

# Cortical vein thrombosis: the diagnostic value of different imaging modalities

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## Abstract

**Introduction** Cortical vein thrombosis (CVT) is a rare disorder, and its diagnosis is challenging. The aim of our study was to evaluate the value of different imaging modalities for the detection of CVT.

**Methods** Thirteen patients with CVT, either isolated ( $n=3$ ) or in combination with sinus thrombosis ( $n=10$ ), and 20 control patients without any venous pathologies were included in this study. The analysis was performed independently by three blinded readers who evaluated the following imaging modalities and sequences separately: non-enhanced computed tomography (NCCT); multi-detector row CT angiography (MDCTA); diffusion-weighted (DWI), T1-weighted (T1w), PD-weighted (PDw), T2\*-weighted (T2\*w), and fluid-attenuated inversion recovery-weighted (FLAIRw) magnetic resonance (MR) sequences; as well as venous MR angiography (vMRA). The sensitivity, specificity, positive (PPV) and negative predictive values, and interobserver agreement of the different modalities were calculated.

**Results** T2\*w showed the highest sensitivity for the detection of CVT (97.4%), followed by T1w (70%).

FLAIRw and vMRA had a sensitivity of 50% and 41.7%, respectively, whereas the sensitivity of NCCT, MDCTA, DWI, and PDw was below 30%. The specificity and PPV of all modalities was 100%, with good to perfect interobserver agreement.

**Conclusion** T2\*w was the superior MR imaging sequence for diagnosing CVT. Besides T2\*w, only T1w reached a sensitivity of over 50% for CVT, followed by FLAIRw, and vMRA. On the contrary, our results suggest that NCCT but also MDCTA might not be suitable for diagnosing CVT.

**Keywords** Cortical vein thrombosis · MRI · T2\*-weighted imaging · Multi-detector row CT angiography

## Introduction

The cortical veins are highly variable in number, size, and localization, which make their radiological evaluation very challenging [1, 2]. A cortical vein thrombosis (CVT) can lead to venous hypertension, edema, infarction, or hemorrhages [2, 3]. Symptoms of CVT include focal or generalized seizures followed by hemiparesis, aphasia, hemianopia, or other focal deficits, often without signs of elevated intracranial pressure [2–4].

CVT can occur either in an isolated form (isolated CVT (ICVT)) or in combination with a thrombotic occlusion of the venous sinuses (combined CVT (CCVT)). ICVT is a very rare diagnosis and has only been reported in case reports or in small series [4–15]. However, it is difficult to diagnose in vivo because of the lack of a gold standard, and thus, it might be overlooked occasionally [7, 14].

Recently, T2\*w has been shown to be of great diagnostic value for the detection of cortical vein involvement in cerebral venous thrombosis [6, 7, 15]. Non-enhanced

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computed tomography (NCCT) and multi-detector row CT angiography (MDCTA) have been shown to be of great value for the diagnosis of deep cerebral venous thrombosis [16] and sinus thrombosis (SVT), respectively [17, 18]. Yet, there are neither any data on the specificity of the different magnetic resonance (MR) sequences for CVT nor any studies available that address the diagnostic value of NCCT and MDCTA for CVT. Thus, we initialized this blinded, multi-reader study on patients with CVT and on control patients to assess the sensitivity, specificity, positive (PPV) and negative (NPV) predictive value, and interobserver agreement of different imaging modalities including NCCT, MDCTA, and different MR imaging (MRI) sequences for the detection of CVT.

## Materials and methods

The study was approved by our Institutional Review Board and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients who participated in the clinical investigations.

### Definitions

We defined *ICVT* as an isolated thrombosis of one or more cortical veins without involvement of sinus or deep cerebral veins, whereas *CCVT* was defined as a thrombosis of cortical veins in combination with an SVT. The term *SVT* was used to denote an SVT without an involvement of cortical veins.

To facilitate reading, the item *imaging modalities* was used not only to indicate NCCT, MDCTA, and MRI but also refers to the different MR sequences we used. The phrase *extent of thrombosis* specifies the individual veins and sinuses that were affected by a respective occlusion.

### Patients

We used our electronic, in-hospital database of clinical records to search for the key words *cortical*, *venous*, *sinus*, *cerebral*, *isolated*, and *thrombosis* to identify all patients with ICVT or CCVT seen in our institution between 2002 and 2007. Only patients in whom direct signs of a CVT were present on at least one imaging modality were included in the study. Three patients with ICVT and ten patients with CCVT matched the inclusion criteria and constituted the study group (mean age, 44.3 years; range, 7–79 years, ten females). Digital subtraction angiography (DSA) was also available for five of the patients. Table 1 shows demographic data, clinical presentation, and details on available imaging. The mean time interval between the symptom onset and initial imaging was 4.4 days (range, 0–15 days).

In addition, we included a control group of 20 consecutive patients who had initially presented with symptoms of venous thrombosis including severe headache ( $n=20$ ) and drowsiness ( $n=5$ ), but for whom imaging showed no pathological intracranial findings and for whom clinical and imaging follow-up was uneventful (mean age, 33.2 years; range, 16–73 years; 12 females). In ten of these patients, MRI with T2\*-weighted (T2\*w), PD-weighted (PDw), diffusion-weighted (DWI), T1-weighted (T1w), and fluid-attenuated inversion recovery-weighted (FLAIRw) sequences, as well as venous time-of-flight MR angiography (vMRA) were available; in the other ten patients, NCCT and MDCTA had been conducted.

### Imaging parameters

All examinations were conducted under the following clinical routine conditions. Both NCCT and MDCTA were performed on a 4 ( $n=7$  cases) or 64-detector row CT ( $n=16$  cases). For NCCT, the following parameters were used: 120 kV, 300 mAs, a collimation of 2.5 mm, a section width of 5 mm, and a reconstruction increment of 5 mm. For MDCTA, the following parameters were used: 120 kV, 120 to 140 mAs, and a collimation of  $4 \times 1.0$  or  $64 \times 0.62$  mm. Venous catheters (18 gauge) were placed in the antecubital vein to apply 120 mL of contrast agent with an iodine concentration of 300 mg/mL after a delay of 35 s at flow rates between 3 and 5 mL/s.

MRI was performed on 1.5 T scanners using the following sequences: DWI (b-values, 0 slice thickness=5 mm; field of view (FOV)=210 mm; matrix size=128; 23 slices) PDw acquired as a dual-echo spin-echo acquisition with T2w (TR=2,210 ms; TE=85/14 ms; slice thickness=6 mm; FOV=210 mm; matrix size=256; 23 slices), T1w (TR=665 ms; TE=14 ms; slice thickness=6 mm; FOV=210 mm; matrix size=256; 23 slices), T2\*w (TR=1,000 ms; TE=22 ms; slice thickness=5 mm; FOV=210 mm; matrix size=256; 23 slices), FLAIRw (TR=7,500 ms; TE=74 ms; inversion time (TI)=2,500 ms; slice thickness=5 mm; FOV=220 mm; matrix size=256; 19 slices), and vMRA with arterial saturation pulses (TR=24 ms; TE=5.6 ms; flip angle=50°; slice thickness=3 mm; FOV=210 mm; matrix size=256; 50 slices).

