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Review Article

Current imaging modalities for diagnosing cerebral vein thrombosis – A critical review

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ABSTRACT

Cerebral vein thrombosis (CVT) is a rare presentation of venous thromboembolism. Prompt and accurate diagnosis is essential as delayed recognition and treatment may lead to permanent disability or even death. Since no validated diagnostic algorithms exist, the diagnosis of CVT mainly relies on neuroimaging. Digital subtraction angiography (DSA) is the historical diagnostic standard for CVT, but is rarely used nowadays and replaced by computed tomography (CT) and magnetic resonance imaging (MRI). High quality studies to evaluate the diagnostic test characteristics of state of the art imaging modalities are however unavailable to date. This review provides an overview of the best available evidence regarding the diagnostic performance of CT and MRI for the diagnosis of CVT. Notably, available studies are observational, mostly small, outdated, and with a high risk of bias. Therefore, direct comparison between studies is difficult due to large diversity in study design, imaging method, reference standard, patient selection and sample size. In general, contrast-enhanced techniques are more accurate for the diagnosis of CVT then non-contrast-enhanced techniques. CT venography and MRI have been both reported to be adequate for establishing a final diagnosis of CVT, but choice of modality as used in clinical practice depends on availability, local preference and experience, as well as patient characteristics. Our review underlines the need for high-quality diagnostic studies comparing CT venography and MRI in specific settings, to improve clinical care and standardize clinical trials.

1. Introduction

Cerebral vein thrombosis (CVT) refers to dural sinus as well as cerebral vein (cortical and deep vein) thrombosis, and is a rare but potentially life threatening presentation of venous thromboembolism [1]. It accounts for 0.5–1% of all strokes in the adult population with an incidence of 1.32 per 100,000 person-years [2,3]. The clinical presentation of CVT is highly variable and nonspecific. Since there are no validated diagnostic algorithms incorporating decision rules or D-dimer tests, the diagnosis of CVT mainly relies on neuroimaging [2,4]. Neuroimaging is also the main method for evaluation of CVT related complications relevant for prognosis and therapeutic management [2,5]. Therefore, knowledge of the diagnostic performance of available imaging modalities is of great importance for optimal management of the individual patient.

Different imaging modalities and techniques can be used for the diagnosis of CVT in adults. Digital subtraction angiography (DSA) once was the diagnostic standard for CVT but is rarely used nowadays due to its invasive nature which harbours a small risk for serious complications, including neurologic complications (i.e. neurologic sign or symptom or worsening of a preexisting neurologic deficit that occurred during the procedure or within 24 h) [6,7]. Neurologic complications are reported to occur in around 1.3% of patients undergoing DSA; with permanent deficits in 0.5% of patients [7]. Additional disadvantages of

Abbreviations: CT, Computed tomography; CVT, Cerebral vein thrombosis; DSA, Digital subtraction angiography; DWI, Diffusion weighted imaging; FLAIR, Fluid-attenuated inversion recovery; GRE, Gradient-recalled echo; MDCT, Multidetector row computed tomography; MRBTI, Magnetic resonance black blood imaging; MRDTI, Magnetic resonance direct thrombus imaging; MRI, Magnetic resonance imaging; MRV, Magnetic resonance venography; NCCT, Non-contrast computed tomography; PC, Phase-contrast; PDw, Proton density weighted; SW, Susceptibility weighted; TOF, Time-of-flight; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; 2D, Two-dimensional; 3D, Three-dimensional

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DSA include radiation exposure, and allergic or nephrotoxic effects of iodinated contrast agents [8]. In current clinical practice, DSA is reserved for exceptional cases, often when reperfusion therapy (such as thrombosuction) is considered [4,9]. Computed tomography (CT)/CT venography and magnetic resonance imaging (MRI) are presently the first line tests used in clinical practice [5,10–12], but each modality and technique has its advantages and disadvantages [13]. Randomized controlled diagnostic trials comparing these imaging modalities are absent, probably because of the low incidence of the disease. Therefore, knowledge of the diagnostic performance of each of these modalities is based on small observational studies. Results on diagnostic accuracy of the different imaging modalities from available studies must be interpreted with caution and cannot directly be compared nor translated into daily clinical practice, due to heterogeneity in study design, patient population (clinical presentation), imaging methods and used reference standard. Consequently, the diagnostic approach for the diagnosis of CVT differs considerably per country and even per hospital [5].

