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Detection of cerebral cortical vein thrombosis with high-resolution susceptibility weighted imaging — A comparison with MR venography and standard MR sequences

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Abstract

Purpose Comparison of the performance of high-resolution susceptibility weighted imaging with standard MR sequences and MR venography to identify cortical vein clots.

Methods A retrospective review of 51 consecutive cases of cerebral venous thrombosis and 27 controls was performed with independent analysis of all MR sequences. Reference standard was obtained with consensus in a separate session by reviewing all MR sequences together.

Results Cortical vein clots were observed in 30 cases including 9 males and 21 females in the age range of 1 month to 70 years (Mean 34.9 ± 20.2 years). Sensitivity, specificity, negative predictive value, positive predictive value and accuracy of susceptibility weighted imaging for the identification of cortical vein clots were 0.93, 1.0, 1.0, 0.96 and 0.97 respectively. For all other sequences, sensitivity ranged from 0.06 to 0.39 and accuracy from 0.60 to 0.73. Combination of all sequences yielded a value of 1.0 for sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the detection of cortical vein clots. Significant result for area under the receiver operating curve was observed only for SWI with a value of 0.91 (p - .000).

Conclusion Susceptibility weighted imaging demonstrates the best sensitivity and accuracy among standard MR sequences including MR venography for the detection of early stage cortical vein clots. However, it needs to be interpreted in combination with other MR sequences for the most accurate evaluation of cortical vein clots.

Keywords SWI · Cerebral venous thrombosis · Cortical venous thrombosis · Cortical vein thrombosis · Cerebral venous sinus thrombosis

Introduction

The coronavirus disease (COVID-19) pandemic and vaccinations for COVID-19 have been associated with a surge in the incidence of cerebral venous thrombosis (CVT) [1]. Higher incidence of cortical vein thrombosis (COVT) was identified in a recent study on neonatal intracranial hemorrhage [2]. In this background and given the challenges to diagnose CVT and COVT on imaging, a heightened awareness of their presence is crucial during the evaluation of imaging [3–5]. Among the imaging techniques, susceptibility contrast of MRI has demonstrated the highest sensitivity to detect COVT. However, in a majority of the studies, a small cohort of cases was used for the evaluation of COVT and the susceptibility contrast was assessed mainly with T2* (GRE) with a lack of blinding to other MR sequences and clinical information [3–13]. Although high resolution susceptibility weighted imaging (SWI) sequence has been used in clinical practice for approximately 2 decades, to the best of our knowledge, its advantages and limitations for the detection of COVT have not been evaluated independently of other MR sequences including MR venography.

