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UNDIAGNOSED CEREBRAL VENOUS THROMBOSIS IN THE PUERPERIUM WITH A FATAL OUTCOME – CASE REPORT AND REVIEW OF LITERATURE

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Abstract: Cerebral venous thrombosis (CVT) is a relatively rare disease that can occur at any age. It quite often affects individuals under the age of 40; increased incidence thereof can be observed in patients with thrombophilia and in women during pregnancy, the puerperium or in women using hormonal contraception. The diagnostics of this disease is associated with some pitfalls and is therefore neglected or delayed. The most important factors complicating the diagnostics are the variability of the cerebral venous system, the non–specificity and the great diversity of the clinical manifestations, as well as the very common necessity to utilize special imaging methods. From an etiological point of view, we distinguish between infectious and non–infectious thrombosis, but the literature describes more than 100 different CVT risk factors. The authors present a case of undiagnosed intracranial venous thrombosis in a 35–year–old woman after childbirth.

Keywords: cerebral venous thrombosis (CVT), risk factors, puerperium, death.

INTRODUCTION

Cerebral venous thrombosis (CVT) is an atypical and often unrecognized form of stroke, usually affecting young individuals. It affects about 5 people per million a year and represents 0.5% – 1% of all strokes. The incidence of CVT during pregnancy and the puerperium in women in developed countries increases to 11.6-12 cases per 100,000 births per year [1, 2]. Overall, intracranial venous thrombosis is three times more common in women than in men [3]. Despite significant advances in diagnostics in recent years, it is still challenging to diagnose this one for several reasons. Correct diagnostics is complicated by a number of factors. The most important are the variability of the cerebral venous system, a number of basal risk factors, non–specificity and a wide variety of clinical manifestations. This is also very often accompanied by the need to utilize special imaging methods. Due to the mentioned pitfalls, the diagnosis of CVT is quite often burdened with errors, is neglected or delayed [2, 4]. The prognosis of a patient with CVT is clearly determined by rapid and proper diagnosis with early initiation of adequate treatment [5].

There are several predisposing causes of CVT. Risk factors for venous thrombosis are generally classically associated with the Virchow's triad – blood stasis, changes in the vascular wall and changes in blood composition [2]. More than 100 different CVT risk factors have been described in the literature. In general, they can be divided into local and general, then acquired and congenital risks, but it is also very common to distinguish between infectious and non–infectious [2, 4, 6, 7].

Predisposing factors for CVT include:

1. Hypercoagulation states – antithrombin III deficiency, protein C, S deficiency, resistance to activated protein C, hyperfibrinogenemia, disseminated intravascular coagulation (DIC), antiphospholipid syndrome
2. Pregnancy and puerperium
3. Hormonal contraceptives
4. Medicines – corticosteroids, tamoxifen, erythropoietin, heparin, vitamin A, lithium
5. Malignancies – lymphomas, leukemias, carcinomas
6. Infections – intracranial (meningitis, abscess), regional (mastoitis, otitis, sinusitis, tonsillitis,

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furuncle), generalized (endocarditis, tuberculosis, infectious hepatitis, aspergillosis, AIDS).

7. Trauma – penetrating head injuries, lumbar puncture, jugular catheterization, neurosurgical procedures.

8. Haematological causes – polycythemia, thrombocythaemia, paroxysmal nocturnal haemoglobinuria, nephrotic syndrome.

9. Systemic diseases – lupus erythematosus, Wegener's granulomatosis, Behcet's disease, sarcoidosis, vasculitis in Crohn's disease and ulcerative colitis.