We aimed to provide an overview of published literature and applied extensive literature searches to identify all relevant papers regarding the diagnostic performance of CT/CT venography and MRI for the diagnosis of CVT (search strategy detailed in Appendix 1). Papers were chosen if written in Dutch or English and evaluating the diagnostic accuracy of CT/CT venography and MRI in cerebral vein thrombosis. We only excluded case-reports and reviews. Notably, in previous publications various terminologies have been used for CVT. In this review isolated thrombosis of the dural sinuses is referred to as cerebral sinus thrombosis and thrombosis of both dural sinus and cerebral veins as CVT.

2. Computed tomography

In the emergency setting, CT is often the imaging test of choice for patients presenting with acute focal neurological symptoms [5,10], since it's widely available, cost-effective and useful to rule out common neurological diagnoses [14]. CVT may present variable on CT (Table 1). A direct sign of CVT on non-contrast CT (NCCT) is direct visualization of a thrombus which is predominantly caused by the protein factor of haemoglobin within red blood cells, often called the “dense clot sign” or “dense vessel sign” (Fig. 1A) [15]. After the administration of a contrast agent the thrombus can directly be visualized as a filling defect within a dural sinus also called “empty delta sign”, which is specific for thrombosis of the superior sagittal sinus [2,9]. On CT indirect signs of CVT are often seen and may occur in 60–80% of cases [14]. Common indirect signs on CT that are highly evocative of CVT are multiple bilateral lesions (e.g. bilateral parasagittal hemispheric lesions are suggestive of superior sagittal sinus thrombosis), bilateral thalamic edema (can be found in deep cerebral vein thrombosis) and temporo-occipital lesions (suggestive for transverse sinus thrombosis) [14,16,17]. Cerebral haemorrhage is also a common finding in patients with CVT, present in approximately 40% of patients [18]. Juxtacortical hemorrhages, small hemorrhages with limited or no edema, localized at the junction between the superficial and deep venous drainage system, are seen in up to 12% of CVT patients and are very specific for CVT and almost exclusively occur in superior sagittal sinus thrombosis [18].

There are several studies that evaluated the diagnostic accuracy of direct and indirect signs on NCCT. These studies (with sample sizes ranging between 7 and 588 patients), which were all retrospective, mostly small and using different reference standards (CT venography, MRI, DSA and/or multiple imaging and follow up), found a sensitivity of 41–100% and specificity of 77–100% (Appendix 2) [19–26,90]. The best reported diagnostic accuracy of the attenuated vein sign on NCCT for the diagnosis of deep cerebral vein thrombosis was a sensitivity of 100% and specificity of 99% [20]. It is important to note that this was found in a small single center retrospective study, including only 8 patients diagnosed with deep cerebral vein thrombosis [20]. The reported accuracy for cerebral sinus thrombosis is a sensitivity of 50–100% and a specificity of 83–100% [20–22,24,25]. An explanation for these wide ranges may be the different scan technologies and acquisition measures used, with a generally lower sensitivity in older studies [23]. Poor interrater variability of the evaluation of direct and indirect signs on NCCT may also play a role [26]. In the specific setting of isolated cortical vein thrombosis, the reported sensitivity and specificity are 25% (95%CI 18–25%) and 100% (95%CI 92–100%), respectively [21]. In these studies, a thrombus was often missed since the “cord sign” or “string sign”, a direct sign of cortical vein thrombosis on CT, is difficult to detect due to its location next to the skull [21].

Because of the linear association between the attenuation of blood and haematocrit levels [27], high haematocrit values can result in a false positive CVT diagnosis [15]. On the other hand anaemia may result in false negative diagnosis. Moreover, subacute thrombosis may also result in false negative diagnoses since the density of thrombi attenuated over time and becomes isodense or even hypodense after approximately 7–14 days [15,28]. Therefore, studies have evaluated whether quantitative assessment of the attenuation and attenuation values compared to haematocrit (H:H ratio) improved the diagnostic accuracy of NCCT for the diagnosis of CVT, but did not find superior sensitivity (64–95%) or superior specificity (54–100%) [13,15,24–26,29–31]. Notably, after the administration of a contrast agent, direct/indirect signs on CT scan can still be absent in up to 30% of the CVT cases (Appendix 2) [9,32–38].