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Materials and methods

This retrospective study has been carried out after the approval from the institutional review board (IRB). The study is HIPPA compliant. The search engine (Primordial, Inc. 2005-2015) in the PACS was used to identify the consecutive cases from the database with the search terms venous thrombosis, venous clots, cerebral venous thrombosis, CVT, cerebral sinus thrombosis, CST, cerebral venous sinus thrombosis, CVST, cerebral sinus venous thrombosis, CSVT, cortical vein thrombosis, cortical vein clot, COVT and venous infarcts from January 2012 to September 2020. Controls were selected from patients who had normal MRI brain and MRV findings with no history of CVT or COVT. The data was entered into a spread sheet with random arrangement of cases and controls. MRI was performed either on 1.5T or 3T magnet. Phased array MR coils with 8 or 16 coil elements were used for 1.5T and 16 coil elements for 3T MRI. The technical parameters of MR sequences are provided in the supplementary Tables 1 and 2. Two neuroradiologists with nearly 40 years of combined experience reviewed the images independently. Venous clots imaged within 7 days of clinical presentation were classified as acute to early subacute, within 8 to 29 days as late subacute and ≥30 days as chronic [3, 4, 8]. Each MR sequence including T1 weighted turbo spin echo (TSE), T2 weighted TSE, FLAIR, diffusion weighted imaging (DWI), enhanced T1 TSE with fat saturation (T1C TSE), enhanced 3D T1 MPRAGE (3D T1c MPRAGE), SWI and MR venography (2D Time of flight (TOF) or 3D phase contrast (PC)) was evaluated independently on PACS on separate occasions over a month. Prominent hypointense signals with engorgement of a cortical vein on SWI was considered a sign of COVT [14]. Signs of cortical vein clot for each of the other MR sequences were considered as hyperintense signals or bulky isointense signals on T1 TSE, iso or hyperintense signals in the lumen of a cortical vein on T2 TSE, iso or hyperintense signals in cortical veins on FLAIR, prominent cord like susceptibility or hyperintense signals in the location of cortical veins on DWI, filling defect in the lumen of a cortical vein on 3D T1c MPRAGE or T1C TSE and hypointense signals in a cortical vein in the raw images of MR venography (MRV). Maximum intensity projection (MIP) images were independently analyzed for the absence of cortical vein or cut off in the flow signals in a cortical vein, but the images were unreliable to identify COVT and only the raw images were used to evaluate the performance of MRV. Detection of cortical vein clot in each MR sequence was scored as either present or absent. The investigators were blinded to the clinical information, diagnosis, and radiology reports. Reference standard for imaging was obtained from a combined analysis of all MR sequences including MRV by the two reviewers with consensus, as used previously [8]. During this review, parenchymal changes including edema and hemorrhage as well as subarachnoid hemorrhage (SAH) were also documented. Sulcal susceptibility signals on SWI and or sulcal FLAIR signals were considered as signs of SAH. The data was transferred to an excel spread sheet and statistical analysis was performed with IBM SPSS V28 software. Inter-rater agreement (IRA) was evaluated with Cohen's weighted kappa κ. Agreement 20–40 was considered fair, 40–60 moderate, 60–80 good and above 80 as almost perfect [15]. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy with 95% confidence interval were calculated for each MR sequence for the identification of cortical vein clots. COVT grading was performed in cases and controls as present — 2, uncertain — 1, and absent — 0. A receiver operating characteristic (ROC) curve was constructed and the area under the curve (AUC) was obtained to evaluate the performance of MR sequences to detect COVT. When applicable, *p*- value less than 0.05 was considered significant.

Results

Among 78 patients evaluated, there were 51 cases of cerebral venous thrombosis and 27 controls. Cortical vein clots (COVT) were observed in 30/51 cases of cerebral venous thrombosis and none of the controls. Among 30 COVT cases, there were 9 males and 21 females in the age range of 1 month to 70 years (Mean 34.9 ± 20.2 years). In 27 controls, there were 17 females and 10 males in the age range of 6 months to 62 years (Mean 22 ± 16.3 years). Demography and clinical presentations for COVT cases are given in Table 1. Cortical vein clots were imaged in 28 cases in the acute to early subacute phase, 2 cases in the late subacute phase and none in the chronic phase. In 30 cases of COVT, totally 115 clotted cortical veins were seen ranging from 1

Table 1 Demography of cases with cortical vein thrombosis (COVT)

Number of cases	30
Sex distribution	Female — 21; Male — 9
Age range	1 month to 70 years (Mean 34.9 ± 20.2 years)
Headache	Present — 21; Absent — 9
Seizures	Present — 12; Absent — 18
Loss of consciousness	Present — 4; Absent — 26
Altered mental status	Present — 7; Absent — 23
Hemiparesis	Present — 3; Absent — 27
Aphasia	Present — 5; Absent — 25