10. Others – malnutrition, dehydration [2, 7].

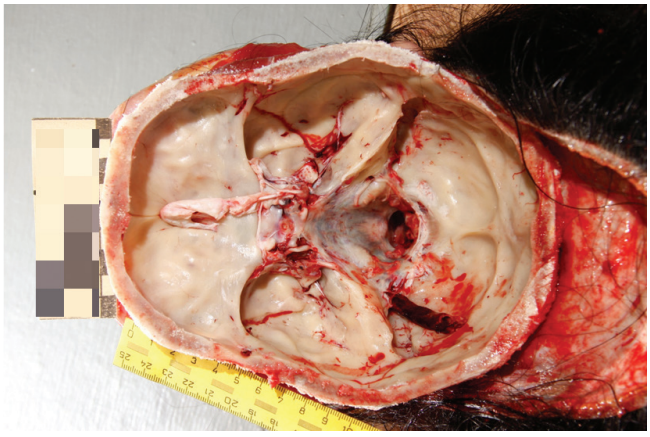
Cerebral venous thrombosis is characterized by a remarkably wide spectrum of symptoms, relatively nonspecific [8]. In contrast to the arterial stroke, which can be easily diagnosed clinically in majority of cases, CVT has no single pattern of presentation and it may be difficult to diagnose it on clinical grounds alone [9, 10]. The diagnosis of CVT usually derives from a suspicion based on the clinical condition and its confirmation with imaging methods. Clinical findings can be divided into two main groups according to the mechanism of the neurological disorder, namely increased intracranial pressure and associated focal findings. In practice, many patients have symptoms as a result of both mechanisms. Headaches, which generally indicate increased intracranial pressure, are the most frequent and often the earliest CVT symptom and occur in almost 90% of patients [2, 4, 6, 8, 9]. The most common type is diffuse progressively developing persistent headache, with migraine and explosive headache quite common as well. Other symptoms include epileptic seizures occurring in almost 40%, followed by nausea and vomiting, followed by focal symptoms (hemiparesis, aphasia, etc.). Another group of clinical presentation is characterized by subacute encephalopathy with qualitative and quantitative impairment of consciousness [7, 9]. Intracranial thrombosis most commonly affects cerebral sinuses (sinus transversus, sigmoid, superior sagittal, rectus and cavernosus), but thrombosis of the deep vein system of the brain is not uncommon. These are characterized by signs of intracranial hypertension, which can lead to rapid loss of consciousness and coma. Isolated thromboses of superficial veins are extremely rare [4, 5].

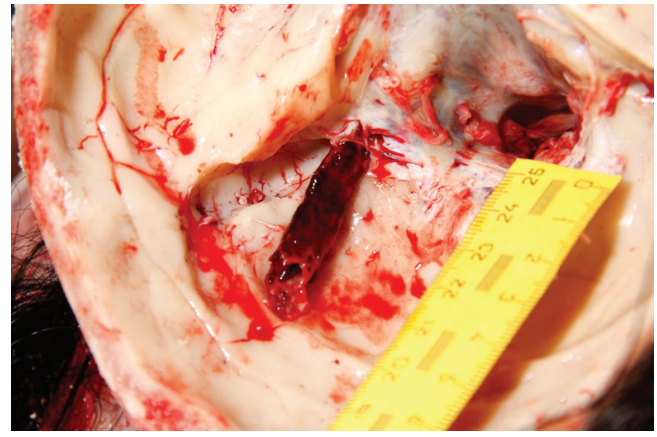
Diagnostics of CVT is complicated especially in the initial stages, the time course and symptoms are very variable and non-specific. In addition to a thorough medical history and objective examination of the patient, a number of laboratory and other examinations, as well as imaging methods, are necessary for proper diagnosis. It is necessary to perform tests within the etiological diagnosis – biochemistry examination, including liver tests, blood count, differential blood count, sedimentation, examination of basic coagulation, C-reactive protein (CRP), examination of renal function. It is also important to carry out specialized sampling to detect hypercoagulation conditions and autoimmune diseases (ANA antibodies, anti-dsDNA, ANCA, ACLA, LA, antithrombin III, fibrinogen, plasminogen, genetic testing, etc.) [2]. D-dimers examination is a quick and reliable test. Normal levels of D-dimers are unlikely for CVT, but cannot be ruled out 100%. If an infectious etiology is suspected, lumbar puncture is indicated, which may also have a therapeutic effect (relieve pain, prevent loss of vision)[2, 11, 12].