DSA was performed on a biplanar DSA unit including selective catheterizations of both internal carotid arteries and the dominant vertebral artery, late venous phases, and oblique projections.

### Image interpretation

A standardized evaluation of the datasets was performed independently on a standard PACS workstation by three experienced neuroradiologists, who were blinded to all clinical data and patient identification information. The

**Table 1** Cortical vein thrombosis patients: demographic data, clinical findings, and available imaging.

Patient	Age/ sex	Clinical symptoms	Available imaging (missing MR sequences)	Delay between imaging modality and symptom onset (days)			
				NCCT	MDCTA	MRI	DSA
1	22/f	Seizure, loss of consciousness, headache, right-sided hemiparesis	NCCT, MDCTA, MRI (PDw)	0 <sup>b</sup>	5	10	–
2	45/f	Seizure, loss of consciousness, paresis of the left arm, headache	NCCT, MRI (FLAIRw, PDw)	19	–	3 <sup>b</sup>	–
3	79/f	Confusion, seizures, right-sided hemiparesis	NCCT, MDCTA, MRI (FLAIRw, vMRA)	0 <sup>c</sup>	1	0 <sup>c</sup>	–
4	60/f	Headache, nausea, left-sided hemiparesis, paresthesia	NCCT, MRI (FLAIRw)	14	–	7 <sup>b</sup>	–
5	29/f	Headache, reduced vigilance, left-sided hemiparesis	NCCT, DSA, MRI (FLAIRw)	15 <sup>c</sup>	–	15 <sup>c</sup>	15 <sup>c</sup>
6	20/f	Headache, vomitus, left-sided paresthesia	NCCT, MRI (DWI, T1w)	16	–	15 <sup>b</sup>	–
7 <sup>a</sup>	48/m	Headache, dysarthrophonia, paresthesia of the right arm, fluctuating vigilance	NCCT, DSA, MRI (FLAIRw, T1w)	7	–	6 <sup>b</sup>	7
8	53/f	Seizure, loss of consciousness, headache	NCCT, MDCTA, MRI (FLAIRw)	1 <sup>c</sup>	1 <sup>c</sup>	1 <sup>c</sup>	–
9	49/m	Nausea, vomitus, headache	NCCT, DSA, MDCTA, MRI	6 <sup>c</sup>	6 <sup>c</sup>	6 <sup>c</sup>	8
10	38/f	Headache, left-sided hemiparesis, reduced vigilance	NCCT, MDCTA, MRI (T1w, PDw)	4 <sup>b</sup>	5	8	–
11	7/m	Headache, right-sided hemiparesis	NCCT, MRI (FLAIRw)	0 <sup>b</sup>	–	3	–
12 <sup>a</sup>	60/f	Seizure, reduced vigilance right-sided hemiparesis	NCCT, DSA, MRI (PDw)	0 <sup>b</sup>	–	8	0 <sup>b</sup>
13 <sup>a</sup>	29/f	Seizure, loss of consciousness, right-sided hemiparesis	MDCTA, DSA, MRI	8	8	0 <sup>b</sup>	12

0 days: imaging performed at day of symptom onset

– imaging modality not available, *CVT* cortical vein thrombosis, *f* female, *m* male, *NCCT* non-enhanced CT, *MDCTA* multi-detector row CT angiography, *MRI* MR imaging, *DSA* digital subtraction angiography, *DWI* diffusion-weighted imaging, *FLAIRw* FLAIR-weighted sequence, *PDw* PD-weighted sequence, *T1w* T1-weighted sequence, *vMRA* venous MR angiography, *T2\*w* T2\*-weighted sequence

<sup>a</sup> Patient with isolated cortical vein thrombosis

<sup>b</sup> First-line imaging

<sup>c</sup> Different imaging modalities performed at the same day

different imaging modalities were analyzed separately in randomized reading orders using a standardized evaluation form.

For each modality, the readers evaluated direct and indirect signs of a thrombosis. The absence or presence of the following direct signs of a thrombosis were noted: hyperattenuated cerebral veins (i.e., hyperattenuated vein sign [16]) or sinuses (i.e., cord sign [16]) on NCCT; venous filling defects or missing vein on MDCTA; hyperintense veins or sinuses on DWI, T1w, PDw, and FLAIRw; hypointense veins or sinuses on T2\*w (delineated as pronounced, extracerebral “tubular, serpentine, or rounded” [7] hyposignal which is larger in diameter than the vascular structures on other sequences, an appearance which has been described as blooming); and lack of venous flow void on vMRA. Note that both source images and maximum intensity projection reconstructions of the vMRA and the

MDCTA were analyzed and that only the DWI images with a b-value of 1,000 were evaluated.

Based on these findings, the readers decided whether they interpreted a respective modality as indicative of a CVT or an SVT and noted the extent of the respective thrombosis.

#### Means of confirming diagnoses—consensus reading

After having evaluated all datasets, the readers performed a consensus reading to obtain a reference standard. They collaboratively reviewed all available imaging modalities including follow-up imaging and studied the clinical records to take into account all clinical and outcome information. They subsequently determined in consensus (1) the overall presence of an ICVT or a CCVT, (2) the extent of the respective thrombosis, (3) the presence of an

edema, or (4) the presence of a hemorrhagic venous infarction.

If there were discrepant findings between the different modalities, the reference standard for the cortical veins was based on the results of the T2\*w, and the reference standard for the sinuses was based on the source images of the vMRA or MDCTA. Whenever DSA was available, it was additionally evaluated. PDw and FLAIRw were given precedence for intracerebral edema, and T2\*w was given precedence for hemorrhage.

### Statistical analysis

All patient and image interpretation data were entered into a database and analyzed with standard software. The sensitivity, specificity, PPV, and NPV of the different modalities were calculated.

To account for time-dependent signal changes of thrombus material on T1w and PDw, we grouped the patients into either acute thrombosis (imaging performed within 0 to 5 days after symptom onset,  $n=5$ ) or subacute thrombosis (imaging performed within 6 to 15 days after symptom onset,  $n=8$ ) and then performed subgroup analyses of the sensitivity, specificity, PPV, and NPV. This was not done for FLAIRw due to the limited number of cases for which it was available.

To determine the interobserver agreement regarding the presence of a CVT or SVT, multirater  $\kappa$  values were calculated as described in the literature [19]. Multirater  $\kappa$  values can range from  $-1.0$  to  $1.0$ , with  $-1.0$  indicating perfect disagreement below chance,  $0.0$  indicating agreement equal to chance, and  $1.0$  indicating perfect agreement above chance [19].

## Results

### Consensus reading

Table 2 summarizes the results of the consensus reading. The frontal cortical veins were involved in all but one of the CVT patients, and the superior sagittal sinus (SSS) was affected in all patients with CCVT. On average, 5.9 cortical veins were affected (range, 2–8), as demonstrated by T2\*w (Figs. 1, 2, 3, and 4). In all other modalities, a fewer number of cortical veins showed direct signs of CVT.

