [8]. Since there is no specific CVST marker, imaging techniques are essential in the management of CVST patients, especially newborns. The imaging modalities remained similar in both age groups, nevertheless, the neonates were examined by means of head ultrasound more often, while CT without contrast was less common [3]. According to one study, an attenuation of the affected sinus is increased in patients with CVST on the computed tomography, and consequently, increased densitometric values are present in the site of venous thrombosis [13].

Furthermore, in most cases, magnetic resonance with angiography in venous time is believed to be sufficient to confirm CVST. Numerous studies found that the sagittal and transverse sinus are some of the most frequent sites of neonatal CVST, while more than half of the infant population presented multiple sinus involvement [14].

Treatment

In the available recent literature, most children are treated using anticoagulation (65–97%) [15,16,17]. Enoxaparin and unfractionated heparin (UFH) are reported to remain the first choice of CVST treatment in both neonates and older children, while direct oral anticoagulants (DOACs) were used rather only in older patients [3]. Debates are still ongoing on whether anticoagulation is a safe therapeutic option, especially among newborns because of hemorrhagic risk. On the other hand, a recent study revealed that this therapy was initiated in 82% without complications [1]. Moreover, in another study, none of the treated infants, including those with pre-treatment hemorrhage, suffered from a worsened or new hemorrhage [14]. Anticoagulation seems to be associated with a lower risk of severe neurological and cognitive impairment since children treated with anticoagulants had better outcomes at the follow-up, including long-term complications [18]. What is more, in the study carried out by Sutter et al. [19], almost half of the patients treated with anticoagulation presented complete recanalization on imaging, and more than $^{1}/_{3}$ had partial recanalization. Notably, none of those patients suffered from adverse events resulting from this therapy.

In some cases, additional treatment might be needed, especially when other clinical conditions are present. A study of 35 children with papilledema in association with CVST revealed that all of them required acetazolamide and/or lumbar puncture aside from anticoagulation [15]. Importantly, some CVST patients might require endovascular therapy. The most frequent indications include worsening of Glasgow Coma Scale (GCS) and other symptoms despite anticoagulation. Complete resolution of the symptoms and the complete recanalization associated with it can be achieved in more than half of this patient group [17].

Neurological complications and outcomes

A cross-sectional analysis by Proaño et al. [20] evaluated the outcomes of children with CVST. They found that the median age was 8 years, and the highest prevalence was observed in neonates. Long-term neurological complications were reported in 40–60% of the survivors, while ¼ of the children suffered a stroke. The children who had a stroke as a complication of CVST were more likely to require mechanical ventilation and had increased mortality. According to Teksam et al. [21], ischemic and hemorrhagic brain injuries are very common complications of CVST, especially in neonates and infants, which may be a result of immature compensating mechanisms. However, the brain lesions observed in imaging studies were smaller in the neonates compared to the older children.

Another study investigated 42 children diagnosed with CVST. Three patients died quickly due to CVST, and two patients died later. The follow-up for the survivors ranged from 6 months to 10 years. The researchers found that $^{2}/_{3}$ of the children developed neurological complications or cognitive difficulties. Less than 5% of

this population suffered from permanent hemiparesis, 7% had reduced visual acuity and 5% had epilepsy. $^1/_3$ of the children were diagnosed with idiopathic intracranial hypertension (IIH), however, no children diagnosed with cognitive dysfunction developed IIH. It was also established that a favorable cognitive outcome was observed more often in older children, those without parenchymal lesions. Later and/or sigmoid sinus involvement also resulted in better cognitive outcomes, albeit it increased the risk of IIH [22].

A study from 2009 by Mallick et al. [23] supports the above findings. The follow-up ranged from 5 months to 6 years and during its period 9% of the patients died. In the remaining children, more than $^1/_3$ developed IIH. Less than 10% of the children had residual hemiparesis and only one child had residual sixth nerve palsy.

DeVeber et al. [2] reviewed the medical records of 160 children, 69 of whom were newborns, and assessed the neurological outcome in 143 of them. From the beginning of CVST to the last follow-up neurological deficits were present in 38% of the children. The most common neurological deficits were motor impairment present in 80% of cases, cognitive impairment in 10%, developmental delay in 9%, speech impairment in 6% and visual impairment also in 6%. Moreover, other neurological deficits occurred in 26% of the patients.

Seizures

Other frequently present neurological complications are seizures since they might be observed in 15–25% during follow-up (newborns accounted up to 57%) [2,14]. The occurrence of infarction in all the age groups and the occurrence of seizures as a symptom of CVST were the two main factors associated with adverse neurological outcomes. What is more, as mentioned before, seizures may not only be complications, but also one of the symptoms of CVST in children. In a 2020 study, twenty-four children were enrolled into a one year follow-up, assessing seizure recurrence, the use of antiepileptic medications, the diagnosis of epilepsy and the Engel score. On admission 37.5% of this group suffered from acute seizures, while after one year a quarter of the patients were diagnosed with epilepsy. Unfortunately, there are no clinical predicting factors, and thus further research is still needed to better understand and prevent serious neurological complications [24].

Cognitive impairment

Compared to the previously mentioned studies, in a study by De Schryver et al. [25], the percentage of children with neurological deficits and cognitive impairments after CVST appears to be much lower. In their study during a follow-up evaluation of 12 children, only one of them presented with mild impairment of skilled movements, while the rest of the patients had no neurological abnormalities. In most of the children cognitive development was assessed. The measured intelligence scores were average or above average. Mild cognitive problems were found in less than 20% of this group: difficulty with written language and diminished cognitive efficiency. The assessment of cognitive development was not possible in two children due to their young age and insufficient language skills. Similar results were observed in a study by Hetherington et al. [26] where the children achieved a mean intelligence score slightly below average (97.8 IQ).

Infants

Christensen et al. [14] collected medical records of 26 preterm infants, a group previously not included in any of the studies. The median gestational age was 34.9 and the median birth weight was 2400 g. 50% of the pre-term infants showed no neurological impairment during follow-up. Nonetheless, 25% of the children developed mild-moderate impairment and 25% severe impairment. According to the authors, the neurocognitive outcomes were not favorable, which may be related to brain parenchymal lesions in most of the patients. Furthermore, another recent study indicates that newborns not only need longer hospital stays but also have higher mortality rates compared to older children [3].

CONCLUSIONS

CVST presents a diagnostic challenge for many clinicians. Its diverse etiology and lack of specific symptoms, especially in younger patients, delays the diagnosis or even leaves the thrombus unrecognized. CVST is a severe diagnosis with a possibility of serious neurological complications or even death. Therefore, it is important to raise vigilance among healthcare professionals. On the other hand, the use of imaging techniques is usually sufficient to make a proper diagnosis. Although there are running discussions on the safety and dose of anticoagulation medicaments, it seems that this therapy enables physicians to achieve favorable outcomes. Unfortunately, taking the rarity of this condition into consideration, there is still not enough literature on this subject in the pediatric population. Further research is essential to asses all the aspects of the disease.

Author's contribution

Study design – A. Dąbrowska, J. Mastalerz, M. Szyszka
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