Recently, a meta-analysis summarizing the diagnostic accuracy of CT (non-contrast- and contrast-enhanced) for CVT has been published [39]. Twenty-four eligible publications, including 48 studies with varying study designs and diagnostic standards were included, for a total of 4595 individual patients. Overall, CT was found to have a reasonable diagnostic accuracy with a pooled sensitivity of 79% (95%CI 76–82%) and a pooled specificity of 90% (95%CI 89%–91%). For the diagnosis of cerebral sinus thrombosis, the pooled sensitivity and specificity of CT were 81% (95%CI 78–84%) and 89% (95%CI 88–91%), respectively. Subgroup analyses showed no significant difference of the diagnostic accuracy in suspected acute, sub-acute or chronic CVT. The authors also found that visual assessment (evaluation of direct/indirect signs) was more accurate than quantitative assessment (attenuation evaluation) [39].

In summary, while CT is useful as primary imaging modality in patients with suspected acute CVT, additional imaging is generally required to diagnose and rule out CVT with more certainty [2,5,15,26,40].

Table 1
(Non-)contrast-enhanced computed tomography (CT) findings in cerebral vein thrombosis.

	Direct signs	Indirect signs
Non-contrast CT (NCCT)	• Dense clot sign: direct visualization of the thrombus in the cerebral sinus and veins • Cord or string sign (dense vessel sign): linear or cord-like density of a thrombosed cortical vein	• Haemorrhagic infarction • Brain oedema • Mass effect • Subarachnoid haemorrhage
Contrast-enhanced CT (CECT)	• Empty delta sign: thrombosed sinus seen as triangular area of enhancement with relatively low-attenuation center	• Same findings as on NCCT

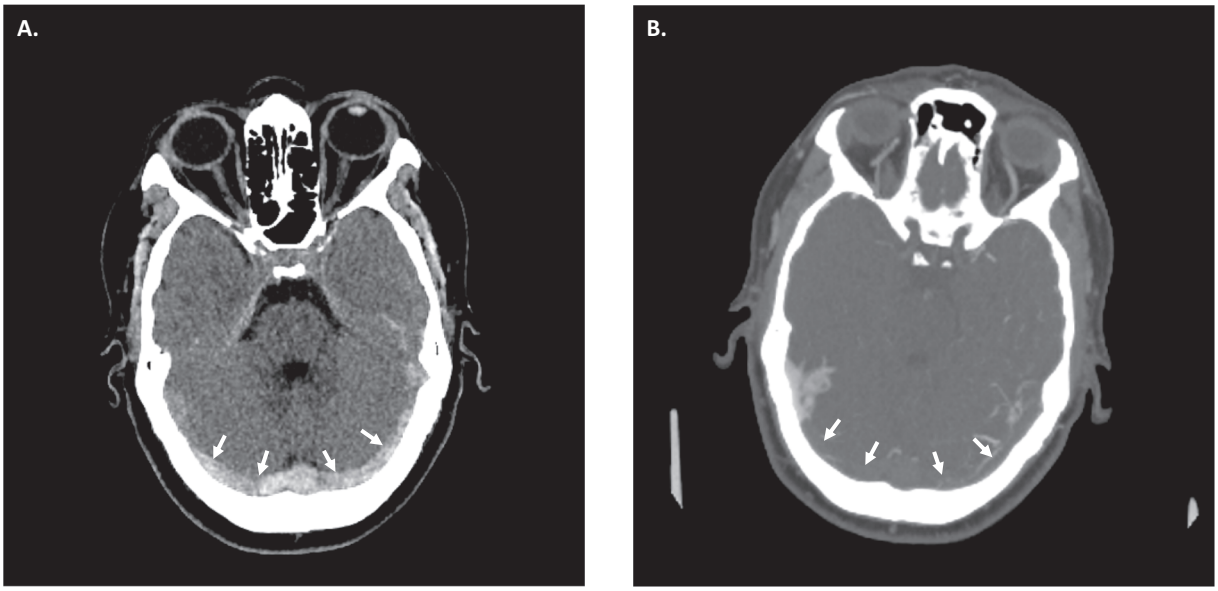

Fig. 1. Axial CT images of a patient with acute sinus thrombosis; A. Non-contrast CT image shows a hyperdense aspect of both transverse sinus (arrows) and B. CT venography after administration of iodinated contrast agent shows a filling defect in both transverse sinus (arrows).

Table 2
Different MRI techniques.