### Blinded readings—overall diagnosis of CVT and SVT

Each of the readers performed 160 readings; thus, there were 480 readings in total. A CVT was correctly diagnosed in 105 readings (21.9%) with no false positives, but there were 135 false negatives (28.1%). An involvement of the

sinus was correctly found in 129 readings (26.9%), misdiagnosed in three false positive readings (0.6%), and missed in 57 false negatives (11.9%).

T2\*w showed the highest sensitivity for CVT with 97.4% (Figs. 1, 2, 3, and 4), followed by T1w (70%, Fig. 1), FLAIRw (50%, Fig. 4), and vMRA (42.7%; Figs. 1, 2, and 3). The sensitivity of NCCT (Fig. 5), MDCTA (Figs. 3 and 5), DWI (Fig. 4), and PDw (Figs. 1 and 2) was below 30%. The subgroup analysis revealed a sensitivity of 25% and 26.7% for PDw and a sensitivity of 60% and 80% for T1w for acute and subacute CVTs, respectively. All modalities showed a specificity of 100%. The  $\kappa$  values ranged from 0.73 (T1w) to 1.0 (FLAIRw) for CVT and from 0.63 (NCCT) to 1.0 (MDCTA and FLAIRw) for SVT. Table 3 details the sensitivity, specificity, PPV, NPV, and interobserver agreement of the different modalities for the diagnosis of CVT or SVT.

### Blinded readings—extent of thrombosis

Concerning the individual venous structures, T2\*w showed the highest sensitivity for a thrombotic occlusion of the frontal, parietal, and occipital cortical veins (86.1%, 94.6%, and 50%, respectively), while vMRA was most sensitive for an involvement of the temporal cortical veins (33.3%). With regard to the sinuses, MDCTA was superior for all sinuses except the right transverse sinus, for which FLAIRw and PDw had the highest sensitivity. For details on the sensitivity, specificity, PPV, and NPV of the different modalities regarding the extent of the thrombosis, see Table 4.

## Discussion

To our knowledge, this is the first study on CVT to use a blinded, multi-reader set-up and a control group. This is also the first time that a study has reported on the specificity, not just on the sensitivity, of the different modalities for this disease. We found a high sensitivity and specificity for T2\*w, followed by T1w, FLAIRw, and vMRA, while the value of both NCCT and MDCTA for diagnosing CVT was poor.

Most of our patients presented with CCVT; we identified only three patients with ICVT. This finding reflects the fact that ICVT is a very rare diagnosis, which has only been reported as single case reports or small series [4–15]. In our patients, the frontal veins were involved in all but one case, followed by the parietal veins as second most frequent localization of CVT. This predilection of the frontal cortical veins is in accordance with available studies on CVT [4–15]. A thrombosis of the temporal or occipital veins was found rarely, and none of our patients presented with an

**Table 2** Results of the consensus reading.

Nb.	Affected veins	Affected sinuses	Direct signs <sup>b</sup>										Indirect signs <sup>c</sup>							
			NCCT		MDCTA		PDw		FLAIR		T1w		T2 <sup>w</sup>		DWI		vMRA		Edema	ICH
			V	S	V	S	V	S	V	S	V	S	V	S	V	S	V	S		
1	Bilaterally frontal, parietal	SSS; LTS	+(1)	-	-	+	NA	+(5)	+	+(5)	+	+(6)	+	+(3)	+	+	+	+	+	+
2	Bilaterally frontal, parietal	SSS	-	-	NA	NA	NA	NA	NA	+(3)	+	+(5)	+	-	+	+	-	+	+	-
3	Left side frontal, parietal	SSS; RTS, LTS RSS	+(1)	+	-	+	-	NA	NA	-	+	+(6)	+	-	NA	+	+	+	+	+
4	Bilaterally frontal, parietal left side: occipital	SSS; LTS, LSS,SS	-	-	NA	+(2)	+	NA	NA	+(6)	+	+(8)	+	-	-	+	-	+	-	-
5	Bilaterally frontal	LTS, LSS,SS	-	+	NA	-	+	NA	NA	+(4)	+	+(4)	+	-	+	+	+	+	+	+
6	Bilaterally frontal, parietal	SSS; RTS, RSS	-	+	NA	+(4)	+	+(4)	+	NA	+	+(6)	+	NA	+	+	+	+	-	-
7 <sup>a</sup>	Left side frontal, parietal temporal	-	-	NA	-	-	-	NA	NA	NA	NA	+(2)	-	-	-	+	+	+	+	+
8	Bilaterally frontal, parietal	SSS; LTS	-	+	+	-	-	-	-	+(1)	+	+(8)	+	-	-	+	+	+	+	-
9	Bilaterally frontal, parietal	SSS; RTS	+(2)	+	-	+	-	NA	NA	-	+	+(6)	+	-	-	+	+	+	+	-
10	Bilaterally frontal, parietal, occipital	SSS, ISS, SS, LTS, LSS	+(2)	+	-	+	NA	-	+	NA	+	+(8)	+	-	-	+	+	+	+	+
11	Bilaterally frontal, parietal, temporal	SSS, RTS, LTS	-	-	NA	+(2)	+	NA	NA	+(2)	+	+(4)	+	-	-	+	+	+	+	+
12 <sup>a</sup>	Left side parietal	-	-	-	NA	NA	+	+(1)	+	+(5)	+	+(8)	+	-	-	+	+	+	+	+
13 <sup>a</sup>	Bilaterally frontal, parietal	-	NA	-	-	-	-	+(1)	-	+(1)	-	+(6)	-	-	-	-	-	-	-	-