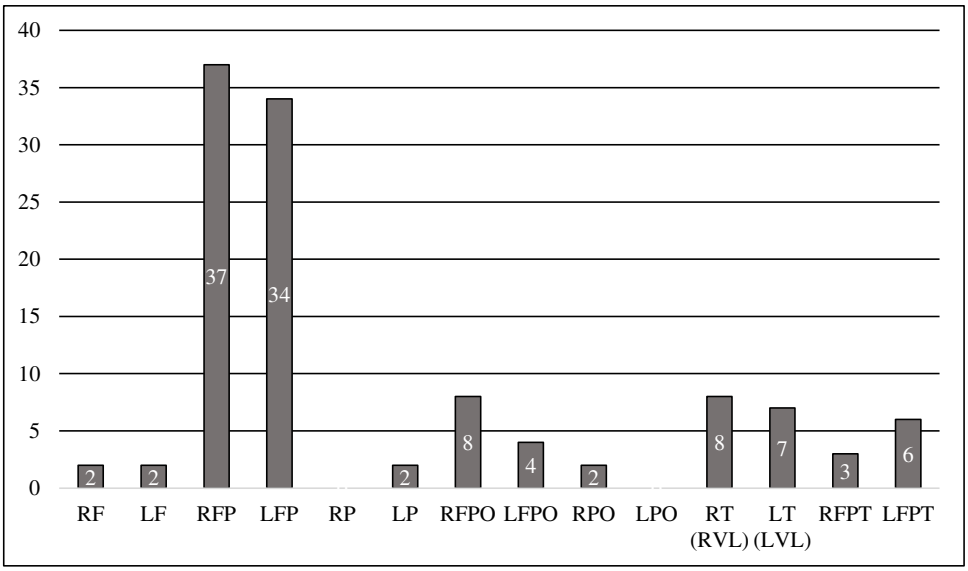

Fig. 1 A chart representing the spatial distribution of 115 clotted cortical veins in 30 cases of cortical venous thrombosis. Abbreviations for location of cortical vein clots: RF – Right Frontal; LF – Left Frontal; RFP – Right FrontoParietal; LFP - Left FrontoParietal; RP – Right Parietal; LP – Left Parietal; RFPO - Right FrontoParieto-Occipital; LFPO - Left FrontoParieto-Occipital; RPO – Right Parieto-Occipital; LPO - Left Parieto-Occipital; RT – Right Temporal; RVL – Right Vein of Labbe; LT – Left Temporal; LVL – Left Vein of Labbe; RFPT – Right FrontoParietoTemporal; LFPT – Left FrontoParietoTemporal

to 12 (Mean 3.8±3.3) clotted veins per case. Majority of the clots were found in the frontoparietal regions (Fig. 1). In 30 cases of COVT, associated dural sinus thrombosis was seen in 26, isolated COVT in 4, underlying parenchymal hemorrhage in 19 and edema with or without parenchymal hemorrhage in 25 cases. COVT was detected on SWI in 28/30 cases, on MRV raw images in 10/30 cases, on T1 TSE in 8/30 cases, on FLAIR in 8/30 cases, on DWI in 6/30 cases and on T2 TSE in 3/30 cases. 3DT1c MPRAGE was obtained in 20/30 COVT cases with demonstration of cortical vein clots in 8 cases. T1C TSE was obtained in 18/30 COVT cases with detection of cortical vein clot in a single case. Cortical vein clots were detected only on SWI and no other MR sequence in 8 cases. In 2 cases presenting in the late subacute phase, SWI failed to detect COVT as there was no susceptibility signal in the clots. In both cases, T1 TSE, FLAIR and DWI were helpful to identify the clots from the hyperintense signals. Sensitivity, specificity, PPV, NPV and accuracy for the detection of COVT by each MR sequence as well as combination of all sequences without and with SWI are given in Table 2. SWI demonstrated the highest sensitivity of 93% and the highest accuracy of 97% among all MR sequences to identify COVT. The combination of all MR sequences resulted in 100% sensitivity and accuracy. The ROC curve analysis demonstrated an AUC of 0.91 (0.80, 1.0) (p – 0.000) for the SWI sequence. The AUC of all other sequences showed insignificant results (Fig. 2; Table 3).

Sulcal SAH was observed on SWI in 10/30 cases and on FLAIR in 16/30 cases of COVT. For the presence of COVT, agreement with parenchymal hemorrhage was κ 0.65 (0.48–0.82) and with vasogenic edema with or without parenchymal hemorrhage was κ 0.62 (0.45–0.80). Inter-rater agreement analysis (κ) revealed an agreement of 0.84 (0.71–0.97) for SWI, 0.49 (0.35–0.63) for T1 TSE sequence, 0.85 (0.75–0.95) for T2 TSE sequence, 0.61(0.52–0.71) for FLAIR sequence, 0.54 (0.44–0.64) for MRV source images,

Table 2 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of each MR sequence and combination of all MR sequences without or with for the demonstration of cortical vein clots. 95% confidence intervals are given in parentheses.