Type	Sequences
Non-contrast-enhanced flow related MRI	*Gradient echo*: 2D TOF MRV, 3D TOF MRV, 2D PC MRV, 3D PC MRV
Native contrast thrombus MRI	*Spin echo*: T1-WI FSE/TSE, T2-WI FSE/TSE, FLAIR, PDw, MR Black Blood Imaging (MRBTI: T1-WI 3D SPACE), 3DT1 TSE SPAIR *Gradient echo*: DWI, MR Direct Thrombus Imaging (MRDTI: T1-WI magnetization prepared 3D gradient TFE) *Gradient echo susceptibility weighted*: T2*WI, T2*WI SE EPI, T2*SW, T2*GRE, GRE
Contrast-enhanced (T1 SE or GRE) MRI	*Spin echo*: CE T1-WI SE/FSE *Gradient echo*: 3D T1 GRE/MP-RAGE, CE T1 GRE, CE MRV (including combo 4D MRV, 3D EC MRV, CE TOF MRV)

Note: MRI: magnetic resonance imaging, D TOF MRV: dimensional time-of-flight magnetic resonance venography, PC MRV: phase-contrast magnetic resonance venography, T1/T2-WI: T1/T2-weighted imaging, FSE: fast spin-echo, TSE: turbo spin-echo, FLAIR: Fluid Attenuated Inversion Recovery, PDw: proton density weighted, SPACE: variable-flip-angle-turbo spin echo, SPAIR: Spectral Attenuated Inversion Recovery DWI: diffusion weighted imaging, TFE: turbo field echo, SE: spin-echo, EPI: echo-planar imaging, SW: susceptibility weighted, GRE: gradient-echo, CE: contrast-enhanced, MP-RAGE: magnetization-prepared rapid gradient-echo.

3. CT venography

CT venography is one of the most often used imaging modalities for the diagnosis of CVT because of its widespread availability and cost-effectiveness [5]. CT venography is a contrast-enhanced helical CT examination performed with a time-optimized contrast bolus in order to enhance the cerebral venous system [17,41]. The diagnosis of CVT can be made by evaluation of the axial thin-section contrast-enhanced source images of a helical CT scan. However, two- and three-dimensional (2D and 3D) reformation techniques (e.g. maximum intensity projection, integral display, and volume rendering) can be used to provide detailed anatomic images of the deep and superficial cerebral veins free from overprojecting bones and brain parenchyma [17,42]. On CT venography, a thrombosed cerebral vein can be visualized as a filling defect (Fig. 1B) [5,9]. Also indirect signs of CVT such as brain edema and subarachnoid haemorrhage can contribute to the diagnosis of CVT [2,5].

In the most relevant studies available, CT venography was found to be a reliable alternative to DSA for diagnosing CVT [40,43,44] with a sensitivity and specificity of both 100% (Appendix 3) [43]. However, quality of this evidence is low, since individual studies included < 100 patients, were observational and suffered from a high risk of bias [40].

Other studies used consensus reading of multiple imaging modalities and final clinical outcome as reference standard rather than DSA (Appendix 3) [10,21,45]. In these studies, CT venography was found to be accurate for diagnosing cerebral sinus thrombosis as well, with a sensitivity of 100% (95%CI 88–100%) and specificity of 100% (95%CI 95–100%) [10,21,45]. However, these studies were also small (n < 34) and retrospective. Notably, CT venography has been shown to be of limited diagnostic value for diagnosing cortical vein thrombosis with a reported sensitivity of 6–75% [21,45]. This is explained by the fact that the 'missing vein', i.e. contrast filling defect, is difficult to distinguish from physiological variations in venous anatomy [21].

Thus, available literature supports the use of CT venography for diagnosing cerebral sinus thrombosis, but less so for cortical vein thrombosis [21].

4. Emerging CT techniques

In past years new CT techniques have been developed that may allow better diagnosis of CVT. With the emerge of multidetector row CT (MDCT), thin slices are obtained with the use of less contrast and shorter scanning time allowing better image quality without significantly increasing overall radiation dose [45,46]. Currently 320-MDCT techniques are used that may acquire brain volumes within a single second.

Several techniques can be used for removing unwanted overlying (bone) structures from the vascular (venous) structures to improve the diagnostic accuracy of CT venography, which is especially needed for 3D interpretation. Previous studies have used the 'graded subtraction'

Table 3
Overview of different contrast-enhanced and non-contrast-enhanced magnetic resonance venography (MRV) techniques with advantages and disadvantages.