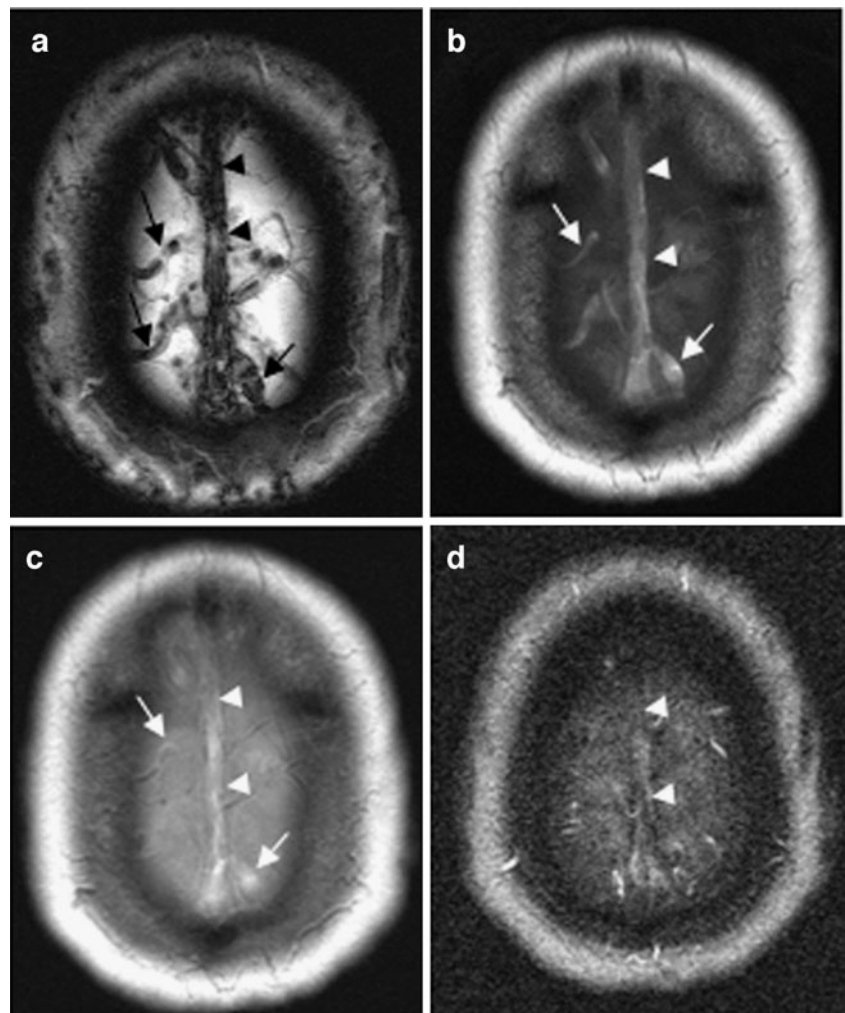
NCCT non-enhanced CT, MDCTA multi-detector row CT angiography, PDw PD-weighted sequence, FLAIR<sub>w</sub> FLAIR-weighted sequence, T1<sub>w</sub> T1-weighted sequence, T2<sub>w</sub> T2-weighted sequence, DWI diffusion-weighted imaging, vMRA venous MR angiography, V veins, S sinuses, ICH hemorrhage, SV sensitivity, SP specificity, CVs cortical veins, SSS superior sagittal sinus, RTS right transverse sinus, LTS left transverse sinus, RSS right sigmoid sinus, LSS left sigmoid sinus, SS straight sinus, NA modality not available

<sup>a</sup> Patients with isolated cortical vein thrombosis

<sup>b</sup> + indicates that direct signs of cortical vein thrombosis (CVT) were present on the respective modality; - indicates the absence of any direct signs of CVT on the respective modality; data in parenthesis indicate number of cortical veins with direct signs of CVT on the respective modality (not for MDCTA and vMRA)

<sup>c</sup> + indicates that indirect signs of CVT were present on the respective modality; - indicates the absence of any indirect signs of CVT on the respective modality

**Fig. 1** Patient with combined cortical vein thrombosis (patient 4). Thrombosis of superior sagittal sinus (*arrowheads*) and both frontal and parietal cortical veins (e.g., *arrows*) is depicted as hypointense signal on T2\*-weighted (T2\*w) (a), hyperintense signal on T1-weighted (b) and PD-weighted (c), and lack of flow signal on venous magnetic resonance angiography (vMRA; d, source image). Please note that the largest number of affected cortical veins is revealed by T2\*w, while the evidence of “missing veins” on vMRA is questionable



involvement of the anastomotic vein of Labbé. As in the literature, the SSS was the sinus that was most often affected in our CCVT patients, which is easily understood by recognizing that CCVT usually develops secondary to SVT via retrograde thrombus propagation from the occluded sinus [4].

#### NCCT

In most institutions, NCCT is often performed as the first line of investigation in the emergency setting. While the direct signs on NCCT have a high sensitivity and specificity for a thrombosis of the deep cerebral veins, their sensitivity for the diagnosis of an SVT has been shown to be below 75% [16, 20, 21]. These findings are consistent with our observations regarding the affection of the sinuses. With regard to the involvement of cortical veins, we also found a very low sensitivity of the dense vein sign. This is most probably due to their localization in immediate vicinity to the skull, resulting in partial volume effects [16]. Thus, we must conclude that NCCT is not

suitable for the exclusion of CVT, although it has a high PPV for this diagnosis.

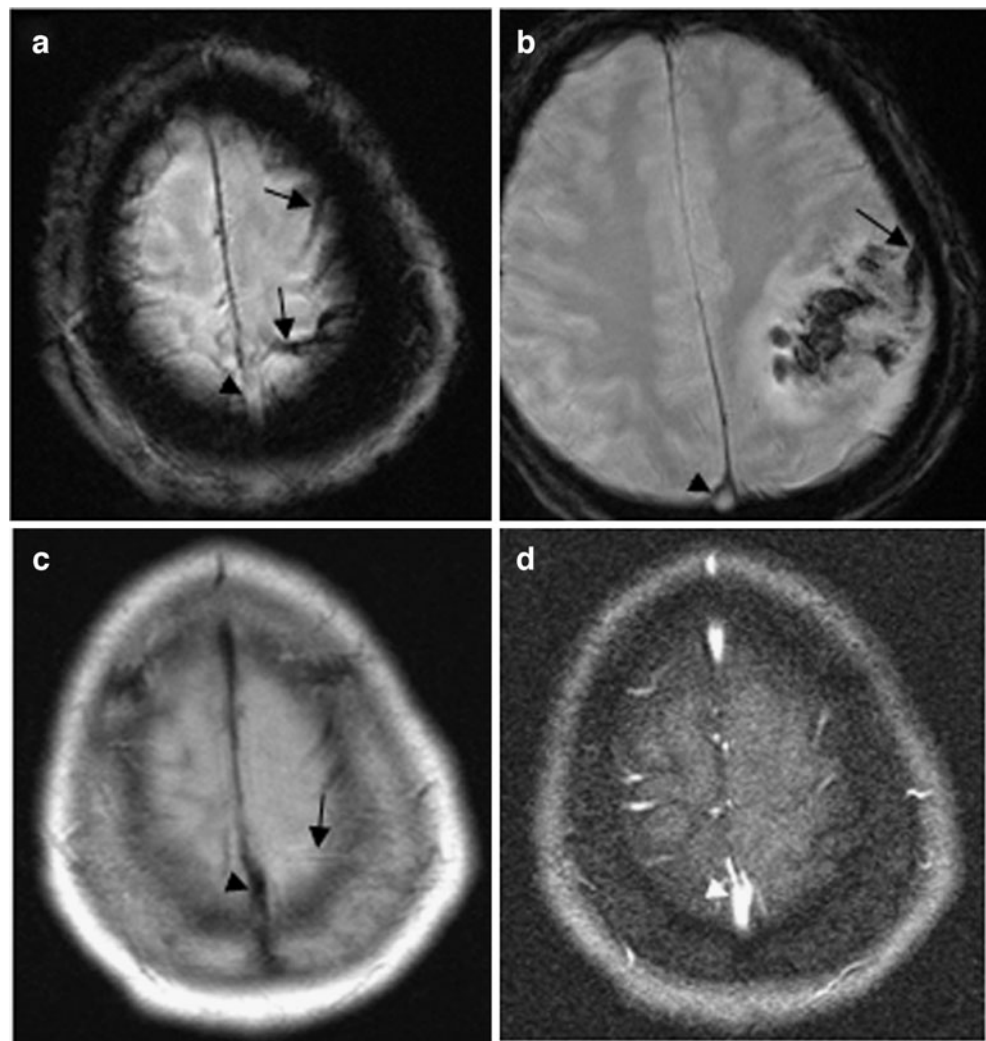
#### Angiographic techniques

##### DSA

DSA was the gold standard for the diagnosis of cerebral venous occlusive diseases, but it has been replaced by MRI and MDCTA [15, 16, 22, 23]. Although some authors still discuss whether DSA has a higher sensitivity for the diagnosis of CVT than the other imaging techniques [7], no systematic studies on this topic exist.

