CT and MRI examination in diagnosis of cerebral venous and sinus thrombosis

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Abstract
Cerebral venous and sinus thrombosis (CVST) is a central nervous system pathology difficult to diagnose due to vague and uncertain clinical symptoms. Nowadays, broad application of neuroimaging has completely modified our knowledge about this condition. Early diagnosis of CVST allows introduction of prompt and appropriate treatment, which is extremely important since changes in brain parenchyma as well as thrombotic changes in sinus durae matris and cerebral veins are potentially reversible. All of the above facts determine the significance of diagnostic imaging methods: computed tomography (CT) either non- or contrast enhanced, CT venography, magnetic resonance (MR) imaging, MR venography and digital subtraction angiography. The aim of this work is to present up-to-date possibilities of diagnostic imaging in recognizing CVST.

Key words
Cerebral venous sinus, thrombosis, CT-venography, MR-venography

INTRODUCTION

Approximately 35-50 years ago, cerebral venous and sinus thrombosis (CVST) was regarded as a rare disease connected with bad prognosis and a high mortality rate up to 50% [1]. This conception has been progressively changing for the last 20 years, mostly due to the rapid development of imaging diagnostic methods, i.e. angiography, computed tomography and magnetic resonance, which help understand the background of the disease, the diversity of its clinical symptoms, as well as enable early and prompt diagnosis. This, in consequence, enabled the introduction of adequate treatment (heparin), which led to reduction in mortality. Before the era of diagnostic imaging, a diagnosis could only be made during the postmortem examination, performed for the first time by Morgagnie in 1766. However, only precise early diagnosis has a decisive impact on the prognosis [2]. The estimated annual morbidity is currently indicated to be approx. 2-8 cases per million in the general population [3, 4, 5, 6, 7]. The disease may appear at any age and in both genders, but is more frequent in women (71-75%) and in young people, under the age of 50 [3, 8]. Three peaks of incidence are observed:
1) infants and young children: explained by more frequent diseases at this age which lead to dehydration, malnutrition and infection;
2) young women at premenopausal age (20-35 years): mainly due to pregnancy, puerperium and the use of contraceptives;
3) older patients: because of more common malignant diseases or pathologies linked with abnormal state of nutrition and/or hydration [9, 10, 11, 12, 13].

Etiology. More than 100 etiological agents of cerebral venous and sinus thrombosis are described in the literature [6, 7]. Nevertheless, in approximately 20-25% of patients it is not possible to identify any of them [6, 7, 9, 14]. On the other hand, in up to 38% of patients, several risk factors of the disease co-exist, which significantly increases the probability of CVST development [6, 9, 15, 16].

Etiological factors can generally be divided into infectious and non-infectious agents. In the era of advanced antibiotic therapy the former group of etiological factors is responsible for only around 10-12% of CVST cases. On the other hand, in the latter group of etiological agents, 70% of cases are caused by primary and secondary coagulopathies [5, 9, 10, 14, 15, 16].

Among adult patients, apart from general infections and diffuse proliferation diseases, CVST may be induced by the following factors: oral contraceptives, pregnancy, antiphospholipid syndrome, primary coagulation syndromes (factor V mutation, AT III deficiency) and blood dyscrasias (e.g. trombocytothemia, polycythemia, anaemia iron deficiency). In neonates and small infants, cerebral vein thrombosis usually accompanies acute systemic diseases proceeding to shock and dehydration. Most CVST cases associated with pregnancy appear in the third trimester and even more frequently in puerperium. Additional risk factors include perinatal infections, caesarian section and assisted labour. An increase of incidence is observed currently in the group of young men taking anabolic steroids.

In a case of neoplasmatic disease, other mechanisms are mobilized. The propensity for the formation of clots may result from infiltration of vascular walls or sinuses and production of abnormal coagulations factors. Medicines used in cancer therapy are also important (e.g. tamoxifen) [5, 11, 13, 14, 15, 16].

Clinical symptoms. The spectrum of clinical symptoms observed in CVST is very broad. Symptoms in this disease vary considerably depending on the extent, localization and
duration of the thrombosis process, as well as on the capacity of collateral circulation. The clinical picture is determined by: the involvement of cerebral veins or sinuses, onset of symptoms (acute, subacute or chronic), period between the beginning of the disease and the onset of symptoms, and background pathology that caused thrombosis. The clinical picture of the disease is further complicated by changeability of symptoms in a single patient, resulting from the simultaneous coexistence of thrombosis and endogenous thrombolysis [7, 10, 11, 13, 15].