MR sequences	Sensitivity	Specificity	PPV	NPV	Accuracy
SWI	0.93 (0.88–0.99)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.96 (0.92–1.0)	0.97 (0.93–1.0)
Enhanced 3D T1 MPRAGE	0.39 (0.16–0.61)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.65 (0.48–0.81)	0.71 (0.57–0.85)
MRV	0.32 (0.16–0.49)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.69 (0.58–0.79)	0.73 (0.63–0.82)
T1 TSE	0.26 (0.16–0.36)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.67 (0.56–0.77)	0.70 (0.60–0.80)
FLAIR	0.26 (0.13–0.38)	0.94 (0.86–1.0)	0.73 (0.46–0.99)	0.66 (0.55–0.78)	0.67 (0.56–0.78)
DWI	0.19 (0.04–0.33)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.65 (0.54–0.76)	0.68 (0.57–0.78)
T2 TSE	0.10 (0.04–0.17)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.62 (0.51–0.73)	0.64 (0.53–0.74)
Enhanced T1 TSE with fat saturation	0.06 (−0.05–0.16)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.59 (0.43–0.74)	0.60 (0.45–0.74)
Combination of all sequences excluding SWI	0.74 (0.59–0.90)	0.94 (0.86–1.0)	0.89 (0.76–1.0)	0.84 (0.74–0.94)	0.86 (0.78–0.94)
Combination of all sequences including SWI	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)

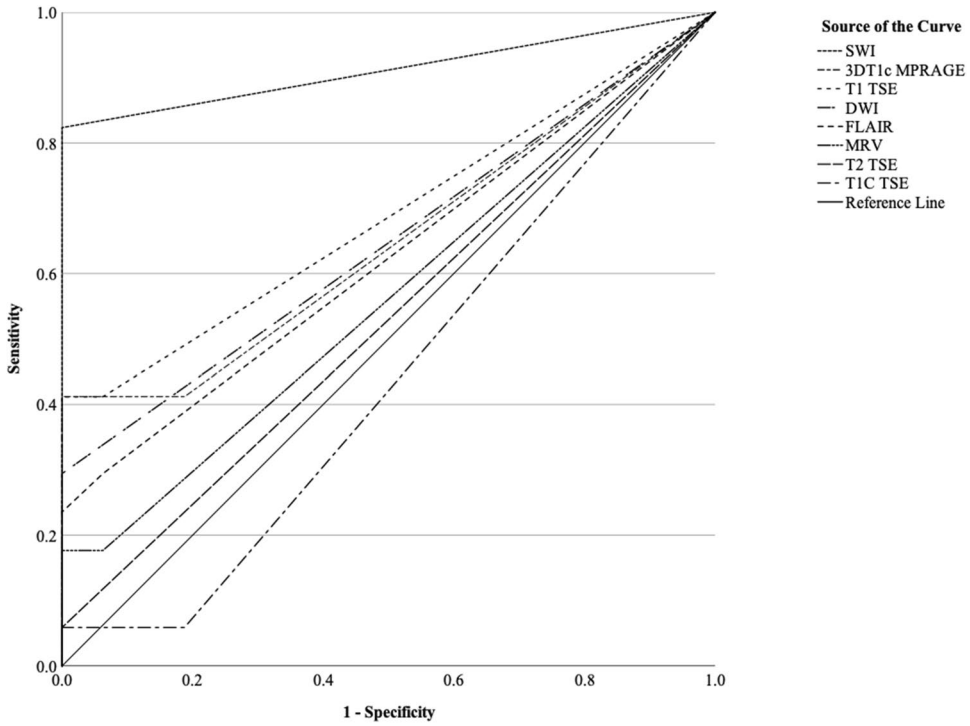

Fig. 2 Receiver operating curve analysis on the performance of MR sequences to detect cortical vein clots. Results for the area under the curve are represented in Table 3

0.73 (0.59–0.87) for T1C TSE sequence and 0.66 (0.51–0.81) for 3D T1c MPRAGE sequence. MRI was performed on 1.5T magnets in 19/30 cases and on 3T magnets in 11/30 cases of COVT. SWI showed 95% sensitivity and 98% accuracy on 1.5T to detect COVT. Sensitivity and accuracy on 3T for SWI were 90% and 97% respectively for the identification of COVT (supplementary Tables 3 and 4).