The DSA diagnosis of CVT relies on indirect signs such as delayed local venous drainage, lack of opacification of the corresponding brain region, “missing” cortical veins, a partially visualized vein that abruptly stops or is surrounded by dilated cortical veins, and cortical collaterals appearing as “corkscrew-vessels” [7, 24]. On angiography, all that may be seen is vascular congestion in the region of drainage of the occluded vein because the thrombosed vein

**Fig. 2** Patient with isolated cortical vein thrombosis and large left parietal intracerebral hemorrhage (**b**) (patient 7). Isolated thrombosis of left frontal and parietal cortical veins (e.g., *arrows*) is depicted as hypointense signal on T2\*-weighted (**a, b**) and the impression of “missing veins” on the left side compared to right on venous magnetic resonance angiography (**d**, source image). Please note that there is no hyperintense signal present in the affected veins on PD-weighted (**c**) and that there is a regular flow signal within superior sagittal sinus on all sequences (**a–d**, *arrowheads*)



itself often does not opacify. Thus, DSA only allows an indirect visualization of a thrombosis. Another important limitation of DSA in the interpretation of these signs is the high variability of the number and location of the cortical veins both intra- and inter-individually. The pattern of cortical venous drainage is variable and often asymmetric, which impairs the identification of a “missing vein” [1, 2, 7]. The lack of contrast filling of a vessel in a certain cortical region does not necessarily indicate a CVT but can simply indicate the absence of a vein in this specific region as anatomic variation. These drawbacks of DSA, which are true for all angiographic techniques, including MDCTA and vMRA, do not support DSA being superior to MRI for diagnosing CVT.

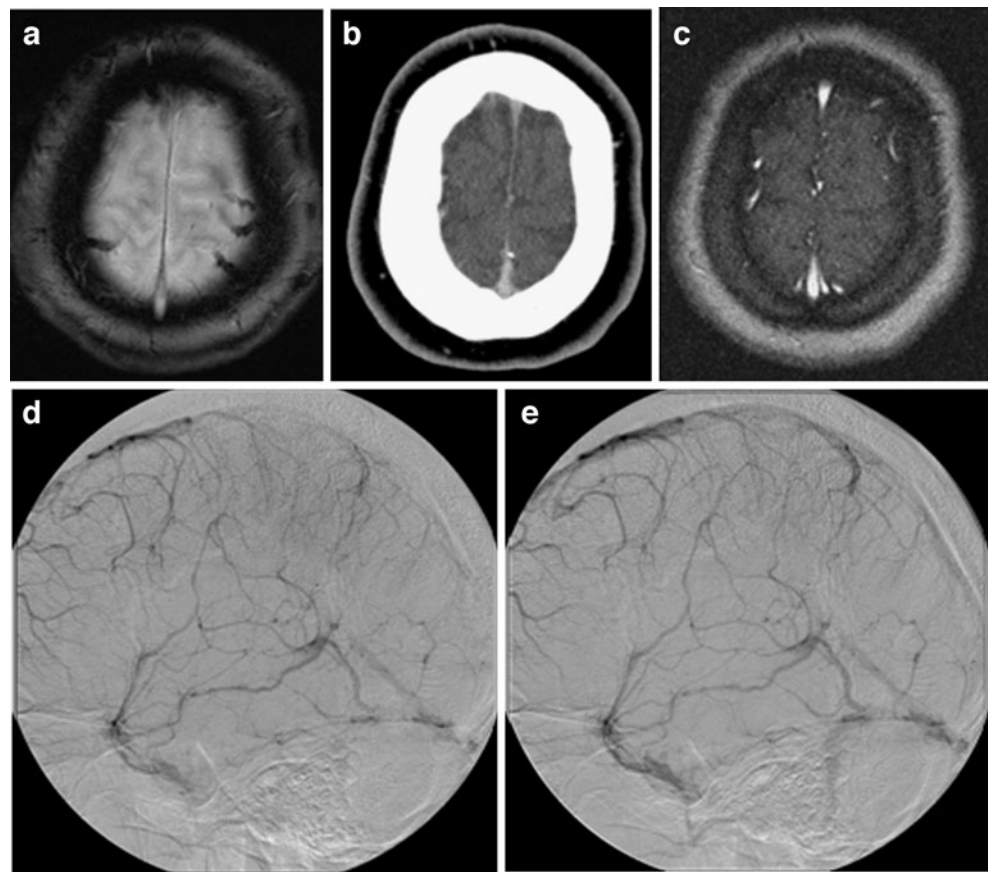
#### MDCTA

MDCTA allows the visualization of the cerebral venous structures with a high spatial and temporal resolution [25] and has an excellent sensitivity and specificity for the

detection of SVT [17]. Thrombotic material in MDCTA is visualized indirectly, like DSA, by demonstration of contrast filling defects. Therefore, this technique is less prone to flow artifacts than vMRA [17].

While we confirmed the diagnostic value of MDCTA for the sinuses, we revealed a low sensitivity for the detection of CVT. Our findings indicate that when MDCTA is the only imaging modality, it is difficult for the reader to distinguish between a “missing vein” that indicates a CVT and one that indicates an anatomic variation. Furthermore, we observed cases in which MDCTA did not show a filling defect in cortical veins that clearly demonstrated direct signs of thrombotic occlusions on the other imaging modalities (Fig. 5). This might be due to the small diameter of the cortical veins and to partial volume effects from the enhancing walls of the vessels as suggested by the empty delta sign on a prior contrast-enhanced CT [20]. Our results suggest that MDCTA—although of great value for SVT—might not be suitable for the diagnosis of CVT, a finding that should be validated in further studies.