The most commonly observed clinical symptom is headache which, according to different authors, is present in 74 – 95% of patients [10, 13]. Further symptoms in order of prevalence include: swelling of the optic nerve disc, focal or generalized epileptic seizures, focal neurological symptoms (sensory or mobility deficits – hemiparesis). Other symptoms of CVST include: aphasia, haemianopsia, consciousness disorders of different intensity – even coma, mental health disorders, cranial nerve palsies and cerebellar symptoms.

It should not be forgotten that CVST may give no symptoms. This often happens in cases of thrombosis of the transverse and sigmoid sinuses [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19].

**Anatomy.** The sinuses of cerebral dura mater are vessels of large diameter which do not contain valves. These sinuses connect with the superficial veins of the head through the emissary veins (venae emissariae vel Santorini) and diploic veins. They are the main channels which gather venous blood from the brain, the major part of the orbit, the labyrinth, as well as from dura mater and bones of the skull.

Generally, the blood stream flows from the anterior and upper part posteriorly and downwards. The main outflow is through the jugular foramen to the internal jugular vein.

The system of dura mater sinuses can be divided into two groups: upper and lower. The upper group includes the sagittal sinuses (superior and inferior), rectus, transverse and sigmoid sinuses. The lower group includes the cavernous sinus, intercavernous sinuses, superior and inferior petrous sinuses. Each sinus group has its collecting point which drains the blood of several sinuses or veins and passes it through to the jugular foramen. Confluens sinuum is the collecting point of the upper group which, after draining blood from the major part of brain and skull, passes it through the transverse sinus to the jugular foramen. The cavernous sinus is a collecting point of the lower group which receives blood mainly from ocular veins and passes it through the petrous sinuses to the sigmoid sinus and further to the internal jugular vein.

All the sinuses, however, form one communicating system; therefore, closing of lumen in one of the sinuses can be compensated. Furthermore, connections with extracranial veins constitute an additional ‘security’ system (Fig. 1) [20, 21].

**Diagnostic imaging.** Imaging studies are an essential and basic tool for detecting deep cerebral venous and sinus thrombosis. In most patients, the serum D-dimer level is elevated; however, its normal value does not exclude the presence of CVST, especially in patients with headaches [22, 23].

In most centres, unenhanced CT scan of the head is the first, basic examination in patients with non-specific clinical symptoms [12]. More precise diagnosis and assessment of brain vessels is possible, however, in head CT with intravenous contrast administration. Other non-invasive imaging methods of cerebral veins and sinuses include brain MRI and MR venography. These examinations are particularly useful in the case of a negative or ambiguous result of unenhanced CT scan of the head.

CT venography technique has also been recently improved. It shortens the time of diagnosis and accelerates implementation of proper therapeutic decisions; in some centres it is assessed as being comparable with MR venography. Classical vascular examination – digital subtraction arteriography (DSA) is currently reserved for therapeutic purposes, such as local thrombolysis and mechanical thrombectomy in already diagnosed patients whose state of health is deteriorating [13].

**Computed tomography without intravenous contrast administration.** This method still remains the method of choice in patients with a non-specific clinical picture and with low suspicion of CVST. It is usually performed in order to exclude subarachnoid haemorrhage and haemorrhagic stroke. In about 20-38% of patients, the head CT examination may be normal [8, 12, 13].

Direct symptoms of a clot in a vessel are not frequent in CVST and occur in approximately 33% of clinical studies [12]. They include: ‘dense clot sign’ (Fig. 2), or in the case of the superior sagittal sinus, the ‘delta sign’, corresponding to a slightly increased density of the sinus which is associated
with the presence of an acute blood clot in the sinus; as well as the ‘cord sign’, corresponding to an increase in density in the brain cortical vein. This term applies, however, only to that location.

More often, however, indirect symptoms of sinus or cerebral veins thrombosis are observed on CT images. They include: generalized swelling of the brain, intracerebral haemorrhagic loci (32.8%), venous infarction being the most specific indirect symptom (13.1%), swelling of the brain white matter (11.5%), and focal edema (3.3%) [8].

**Computed tomography after intravenous contrast administration.** The direct symptom of the presence of a clot in contrast CT is the so-called ‘empty delta sign’, which means the lack of enhancement of the clot located in the superior sagittal sinus on the background of the enhancing leptomeningeal and circulating blood. Such a symptom is considered to be pathognomonic for this disease. However, it may disappear in a chronic phase of the disease when an organized, partly recanalized clot is seemingly enhanced [5, 12, 17].

The indirect symptoms of CVST present in approximately 20% of patients include: enhancement of the cerebral and cerebellar falx, enhancement of gray matter gyri, and enlargement of venous collateral circulation [7, 9, 10, 12, 13, 15, 17].