Discussion

Previous investigators have shown the best sensitivity for the susceptibility contrast among MR sequences to detect cortical vein clots [3–7, 9, 11]. Multimodality comparison of noncontrast CT, CT venography with multidetector CT and MR sequences by Linn J et al. further established the superiority of susceptibility contrast to identify COVT [8]. The majority of these studies, mainly evaluated the susceptibility contrast of COVT with T2* GRE from a small cohort of cases [3–7, 9, 11, 16]. Recently, Boukerche et al. were able to demonstrate the success of SWI to distinguish cortical vein clots from deoxyhemoglobin of patent veins, although the sequence is designed deliberately to make the patent cortical veins appear hypointense from the physiological deoxyhemoglobin [14]. In our study, we used a relatively large cohort of COVT cases to compare SWI against other MR sequences and the results revealed the best sensitivity of 93%, NPV of 96% and accuracy of 97% for SWI to identify cortical vein clots (Table 2). All other MR sequences including enhanced 3D T1 MPRAGE and MRV demonstrated poor sensitivity ranging from 6% to 39% to detect COVT. Further, only SWI among all MR sequences demonstrated significant results for the area under the ROC curve to identify COVT (Fig. 2, Table 3). The success of susceptibility contrast to detect COVT is mainly based on T2* GRE sequence with a lack of blinded assessment of the sequence in majority of the previous studies, as it was interpreted in combination with other MR sequences and clinical information [3–7, 9, 11]. Nevertheless, blinded assessment of T2* GRE performed in a few studies established the superiority of the sequence over others for the demonstration of COVT [3, 16]. Although, the SWI sequence has been used in clinical practice close to two decades, only recently was it tested in a relatively large cohort of isolated COVT

Table 3 The area under the curve for each MR sequence in ROC curve to detect cortical vein clots. 95% confidence intervals are provided in parentheses. *P* value less than .05 is considered significant

MR sequences	Area	*p* - value
SWI	0.91 (0.80, 1.0)	.000
3DT1c MPRAGE	0.65 (0.46, 0.84)	.140
MRV	0.56 (0.37, 0.76)	.540
T1 TSE	0.69 (0.50, 0.87)	.066
FLAIR	0.62 (0.43, 0.82)	.228
DWI	0.65 (0.46, 0.84)	.150
T2 TSE	0.53 (0.33, 0.73)	.773
T1c TSE with fat saturation	0.44 (0.24, 0.64)	.564