**Fig. 3** Patient with isolated cortical vein thrombosis (patient 13). Isolated thrombosis of frontal and parietal cortical veins, bilaterally, is depicted as hypointense signal on T2\*-weighted within the affected veins (**a**). There is an impression of “missing veins” on the left side compared to right on both multi-detector row CT angiography (**b** source image) and venous magnetic resonance angiography (**c**, source image), yet this is not easily recognized without knowledge of the T2\*-weighted images; digital subtraction angiography shows a delayed venous drainage (**d**, **e**)



#### Venous MRA

While the sensitivity of vMRA for SVT was 81.5%, it was below 50% for CVT in our patients, which is comparable to the previous report by Idbaih et al. (37%, [15]). We used two-dimensional time-of-flight vMRA, because it is widely used both in clinical routine and in studies on CVT [6, 7, 15]. In this sequence, a thrombosis presents as a lack of flow signal in the respective venous structure. With regard to CVT, vMRA in general suffers from the same limitations as DSA and MDCTA, namely, the considerable anatomical variations of the CVs. There are two additional reasons for this limited value of time-of-flight vMRA: a subacute, hyperintense thrombus could potentially simulate normal venous flow signal [26], and a lack of flow signal in a respective vessel might result from in-plane flow [27]. Promising, new vMRA techniques exist such as high-resolution contrast-enhanced gradient-echo MRA, time-resolved MRA [28], and their potential value for CVT, especially at higher field strengths, should be addressed in future studies.

#### T1w, PDw, FLAIRw, and DWI

Although MRI is regarded as the current gold standard for cerebral venous occlusions [15, 22, 23], it has several

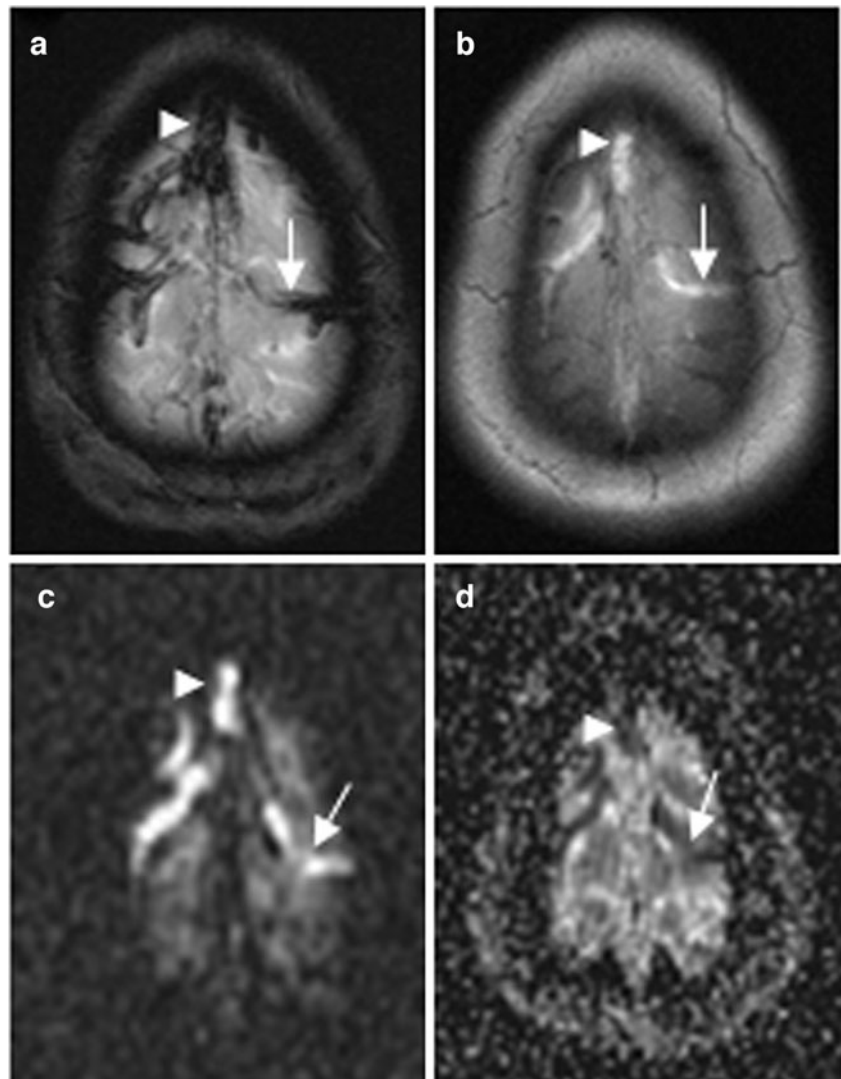
diagnostic pitfalls due to the complex, time-dependent signal characteristics of the thrombotic material in the different MR sequences [7, 29, 30], which are similar for ICVT and for SVT [4, 7].

In the case of an acute thrombosis, the intravascular clot shows a hypointense signal on T2w or FLAIRw and an iso- or slightly hyperintense signal on T1w in most case [7, 15, 30, 31]. Thus, the clot may be poorly distinguished from the normal blood flow signal, resulting in a low sensitivity of these sequences during the first days of a thrombosis, especially if small veins are affected. Within the second week after symptom onset, the thrombus material is reported to be typically hyperintense in both T1w and T2w or FLAIRw, which makes these sequences potentially more valuable for the diagnosis of a subacute thrombosis [7, 15, 30].

In accordance with the literature [15], T1w was the second most sensitive sequence for CVT (70%) independent of thrombus age and was also found to have a high specificity for CVT. We found a higher sensitivity of T1w for subacute CVT (80%) than for acute CVT (60%). Regarding sinus involvement, T1w was considerably more sensitive in the acute phase (91.7%) than in the subacute phase (41.7%) in the blinded readings. The last finding is somewhat surprising: the consensus reading revealed direct signs of SVT in all subacute cases. The most probable



**Fig. 4** Patient with combined cortical vein thrombosis (patient 1). Thrombosis of the superior sagittal sinus (*arrowheads*) and frontal and cortical veins (e.g., *arrows*) is depicted as hypointense signal on T2\*-weighted (a), hyperintense signal on fluid-attenuated inversion recovery and as diffusion restriction on diffusion-weighted, B1000 (c) and apparent diffusion coefficient map (d)



explanation for this discrepancy is a misinterpretation of the hyperintense signal in the sinuses on T1w as flow signal in some of the blinded readings. This underlines the challenge radiologists are faced with in interpreting MR sequences for venous system thrombosis.