**Computed tomography venography.** This examination is one of the newer methods which can be applied in diagnostics of CVST. It involves making two- and three-dimensional reconstructions from the venous phase of CT angiography, and assessing veins and sinuses for the presence of thrombi. The sensitivity of CT venography in imaging cerebral venous anatomy is approximately 95%, and it is more effective than DSA and MRI in imaging the cavernous sinus, inferior sagittal sinus and Rosenthal’s vein.

As in an ordinary CT examination, symptoms of CVST in CT venography can be divided into direct ones – when a blood clot is shown, and indirect ones – when changes due to impaired venous outflow are visible (Fig. 3). The superiority of CT venography over the classical CT contrast examination is linked with its excellent ability to demonstrate the lack of contrast in superficial sinuses and cortical veins. Furthermore, volumetric reconstructed images enable good visualization of collateral circulation.

In the case of the cavernous sinus thrombosis, the most reliable diagnostic criterion in CT venography is the presence of a large lack of contrast filling characterized by densities other than fat densities, accompanied by sinus enlargement. A drawback of this method is difficulty in reconstructing MIP images from native data – this process requires bone subtraction contiguous to the sinus, which is difficult to perform without simultaneous removal of a part of the sinus [5, 12, 13].

**Magnetic resonance imaging (MRI).** In many centres, MRI is the method of choice in diagnosis and monitoring of CVST, as a non-invasive examination which gives high contrast resolution. Some authors claim it to be three times more sensitive in detecting CVST than CT, regardless of the disease duration (4,10). MRI sequences classically used in the assessment of brain tissue include spin echo (SE), turbo spin echo (TSE) and inversion and recovery sequence (FLAIR). These sequences allow the detection of oedema and acute post-ischemic foci. The addition of gradient echo T2* sequence increase (GRE) increases the sensitivity of detection of early and late phase intracranial haemorrhage. The diagnosis of CVST in magnetic resonance imaging is made after detection of a clot located in a sinus, or (much
less often) in a cortical vein or in deep cerebral veins. The appearance of the clot in MRI may be very diverse – it depends on the sequence, but also on time elapsed from its formation.

In conventional sequences, the correctly patent sinus or vein is seen as a ‘flow void’ structure – i.e. loss of signal effect associated with the flow (structure without signal). This is particularly conspicuous when the imaging plane is perpendicular to the direction of movement (e.g. images in a coronal plane are the best in visualizing the upper sagittal sinus, transverse or sigmoid sinuses). Whereas, this effect is reduced in a plane parallel to the sinus. The clot may therefore be seen as the lack of signal loss (flow void), which is often best seen on T2-weighted images in spin echo or in the FLAIR sequences. Simultaneously, the sinus signal is different and the clot may be visible (direct symptoms). Signal intensity of a clot in T1- and T2-weighted images varies over time according to the characteristics of the extravasated intracranial blood, and evolves by stages of oxyhemoglobin, deoxyhemoglobin, methemoglobin and haemosiderin.

**Acute phase (0-5 days):** the clot signal is mainly isointense on T1-weighted and hypointense on T2-weighted images because of the presence of deoxyhemoglobin in erythrocytes trapped in a clot. Such an image is observed in approximately 10 – 30% of cases. In this phase, radiologist must be especially careful because the signal on T2-weighted images may be so low that it will imitate a normal ‘flow void’ in the sinus. In such a case, T1-weighted images should be accurately inspected for the absence of signal loss and the presence of a clot, which is unfortunately isointense to the brain tissue. The GRE-T2* sequence, in which deoxyhemoglobin emits a lower signal than moving blood, should help in that case. In this phase, it is often necessary to administer contrast medium or perform MR venography to confirm the diagnosis.

**Subacute phase (6-30 days):** the signal is mainly hyperintense, both on T1 and T2-weighted images (Fig. 4). The signal transition from hypointensity to hyperintensity is connected with the transformation of intracellular methaemoglobine to the extracellular methaemoglobine as a result of red blood cells lysis. This phase is the easiest for diagnosing a clot in MRI examination because the signal intensity in the sinus differs the most from the normal state. Finding an increased signal both on T1- and T2-weighted images is almost always an abnormal symptom. It appears in around 55% of patients with clinical symptoms of CVST.

**Chronic phase (>30 days):** assessment of the presence of a clot is hindered by different evolution possibilities of the same clot. The involved sinus may remain totally thrombosed or either partially or fully patent. About 15% of patients have imaging examinations in this phase of the disease. Typically, the signal of a chronic clot is iso- or hyperintense on T2-weighted images and isointense on T1-weighted images. Even images post-contrast enhancement may be misleading because the contrast enhancement of the sinus does not necessarily prove its patency – an organized clot may also enhance through its internal vascularization [3, 5, 7, 8, 10, 12, 13].