Significant progress has been made in the diagnosis of CVT in the last two-three decades, mainly thanks to new imaging techniques [7]. Magnetic resonance imaging (MRI) is currently, the best method of examining the brain when CVT is suspected. Its advantage is also the possibility to perform MR angiography with the production of a cerebral venogram. MRI can be false negative if performed in the acute stage of thrombosis. Brain computed tomography (CT) remains an important test to rule out other acute brain diseases. Direct signs of CVT are present in about 1/3 of cases. Most often it is the so-called delta symptom following the administration of contrast, spontaneous hyperdensity in the course of the sinus – "dense triangle" – is less common. Indirect signs, such as edema, atypical ischemia, hemorrhagic infarction, are usually present in 2/3 of patients. Other complementary methods are post-contrast CT and CT venography. With the arrival and availability of MRI, cerebral artery angiography lost its exclusive position in the diagnosis of CVT. However, it still remains an irreplaceable method, when there are doubts present even after MRI examination, but also in cases where interventional, endovascular procedure is considered [2, 4, 5, 7, 8].

CASE REPORT

This was a 35-year-old patient, giving birth to her fifth child, who fell unconscious on the second day after spontaneous birth following previous headaches. She was a single, unemployed, Roma ethnicity patient, smoker, with a negative family and personal history. She was hospitalized once during pregnancy, at the beginning because of imminence of miscarriage. The patient was undisciplined, did not follow the treatment regimen. During her pregnancy, she visited the prenatal





Figures 1, 2. Sinus sigmoideus thrombosis.

clinic only once, at which point sampling for infectious diseases (hepatitis B, toxoplasmosis, syphilis) were performed with a negative result. Subsequently, the patient was brought by the ambulance to the gynecology and obstetrics department on the day of birth. This was her fifth spontaneous delivery with partial abruption of the placenta in the 38th week of pregnancy. Delivery was carried out without complications. On the 2nd day of hospitalization in the morning, the patient complained of a headache and shortly thereafter fell unconscious, repeatedly having convulsions. In the obstetric ward, intravenously magnesium sulfate, intramuscularly diazepam was administered, and spatula was placed between the teeth. When the consilium of physicians arrived from the Department of Anesthesiology and Intensive Care (DAIC), patient was unconscious, did not respond to algic stimuli, with persisting muscle twitching, hypoxia. After medication, urgent orotracheal intubation was performed and patient was transferred to DAIC for artificial lung ventilation (ALV) and further intensive treatment. Cultivation examination of cerebro-spinal fluid, urine, examination for tick-borne encephalitis and HIV were performed, with negative results. In addition, an internal, gynecological and neurological examination was performed, which suspected encephalitis. On the same day, following stabilization of the patient, a CT scan of the brain was carried out, which was free of signs of hemorrhage and expansion, but confirmed the picture of hypoxemic encephalopathy. Hyperfibrinogenemia, moderate anemia, hypoproteinemia, later mild leukocytosis, mildly elevated CRP and sedimentation were present in the laboratory tests. Neuro-intensive, antibiotic and symptomatic therapy was initiated with continuous monitoring of vital signs and neurological status. Patient was afebrile, her state of unconsciousness progressed, her neck did not oppose since admission, areflexia was present, mydriasis persisted. Her internal environment has been disrupted and, due to the hemodynamic instability of the patient, continuous vasopressors administration was necessary. On the fifth day of hospitalization, signs of renal failure set in, and on the 6th day of hospitalization, patient died. The examining physician ordered an autopsy, which was performed 38 hours after exitus. The documentation accompanying autopsy included diagnoses: postpartum eclampsia, unconsciousness, cerebral edema, hypoxia, hypoxemic encephalopathy, heart failure, disruption of the internal environment, anemia, chronic bronchitis.

As to the external examination of the body, skeleton was free of traumatic changes and deformities, there were signs of defibrillation on the chest. Abdomen with stretch marks was slightly above chest level, uterus was palpable 3 fingers below the navel. There were signs of injection sites in both elbow pits, on the right outer and left inner wrist, on the back surface of the right hand, in the area of the right inner ankle, with smaller blood bruises in the vicinity. Tattoos were present on the inner surface of the left arm, the inner surfaces of the forearms, and on the outer surface of the left forearm. During the internal examination, extensive organized thrombosis was found in the venous sinuses of the brain (sinus sagittalis superior and sinus sigmoideus – Figs 1, 2). In addition, severe cerebral edema with focal tissue necrosis was present, mildly increased vasculature in pia mater (Fig. 3), dotted secondary hemorrhages in the pons. The middle ear cavities and ethmoidal sinuses showed no pathological signs. Both pleural cavities contained a clear yellow fluid, 250 ml on the right and 300 ml on the left, the lungs were markedly swollen, heavy, enlarged, with isolated hemorrhages under the visceral pleura. Ascites of 900 ml in volume was found in the abdominal cavity, the uterus was in involution, congested postpartum, without placental remnants,

thrombi were present in the vessels within the muscle section.