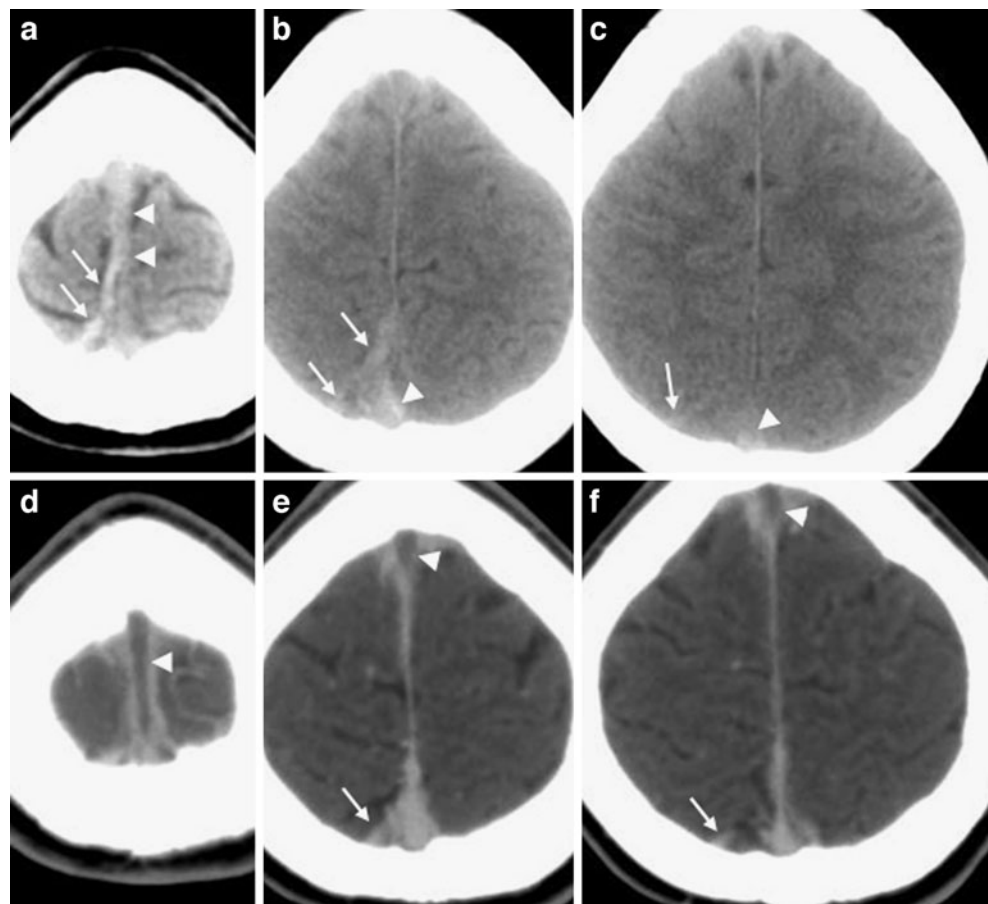
The sensitivity of FLAIRw in our patients (50%) was considerably higher than has been reported [15], yet FLAIRw was only available in six of our patients, which limits the interpretation of these results. Interestingly, we found no data on clot appearance on PDw in the literature. The consensus reading showed that time-dependent signal intensities of thrombus material in CVs on PDw are similar to those reported for T2w and FLAIRw: mostly hypointense in the acute phase, mostly hyperintense in the subacute phase, but with considerable variation. This resulted in a higher sensitivity of PDw for an involvement of the sinuses in the subacute phase (91.7%) compared to the acute phase (88.9%), but resulted in almost no time-

dependent difference with regard to CVT (25% for acute CVT and 26.7% for subacute CVT).

On DWI, diffusion restriction within an intravascular clot resulting in a hyperintense signal on images with a b-value of 1,000 and in a lowered apparent diffusion coefficient value has been reported for both SVT and CVT [15, 32, 33]. Data on its sensitivity vary from 3% to 39% for CVT ([15, 33]; 13.9% in our patients) and from 3.7% (our study) to 41% for SVT [32]. In accordance with the literature, hyperintense clot signal on DWI was only present in cases in which the thrombus was also hyperintense on FLAIRw and T1w [32, 33], indicating that it provides little additional information for the diagnosis of CVT or SVT. Yet, DWI has been proposed to be of prognostic value for potential recanalization of occluded veins [32]. Further studies are necessary to clarify the value of clot imaging in DWI for CVT.

In order to access not only the sensitivity but also the specificity of the different modalities, we chose a study

**Fig. 5** Patient with combined cortical vein thrombosis (patient 3). Upper row (a–c): non-enhanced computed tomography, lower row (d–f): multi-detector row CT angiography (MDCTA). Arrows in a–c indicate hyperdense vein sign in a right parietal cortical vein. Please note that this vein shows no filling defect in MDCTA (arrows in e and f). There is a thrombosis of the superior sagittal sinus (arrowheads in a–c) with a cord sign on non-enhanced computed tomography (a–c) and a filling defect on MDCTA (d–f)



design that included a control group. We would like to point out that the presence of direct signs on any of the MR sequences had a high specificity for CVT (100%) even if their sensitivity was very low, e.g., as low as that of PDw or DWI.

T2\*w

T2\*w was superior to all other modalities for both the presence of a CVT and the involvement of individual cortical veins, with a sensitivity of 97.4% for CVT even in

**Table 3** Sensitivity, specificity, positive predictive value, negative predictive value, and interobserver agreement of the different modalities for cortical vein thrombosis and sinus thrombosis.

Imaging modality	CVT					SVT				
	SV (95% CI) <sup>a</sup>	SP (95% CI) <sup>a</sup>	PPV <sup>a</sup>	NPV <sup>a</sup>	IOA	SV (95% CI) <sup>a</sup>	SP (95% CI) <sup>a</sup>	PPV <sup>a</sup>	NPV <sup>a</sup>	IOA
CT	25 (18.1–25)	100 (91.8–100)	100	52.6	0.82	50 (39.2–54.7)	94.4 (85.4–98.4)	88.2	69.4	0.63
MDCTA	5.6 (1.2–5.6)	100 (97.4–100)	100	63.8	0.92	100 (88.3–100)	100 (94.7–100)	100	100	1
DWI	13.9 (8.1–13.9)	100 (93.1–100)	100	49.21	0.88	3.7 (0.8–3.7)	100 (98.0–100)	100	60	0.94
FLAIRw	50 (37.0–50.0)	100 (92.2–100)	100	76.9	1	100 (85.6–100)	100 (95.2–100)	100	100	1
PDw	25.9 (17.4–25.9)	100 (92.3–100)	100	60	0.93	90.5 (79.9–90.5)	100 (93.8–100)	100	94.7	0.86
T1w	70 (54.6–70.1)	100 (89.2–99.5)	100	76.9	0.73	66.7 (61.3–70.0)	96.2 (91.3–100)	94.1	81.4	0.67
vMRA	41.7 (34.2–41.7)	100 (97.4–100)	100	58.8	0.76	81.5 (72.2–81.5)	100 (93.6–100)	100	88.6	0.88
T2*w	97.4 (92.0–97.4)	100 (92.9–100)	100	96.8	0.94	96.7 (89.6–96.7)	100 (94.6–100)	100	97.6	0.94

PPV positive predictive value, NPV negative predictive value, CVT cortical vein thrombosis, SVT sinus thrombosis, SV sensitivity, SP specificity, CI confidence interval, IOA interobserver agreement, NCCT non-enhanced CT, MDCTA multi-detector row CT angiography, DWI diffusion-weighted imaging, FLAIRw FLAIR-weighted sequence, PDw PD-weighted sequence, T1w T1-weighted sequence, vMRA venous MR angiography, T2\*w T2\*-weighted sequence