In MRI examination similar characteristics of CVST are analyzed just as is carried out in CT examination, i.e. incorrect signal intensity of the sinus, the ‘cord sign’, the
‘delta sign’ and in the post-contast phase the ‘empty delta sign’ (Fig. 5).

Indirect signs of a clot on MRI images are similar to the signs in computed tomography and include: swelling, oedema, infarction – hemorrhagic or not. Veins of collateral circulation are also often visible in the form of ‘flow void’, tortuous structures located within the brain and/or on its surface.

Recently, in the protocol of CVST imaging, gradient echo sequences (GRE) are increasingly more often included in order to detect the presence of blood breakdown products, and therefore to enable visualizing the clot inside the vessel. The GRE sequence is particularly useful in the acute phase of the disease, when the clot signal is not yet increased. Moreover, in a study by A. Idbaih et al., they observed that signal enhancement on GRE T2* images remained higher, even 4 months after the creation of a clot, when it already became decreased on T1-weighted images and in the DWI sequence. This may be helpful in establishing the onset time of the disease. Moreover, it has been demonstrated that this technique has a very high sensitivity in the detection of cortical venous thrombosis – higher than all the other MRI techniques [24, 25].

In addition, MRI examination is often (and most recently it has become a standard) broadened with diffusion weighted imaging (DWI), which allows differentiation between vascular and cytotoxic brain oedema, if such exists. DWI images allow distinguishing between areas at risk of necrosis (cytotoxic oedema) and areas possible to save (swelling in vascular oedema), which is not possible on T2-weighted images [14].

**MR venography.** MR venography is one of the major methods in the diagnosis of CVST. It can be performed in two ways: with or without contrast administration. In the non-invasive method – without intravenous contrast administration, two techniques of data acquisition are used: time-of-flight (TOF) and phase contrast (PC). In these studies, vessels with slow flow, i.e. veins, are visualized. A triad of symptoms is pathognomonic for CVST and include lack of flow in the sinus, its jagged and irregular outline, and the emergence of extended venous collaterals (Fig. 6) [13, 17].

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**Figure 4.** T1-weighted image, transverse plane. High signal intensity of the left transverse sinus in the course of dural venous thrombosis

**Figure 5.** (A) Unenhanced T1-weighted image, transverse plane. Delta sign of the superior sagittal sinus in the course of venous thrombosis. (B) T1-weighted post-contrast image, coronal plane. Empty delta sign in the course of dural venous thrombosis
angiography in CVST has been limited to therapeutic uses. The role of traditional collaterals in imaging cerebral veins has been shown recently to be superior to MR venography (MRV) with or without contrast administration. CT and MR venography, with or without contrast administration, allow direct visualization of clots in the form of lack of contrast filling in dura mater sinuses or cortical veins. Digital subtraction angiography is an invasive method, in which the lack of sinus filling after contrast administration is a symptom of CVST, and which currently remains reserved only for therapeutic purposes.

It is difficult to clearly specify the diagnostic algorithm in patients with suspected CVST. Magnetic resonance imaging performed in different planes and in T1- and T2-weighted images, as well as MR venography, remain the most accurate method of choice in diagnosis and monitoring the treatment of CVST. In order to make the correct diagnosis, different sequences and planes must be assessed.

In CT and MRI examinations with intravenous contrast administration, the direct symptom of the clot presence can be seen. This is the so-called ‘empty delta sign’ which is considered pathognomonic for this disease. CT and MR venography, with or without contrast administration, also allow direct visualization of clots in the form of lack of contrast filling in dura mater sinuses or cortical veins.

Digital subtraction angiography is an invasive method, in which the lack of sinus filling after contrast administration is a symptom of CVST, and which currently remains reserved only for therapeutic purposes.

MR venography with contrast administration is carried out by analogy to the CT venography. It does not depend on the blood flow but only on contrast filling of the vessel. In this method, a lower amount of contrast medium (gadolin derivative) than in CT is used, which eliminates the need to use automatic syringes. The drawback of this technique is lack of possibility to suppress the signal from the arteries. MR venography with contrast administration and CT venography have been shown recently to be superior to MR venography in TOF and PC technique, especially in imaging cerebral small veins [7, 12].

Digital subtraction angiography. Digital subtraction angiography (DSA) is an invasive method involving the administration of contrast medium through a catheter placed in the carotid arteries after puncture of, most commonly, the femoral artery, and assessing the enhancement of venous sinuses. Symptoms of CVST in this method include: lack of contrast filling of a sinus or a part of it (this symptom is non-specific and should be differentiated from sinus hypoplasia), delayed washing out of sinuses and the widening of small collateral veins. Currently, in the age of intensively developed less invasive methods of imaging, the role of traditional angiography in CVST has been limited to therapeutic uses [5, 13].

### REFERENCES