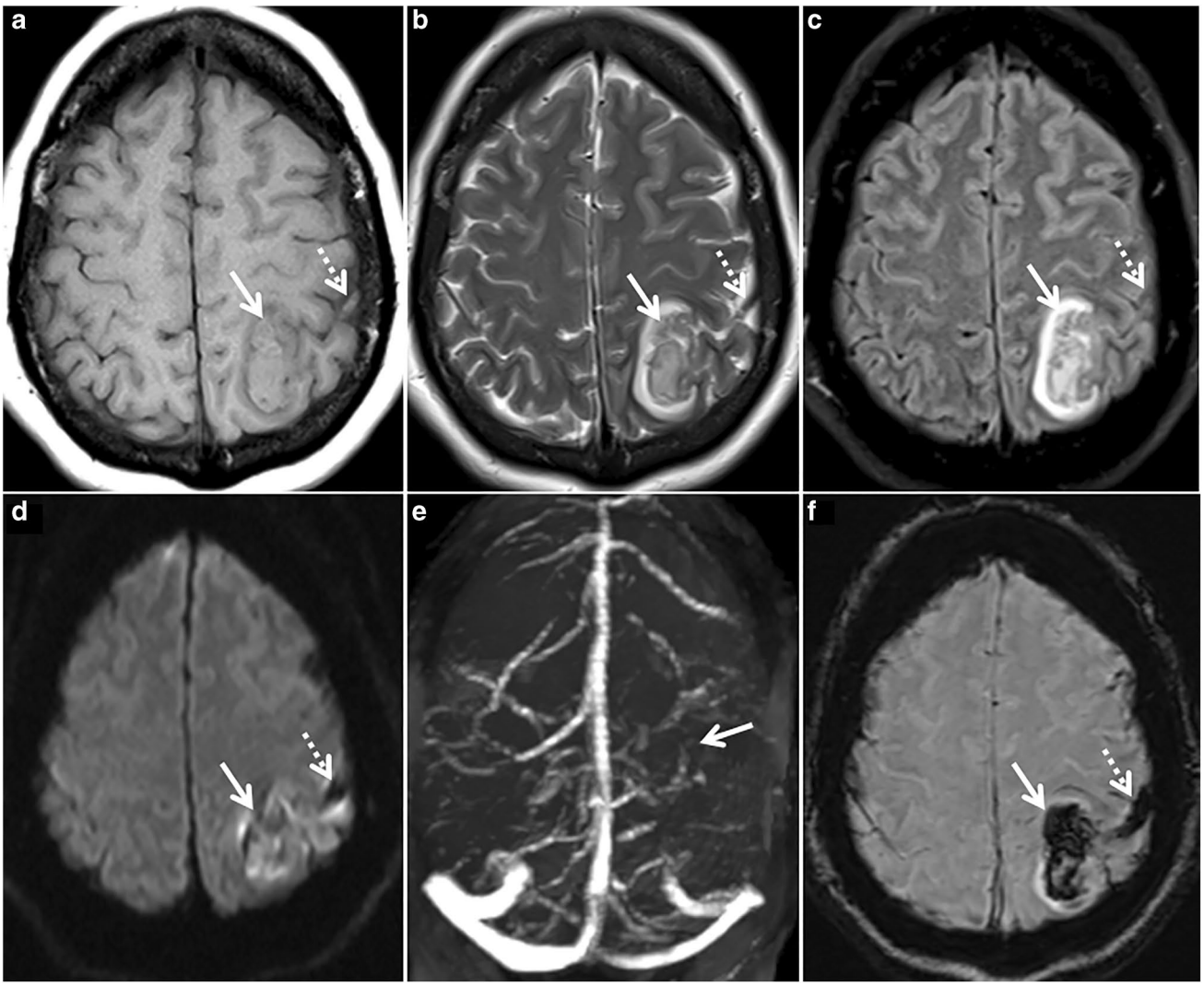

Fig. 3 A case of isolated cortical vein thrombosis with acute left parietal hemorrhage. **a** T1 weighted SE image shows the left parietal clotted cortical vein (dotted arrow) in association with hemorrhage (arrow). Isointense signals in the cortical vein clot mimic normal brain parenchyma. **b** Hypointense signals (dotted arrow) in the clotted vein mimic flow void near the hemorrhage (arrow) on T2 weighted TSE image. **c** Left parietal hemorrhage (arrow) is seen easily on FLAIR image, however the cortical vein clot (dotted arrow) is difficult to identify. **d** Susceptibility signals from the clotted cortical vein (dotted arrow) can be mistaken for CSF signals on this diffusion weighted image. Nearby hemorrhage shows mixed hyperintense signals (arrow). **e** 2D TOF MR venography MIP image shows indirect evidence of a missing cortical vein (arrow), which can be easily mistaken for a normal area devoid of a cortical vein in the absence of comparison to other MR sequences. **f** SWI image shows the engorged clotted cortical vein (dotted arrow) with susceptibility signals appearing like a cord. Susceptibility signals are also seen in the nearby acute hemorrhage (arrow)