	Technique	Mechanism	Advantages	Disadvantages
Non-contrast- enhanced (Non-CE) MRV	Time-of-flight (TOF) MRV (2D (dimensional) or 3D)	Flow-related enhancement	● Sensitive to slow flow (especially 2D TOF) ● Does not require use of a contrast agent ● Relatively short acquisition times (5–8 min)	● False positives: loss of signal due to in-plane saturation ● False negatives: high signal from background tissue with short T1 values that can mimic flowing blood
	Phase-contrast (PC) MRV (2D or 3D)	Velocity-induced phase shift of spins	● Great suppression of background (stationary) tissues ● No false negatives due to methaemoglobin ● Can detect flow in 3 orthogonal planes ● Ability to quantify flow and determine flow direction	● Sensitive to motion artefacts and turbulent flow ● Relatively long acquisition times (> 15 min) ● Need to predict optimal velocity encoding variable (VENC) ● Easily affected by the velocity of blood flow and turbulence
Contrast-enhanced (CE) MRV	3D CE MRV (static)	T1 shortening of Gadolinium	● Great suppression of background signal ● No in-plane saturation effects that are often problematic with the TOF technique ● Relatively fast acquisition time ● Able to assess (partial) recanalization	● Need for a contrast agent ● False negatives: the clot may enhance, simulating an open sinus
	4D CE MRV (dynamic)	Same as 3D CE MRV	● Same advantages as 3D CE MRV ● No need for sophisticated triggering system for contrast injection compared to 3D CE MRV	● Same disadvantages as 3D CE MRV

technique, a non-automated post-processing technique which is time-consuming and operator dependent [41,42,47]. State of the art techniques include mask-subtraction and dual-energy. With mask-subtraction a low-dose non-enhanced CT is subtracted from the contrast-enhanced vascular (CT venography) acquisition [47,48]. With dual-energy techniques bone removal is obtained by postprocessing a dual-energy CT data set that is simultaneously acquired with a low- and a high kilovoltage, where difference in x-ray absorption of different materials depend on x-ray energy [49]. New spectral CT techniques such as photon-counting CT hold promise for further improved visualization of CVT [50,51].

5. Magnetic resonance imaging

Various MR techniques are available to visualize cerebral vascular structures and/or thrombosis. The MRI techniques can be divided into three groups based on how the thrombosis is depicted; 1) non-contrast-enhanced flow related MRI, 2) native contrast thrombus MRI and 3) contrast-enhanced MRI (Table 2). Non-contrast-enhanced flow related MRI, often called non-contrast-enhanced magnetic resonance venography (MRV), includes time-of-flight (TOF) MRV and phase-contrast (PC) MRV (Table 3). With this MR technique a thrombus can be depicted by absence of normal flow patterns (Fig. 2). A thrombus can also be directly visualized with native contrast thrombus MRI techniques. These sequences are used to visualize thrombus by presence of paramagnetic deoxyhaemoglobin, methaemoglobin, or hemosiderin [52]. Moreover, MRI after the administration of an intravenous gadolinium-based agent can be used (contrast-enhanced MRI), which allows direct luminal visualization that is comparable to that of CT venography, where a thrombus can be identified as a filling defect [5]. Compared to CT venography, MRI is more sensitive for the detection of small parenchymal lesions and cerebral edema and has the advantage of not exposing the patient to ionizing radiation [5,12,53]. On the other hand, advantages of CT venography over MRI are the fast acquisition times and the possibility to scan more patients, since many MRI contra-indications exist.

5.1. Non-contrast-enhanced flow related MRI

Most studies that evaluated the diagnostic accuracy of non-contrast-enhanced flow related MRI techniques compared to DSA found an adequate sensitivity and specificity for CVT (Appendix 4) [13,54–57]. Two studies evaluating non-contrast-enhanced PC MRV found that this technique is sensitive for diagnosing CVT with a sensitivity of 100% and specificity of 71% [13,56]. Notably, DSA was not performed in all study participants [13,56]. The non-contrast-enhanced TOF MRV technique also seems highly reliable for CVT in larger cerebral veins and sinuses. However, this technique was not sensitive for assessing smaller veins (i.e. in branches of cortical veins) [55,57,58].

Most studies evaluated the diagnostic accuracy of non-contrast-enhanced flow related MRI techniques compared to the combination of multiple imaging modalities and final clinical outcome or contrast-enhanced MRV (Appendix 5) [21,32,59–68], were adequate sensitivity and specificity for CVT were found too. Non-contrast-enhanced TOF MRV and PC MRV had a sensitivity of 64–100% and 48–100%, respectively, although with wide 95% confidence intervals. Moreover, non-contrast-enhanced flow related MRI was confirmed to be less accurate for identifying cortical vein thrombosis [21,64].