Microbiological examination of the biological material taken at autopsy (pia mater and middle ear swab) was negative. Excisions were taken at autopsy for microscopic examination. Tissue sections were stained with hematoxylin-eosin. Lung sections showed incipient purulent pneumonia in the ARDS (acute respiratory distress syndrome) terrain, with purulent leptomeningitis detected in brain sections (Figs 4, 5). Other macroscopic findings were also confirmed.

The identified extensive thrombosis of venous sinuses of the brain led to severe hypoxic brain damage with the development of severe brain edema with focal brain tissue necrosis, which was also the immediate cause of the patient's death.

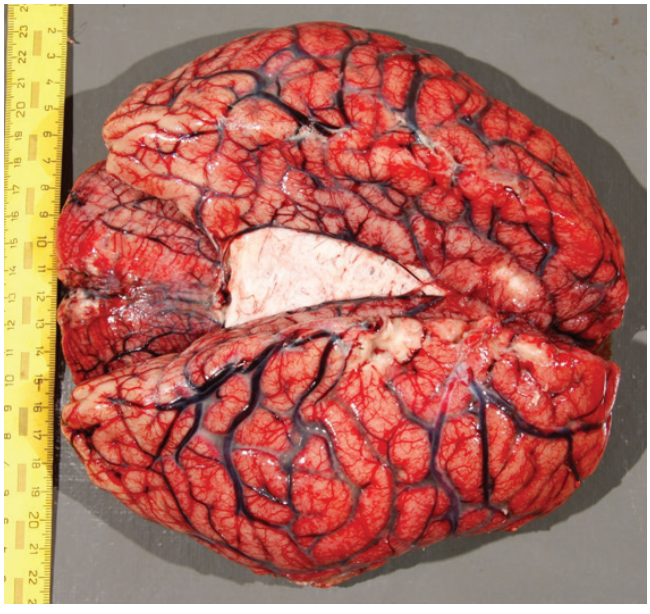
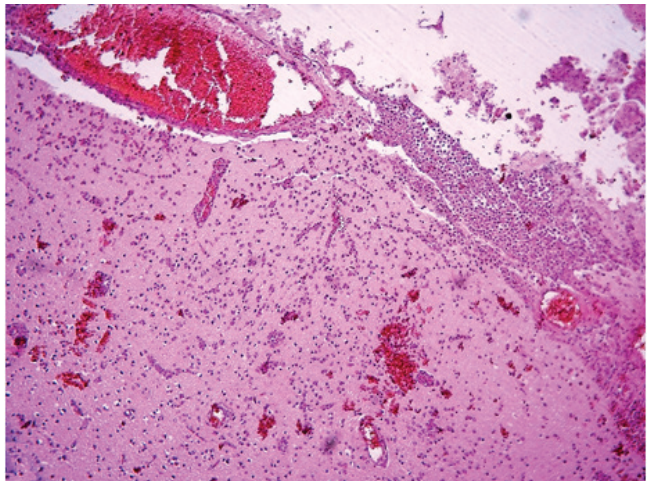


Figure 3. Severe cerebral edema, mildly increased vasculature in pia mater.