cases, showing 100% sensitivity to detect COVT. However, the investigators did not perform an inter-rater agreement analysis and it appears that SWI was interpreted in combination with other MR sequences, CT and clinical information for the evaluation of COVT [12]. To the best of our efforts, a literature search did not yield studies on blinded evaluation of SWI with cases and controls to identify COVT as we have performed in our study. Independent evaluation of SWI in comparison to other sequences in our study, further strengthened the superiority of the susceptibility contrast over other MR sequences to identify acute and the early subacute stages of clots in COVT. SWI failed to identify COVT in 2 cases in our series, since both presented in the late subacute stage with the clots mainly made up of extracellular methemoglobin. Since susceptibility effects are well known to disappear with the formation of extracellular methemoglobin, it seems to be the main reason for the non-visualization of COVT in these 2 cases [3, 4, 8]. Fortunately, the clots were easily identifiable on T1 TSE, DWI and FLAIR sequences in both cases [17]. Our results highlight that SWI is a vital

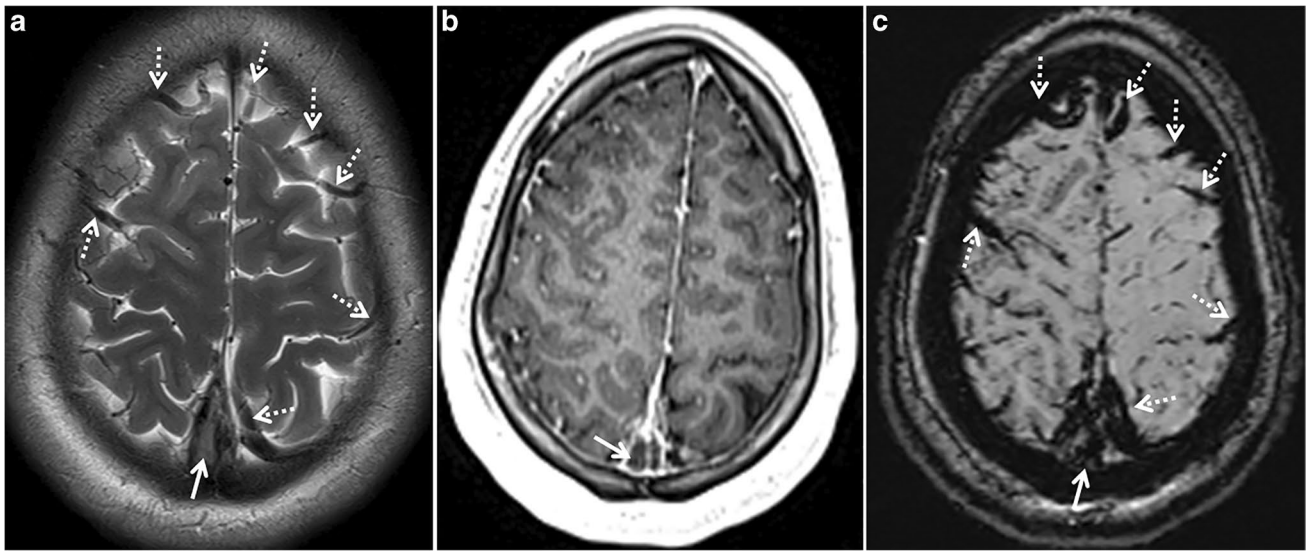

Fig. 4 A case of acute sagittal sinus thrombosis with bilateral frontal and parietal cortical vein clots. **a** T2 weighted TSE image shows the clot in the superior sagittal sinus (arrow). Cortical vein clots (dotted arrows) mimic normal flow voids. **b** Enhanced 3D T1 MPRAGE shows filling defect in the superior sagittal sinus (arrow). Bilateral cortical vein clots are not visualized. **c** SWI image shows the clots in the superior sagittal sinus (arrow) and bilateral cortical veins (dotted arrows)

sequence to evaluate COVT as it can identify the majority of COVT on its own. However, a combination of MR sequences is vital to overcome the limitations of SWI and guide the accurate diagnosis of COVT with MRI.