5.2. Native contrast thrombus MRI

With native contrast thrombus MRI techniques, a thrombus is directly visualized (Fig. 3). In the first 5 days after clot formation, the signal may be isointense on T1-weighted images (T1WI) and hypointense on T2-weighted images (T2WI) as the acute thrombus has a high deoxyhaemoglobin concentration [2,5,14]. Between 6 and

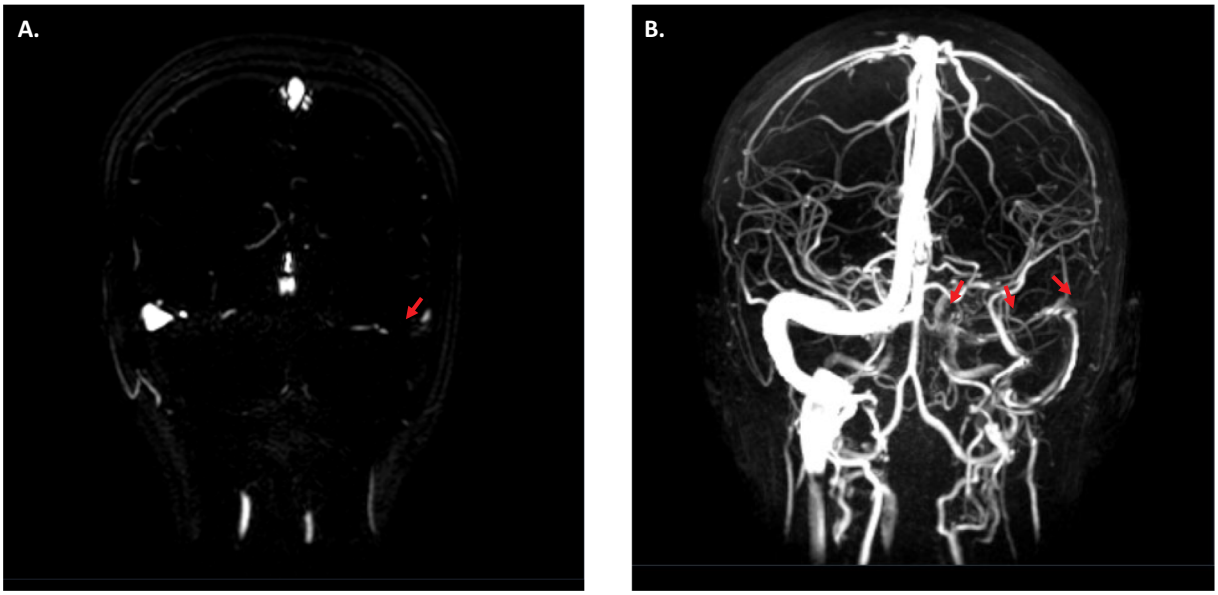

Fig. 2. Coronal Phase Contrast (PC) MR venography (MRV) image of a patient with acute sinus thrombosis of the left transverse and sigmoid sinus; A. Coronal PC MRV image and B. PC MRV maximum intensity projection (MIP) with absence of flow in the left transverse and sigmoid sinus (arrows).