DISCUSSION

This case report confirms that CVT, despite significant progress in diagnostics, is still a serious, in some cases life-threatening diagnosis, which is often unrecognized [2]. Among the major risk factors for cerebral venous thrombosis is a hypercoagulable state [8]. Numerous studies point to the fact that CVT occurs very often in connection with pregnancy and puerperium [2]. Pregnancy induces several prothrombotic changes in the coagulation system (in terms of hypercoagulation) that persist at least during early puerperium. Normal pregnancy is accompanied by increased concentrations of factors VII, VIII, and X and von Willebrand factor and by pronounced increases in fibrinogen. Free protein S (the active, unbound form) is decreased during pregnancy. These changes, which may not completely return to baseline until more than 8 weeks postpartum, begin with conception and result in the hypercoagulable state of pregnancy [2, 13]. In young women, the last trimester of pregnancy and especially the puerperium represent important risk factors for this condition with an incidence estimated about 12 cases per 100,000 deliveries. Advancing maternal age, pregnancy-related hypertension, excessive vomiting in pregnancy and cesarean delivery further increase the risk [6, 8, 9]. Hypercoagulability worsens after delivery as a result of volume depletion and trauma. During the puerperium, additional risk factors include concurrent infection, reduced movement during pregnancy and puerperium, and insufficient supplementation of body fluids [2, 13].

In the case stated, it was a typical occurrence of CVT in a young woman, with the coexistence of several predisposing factors (puerperium, smoking, hyperfibrinogenemia, infection). In the clinical picture,



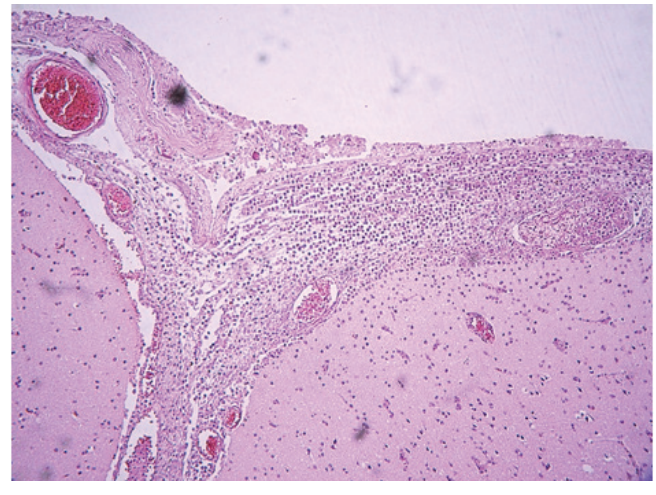


Figure 4, 5. Purulent leptomeningitis in brain sections.

the patient had the most common symptoms of CVT, namely headaches, epileptic seizures, as well as severe impairment of consciousness. As part of the differential diagnostics, almost all important laboratory and other examinations were carried out, as well as CT examination of the brain, which, however, did not reveal thrombosis (literature reports a negative CT finding in the initial stages of up to 30-50%). MRI was not performed (not available at the mentioned hospital). Summarizing the available medical history and clinical data, encephalitis was suspected, which was not confirmed. This case report also points to the possibility of a combination of venous thrombosis and neuro-infection.

The time factor is very important in CVT prognosis. Correct and early diagnosis is the first step to successful treatment [2, 4, 6, 7]. However, rapid advances in imaging technology, including in computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance venography (MRV), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA) have provided effective approaches for early diagnosis. Diagnosis by DSA is the golden criterion, though its invasive nature and high cost limit its use. The combination of non-invasive CT and MRI can facilitate an early diagnosis in most cases, and is thus the current primary diagnostic tool, the method of choice for imaging examinations [14].

It is important to correctly evaluate the findings, correctly interpret false positive and negative findings, thus allowing the initiation of adequate treatment. Therapy consists of general procedures, prevention of complications (monitoring, treatment of epileptic seizures, anti-edema treatment, treatment of infection), as well as anticoagulant therapy and possible endovascular and surgical procedures [2, 4, 6, 7].

In conclusion, cerebral venous thrombosis is a rare nosological entity that is in some cases difficult to diagnose. This case report points to the severity of this disease and the numerous pitfalls in proper diagnosis. Due to the variety of causes, clinical manifestations, but also the fact that this diagnosis is often unrecognized, delayed or misdiagnosed, it can be encountered not only by neurologist, neurosurgeon, radiologist, gynecologist, internist, oncologist, pediatrician, general practitioner, but also by the pathologist and forensic physician.

Conflict of interest

The authors declare that they have no conflict of interest.

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