<sup>a</sup>Data are given in percentages

**Table 4** Sensitivity and specificity for individual venous structures.

Venous structure	NCCT		MDCTA		DWI		FLAIRw		PDw		T1w		vMRA		T2*w	
	SV	SP	SV	SP	SV	SP	SV	SP	SV	SP	SV	SP	SV	SP	SV	SP
Frontal CVs	27.3	100	5.6	100	11.4	100	40	100	10.3	100	48.2	100	27.3	100	86	97
Parietal CVs	6.1	100	0	100	3	100	22.2	100	29.2	100	37	100	36.4	100	94.6	100
Temporal CVs	0	100	0	100	0	100	0	100	0	100	0	100	33	100	16.7	98.4
Occipital CVs	0	100	0	100	0	100	0	100	0	100	0	100	0	100	50	100
SSS	43.3	94.4	100	100	3.7	100	100	100	85.7	100	54.2	97	74.1	100	96.7	100
RTS	8.3	96.3	66.7	100	0	100	100	100	100	93.3	33	94	88.9	96.5	75	98.3
LTS	14.3	95.6	91.7	100	0	100	83.3	100	20	100	16.7	100	55.6	93.8	42.9	100
RSS	0	100	33.3	100	0	100	0	100	16.7	98	33	98.2	0	98.4	16.7	100
LSS	11.1	96.5	100	91.1	0	100	0	100	16.7	96.1	0	98	11	100	0	100
SS	22.2	100	100	97.8	0	100	0	100	0	98	16.7	100	0	100	55.6	95

NCCT non-enhanced CT, MDCTA multi-detector row CT angiography, DWI diffusion-weighted imaging, FLAIRw FLAIR-weighted sequence, PDw PD-weighted sequence, T1w T1-weighted sequence, vMRA venous MR angiography, T2\*w T2\*-weighted sequence, SV sensitivity, SP specificity, CVs cortical veins, SSS superior sagittal sinus, RTS right transverse sinus, LTS left transverse sinus, RSS right sigmoid sinus, LSS left sigmoid sinus, SS straight sinus

the blinded reader set-up and a specificity of 100% for both CVT and SVT. It was the only sequence that was positive in all CVT cases, and its sensitivity for SVT was also considerably high (96.6%). Our findings are in accordance with recent imaging studies on CVT that showed that T2\*w improved the diagnosis of CVT, especially at the acute stage of the disorder when the intraluminal thrombus is not yet hyperintense on T1w [6, 7, 11, 15, 34, 35]. Selim et al. reported that T2\*w echoplanar sequences can enhance the detection of intravascular clots [34]. Others showed that conventional T2\*w gradient-echo sequences have an even higher sensitivity for CVT because they exhibit considerably higher sensitivity to susceptibility differences [6]. An advantage of T2\*w compared to other MR sequences is that the thrombus material shows a hypointense signal for a relatively long time interval from symptom onset. In some cases, T2\*w has even been shown to be positive up to 1 year after symptom onset and in the case of complete clinical recovery, which has to be taken into account if T2\*w is interpreted solely [7, 15].

In one of the control patients, both frontal and temporal cortical veins were judged as hypointense on T2\*w by one of the readers. Although this did not result in a false positive diagnosis of CVT, we would like to comment on the potential pitfalls on T2\*w. In our opinion, the most important sources for false positive results are acute or chronic subarachnoid hemorrhages [36] or superficial siderosis, which present with a hypointense lineal signal within the subarachnoid space or the superficial layers of the cortex, respectively [37]. To distinguish these findings from a hypointense clot, we strongly recommend that only an extracerebral, “well-delineated tubular,” and “rounded” hypointense ([7], “blooming”) should be judged as indicative for CVT.

Our study further enhances the reported value of T2\*w for CVT, as we proved that its sensitivity for CV involvement remains very high even in a blinded reader set-up and that it not only has a high sensitivity but also a high specificity for CVT.

**Interobserver agreement**

The interobserver agreement for CVT was perfect for FLAIRw ( $\kappa=1$ ), good for T1w and vMRA ( $\kappa=0.73$  and  $0.75$ , respectively), and excellent ( $\kappa>0.80$ ) for all other modalities [19, 38], which is considerably higher than has been reported previously for cortical veins [38]. This was most probably due to the fact that our readers were especially focused on the evaluation of the cortical veins. The interobserver agreement for sinus involvement was good to perfect for all modalities, which is consistent with data in the literature [38].

## Limitations

Some limitations of our study need to be taken into account. First, the most important problem for the definite extent of the thrombosis is that the final diagnosis was obtained based on a consensus reading and not on an external reference standard. This is due to the fact that there is no gold standard available for the diagnosis of a CVT besides brain tissue examination. As mentioned in the “Introduction,” this is an intrinsic problem of all imaging studies on this topic, which seems to have been neglected in some previous studies. We used T2\*w as an internal gold standard in the consensus reading, which is reasonable because all available data on CVT in the literature consistently shows the superiority of T2\*w for CVT. Yet, we cannot completely exclude that some affected cortical veins were missed. Second, the presence of indirect signs such as edema or hemorrhage in most patients with CVT might bias the reader towards the diagnosis of CVT or SVT. Third, the retrospective design of the study resulted in the data sets not always being complete for all imaging modalities. The sample size of our study was relatively small, especially with regard to MDCTA. Yet, CVT, especially if isolated, is a rare disease; the 13 patients were assessed by a multiple blinded reader approach, and we included a control group. Thus, the number of cases may not necessarily impair the scope of our observations.

In addition to these limitations, it has to be taken into account that the analysis of isolated MR sequences, as performed here, does not reflect daily clinical practice, in which the complementary information of several sequences is used to establish a diagnosis. Yet, we choose this study design intentionally in order to determine the most useful sequences for CVT and thus to identify an appropriate MR sequence protocol for this challenging diagnosis.

In recent years, susceptibility-weighted sequences, which are more sensitive compared to conventional T2\*w sequences with regard to susceptibility artifacts, are used to assess the cerebral venous system [39]. To date, only a very limited number of case reports on its use in patients with cerebral venous occlusions are available, in which the technique yielded promising results [40, 41]. Yet, care has to be taken, as both normal and occluded veins appear hypointense on this sequence. Further research should address the value of SWI, the potential of higher field strengths, and high-resolution contrast-enhanced vMRA for CVT, using T2\*w as gold standard.

## Conclusion

Our study demonstrated that T2\*w is the superior MR sequence for CVT. Besides T2\*w, only T1w reached a

sensitivity of over 50%, followed by FLAIRw and vMRA. Thus, we recommend that radiologists perform these four sequences if CVT is suspected and that T2\*w should be considered as the future gold standard for diagnosing CVT. On the contrary, our results suggest that NCCT but also MDCTA might not be suitable for diagnosing CVT. Furthermore, we would like to raise the radiologist's awareness to the direct signs of CVT, because the presence of these signs was highly specific for CVT on all studied imaging modalities.

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**Conflict of interest statement** We declare that we have no conflict of interest.

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