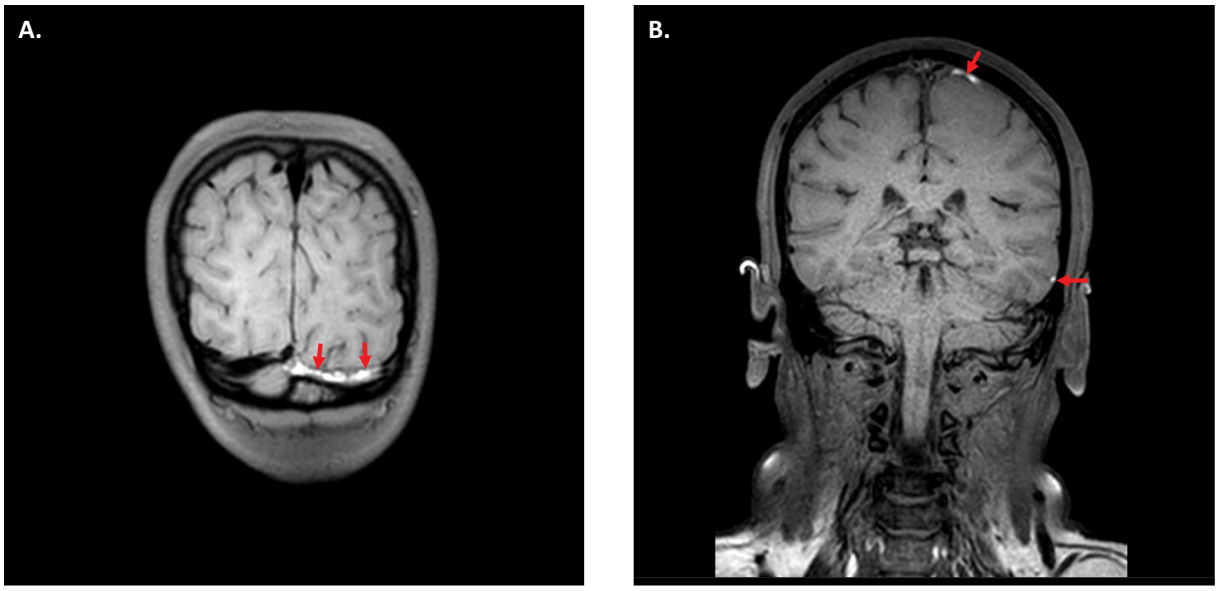

Fig. 3. Coronal 3DT1 TSE SPAIR images: A. with a high signal intensity of the left transverse sinus (arrows) in a patient with acute sinus thrombosis (6–15 days old) and B. with high signal intensity in two cortical veins (arrows) in another patient indicative of acute cortical vein thrombosis (6–15 days old).

15 days, the clot may appear hyperintense on T1WI and T2WI due to a high methaemoglobin concentration [2,5]. After 15 days the thrombus may appear iso to hyperintense on T2WI and isointense on T1WI [2,5]. On gradient-recalled echo (GRE) susceptibility weighted (SW) images, deposited blood breakdown products (i.e. methaemoglobin, deoxyhaemoglobin) can cause exaggerated signal drop-out (Fig. 4) so that intraluminal thrombi can be depicted in stages where the clot may be subtle in other sequences [5].

The combination of different native contrast thrombus MRI techniques had an overall sensitivity and specificity of 84–97% and 28–96%, respectively, for the diagnosis of CVT (Appendices 4 and 5) [32,56,61,69,70[91,92][93–95]. The comparison of these studies and interpretation of their results is complicated by the inclusion of heterogeneous patient populations and different applied MRI sequences, e.g., T1WI, T2WI, fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI) and proton density weighted (PDw) sequences. For the diagnosis of cortical vein thrombosis however, GRE SW MRI was consistently reported to have an adequate sensitivity of 97–98% and specificity of 100% [21,71,72].

5.3. Contrast-enhanced MRI

When DSA was used as reference standard, contrast-enhanced MRI was more accurate for diagnosing cerebral sinus thrombosis than non-contrast-enhanced flow related and native contrast thrombus MR sequences, with a sensitivity and specificity of 83% and 100% versus 8–51% and 80–93%, respectively (Appendix 4) [55]. Other studies used the combination of multiple imaging modalities and final clinical outcome [61–63] or contrast-enhanced MRV [70] alone as reference (Appendix 5). In these latter studies, contrast-enhanced MRI was also more sensitive for CVT than non-contrast-enhanced MRI, with a sensitivity and specificity of 86–97% and 52–100% versus 55–97% and 28–95%,