Deoxyhemoglobin in acute clots typically appears isointense on T1 and hypointense on T2 weighted sequences. Hypointense T2 signals are also observed in early subacute clots from intracellular methemoglobin [4]. These were the main reasons for the lack of distinction of acute clots from brain on T1 TSE and acute as well as early subacute clots from normal flow voids of cortical veins on T2 TSE (Fig. 3). Enhanced 3D T1 MPRAGE offers higher spatial resolution similar to SWI in comparison to 2D T1, T2 and FLAIR sequences. However, enhanced 3D T1 MPRAGE sequence in our series demonstrated poor sensitivity of 39% to detect COVT since the clotted veins remained invisible from the lack of a central filling defect with the surrounding residual intraluminal enhancement. The clotted veins were easily mistaken for regions that were normally devoid of cortical veins (Fig. 4). In a recent study, enhanced 3D T1 MPRAGE also showed moderate to poor sensitivity of 45% to identify COVT [18]. We also observed poor sensitivity of 32% for MRV to detect COVT. Our results are in agreement with the poor success rate of 37% reported by Ibdaih A et al. for MRV to identify COVT [3]. In another study, less than 50% sensitivity was observed for 2D TOF MRV to detect COVT [8]. In our series, noncontrast MRV was obtained in 24/30 of COVT cases using 2D TOF, 3D PC or a combination of both techniques. Enhanced MRV was performed with the TWIST (Time Resolved Angiography With Stochastic Trajectories) technique in 6/30 cases, but it failed to show the cortical vein clots in all 6 cases. The clots were not identifiable on TWIST MRV even after a review with the data from the clinical presentation and the location of clots on other MR sequences. In a recent study, enhanced MRV showed only 57% accuracy for the diagnosis of COVT [19]. Also, CEMRV failed to show cortical vein clots in all 7 cases in another study [13]. Further, Meckel S et al. demonstrated 66% sensitivity for T2* GRE in comparison to 53% sensitivity for 2D TOF MRV and contrast enhanced MRV in combination with 3D VIBE (Volumetric Interpolated Brain Examination) to identify cortical vein clots [16]. Recently, 3D T1 SPACE (Sampling Perfection with Application optimized Contrast using different flip angle Evolution) and 3D T2 SPACE MR sequences were shown to be highly successful to detect COVT [18, 19]. In COVT, parenchymal changes of venous infarct including edema or hemorrhage is known to occur in approximately 81% of cases [20]. It may be worth comparing 3D T1 SPACE and 3D T2 SPACE MR sequences with SWI for the evaluation of COVT, since SWI also offers the benefits of identifying parenchymal hemorrhages.

Limitations of the study

Retrospective assessment is a major limitation of our study. Small patient cohort is another main limitation, although our patient cohort can arguably be considered as relatively large for the evaluation of COVT. In the

majority of our cases, COVT was associated with dural sinus thrombosis and isolated COVT was observed in 4 cases. The presence of dural sinus thrombosis may have influenced the success of SWI to detect COVT in our series. Perhaps isolated COVT offers the best challenge to test the success and limitations of SWI to detect cortical vein clots. However, isolated COVT is a rare event and SWI was able to successfully identify COVT in all 4 cases in our series. Our results reveal, SWI identifies COVT mainly in the acute and the early subacute phases. Although, SWI failed to detect late subacute cortical vein clots with extracellular methemoglobin in 2 cases in our series, some investigators have reported the persistence of susceptibility signals on T2* GRE in late subacute clots [4, 5]. In our opinion, further studies are needed to validate the impressive performance of SWI to demonstrate COVT and understand its limitations.

Conclusions

High resolution SWI sequence offers the best sensitivity and accuracy among standard MR sequences to independently detect acute as well as early subacute cortical vein clots. However, a combination of MR sequences continues to be the most accurate approach to evaluate cortical vein clots since the susceptibility contrast becomes undetectable in the late subacute stages of COVT.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00234-023-03123-y.

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Declarations

The study complies with the ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Waiver of consent was obtained from Institutional Review Board.

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