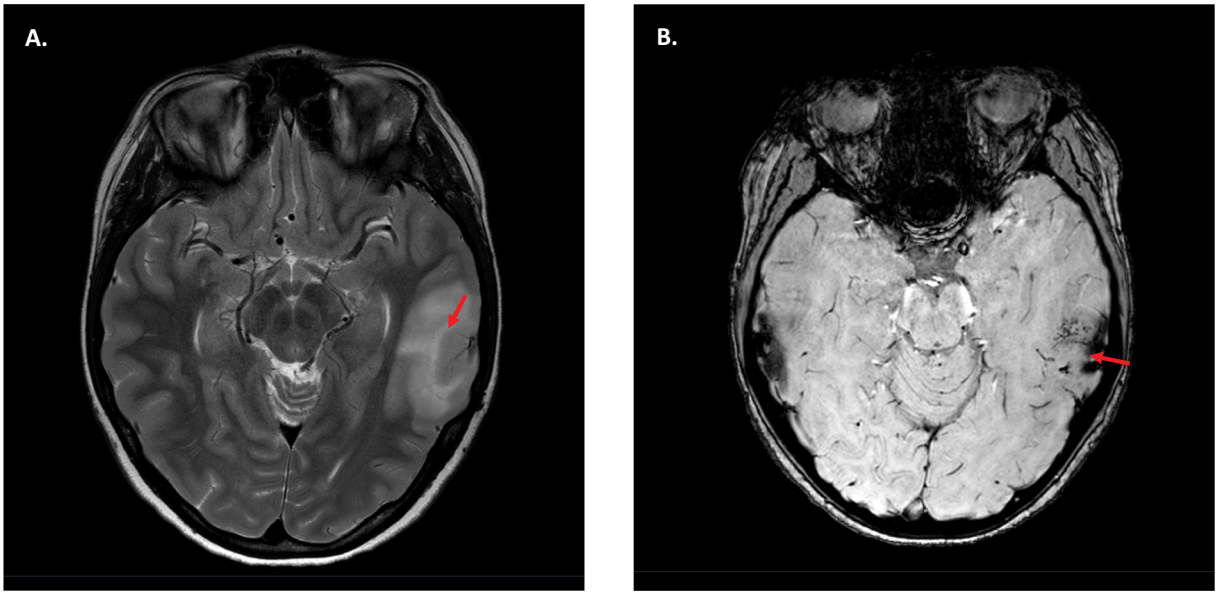

Fig. 4. Transversal native contrast thrombus MR images of a patient with left temporal cortical vein thrombosis with venous haemorrhagic infarction: A. T2 weighted image showing a region of increased signal intensity in the cortex and subcortical white matter in the left temporal lobe and B. Susceptibility weighted image showing multiple susceptibility artefacts indicating haemorrhagic transformation in the pathological region with pronounced blooming artefacts within the thrombosed cortical veins (arrow).

respectively [61–63,70]. Furthermore, in studies that evaluated the diagnostic accuracy of MRI for visualization of cerebral veins (not necessarily in the setting of suspected CVT), contrast-enhanced MRI was found to be superior to non-contrast-enhanced MRI as well [66,73–78].

In a recent meta-analysis the diagnostic accuracy of flow related MRI (MRV; contrast- and non-contrast-enhanced) for CVT was summarized [79]. Subgroup analyses of different MRV techniques confirmed that the diagnostic performance of contrast-enhanced MRV was better than that of non-contrast-enhanced TOF and PC MRV.

6. Magnetic resonance black-blood thrombus imaging

Recently, magnetic resonance black-blood thrombus imaging (MRBTI), a native contrast thrombus MR technique, has been evaluated in the setting of suspected CVT [14,80,81]. MRBTI yielded a sensitivity of 100% and specificity of 96%, even up to the level of individual venous segments, using CT and MRI in combination with clinical and outcome assessments -but not DSA- as diagnostic standard [80]. A very similar native contrast thrombus MR technique, MR Direct Thrombus Imaging (MRDTI), has been shown to be highly accurate for the diagnosis of deep vein thrombosis and for the differentiation of acute versus chronic deep vein thrombosis in the legs [82–87]. Thus, this technique may be of great value for diagnosing CVT as well, especially in complex cases such as in suspected recurrent CVT. Further research is however needed before MRBTI can be used for the diagnosis of CVT in daily clinical practice.

7. MRI versus CT venography

When CT venography was compared to MRI, CT venography had a sensitivity of 100% and specificity of 100% for the diagnosis of cerebral sinus thrombosis (Appendix 6) [41,88,89]. Two of these studies even found that CT venography was better for the evaluation of small vessel anatomy with fewer artefacts than MRI [41,88]. It is important to note that these studies were small (n = 24–36), included patients with suspected CVT but also patients without the suspicion for CVT (follow-up after acute CVT or pre-operative screening), and did not perform the same MR sequences in all included patients.

8. Conclusion

Contrast-enhanced MRI is more accurate than non-contrast-enhanced MRI for diagnosing CVT, as CT venography is more accurate than CT. Both CT venography and contrast-enhanced MRI seem adequate for establishing a CVT diagnosis. Solid evidence to choose one over the other is however unavailable. In practice therefore, clinical availability, local preference and experience mainly determine which modality is used. Large high-quality diagnostic studies are needed to improve clinical care and standardize clinical trials.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.03.011.

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