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MRI of Clot in Cerebral Venous Thrombosis

High Diagnostic Value of Susceptibility-Weighted Images

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Background and Purpose—In cerebral venous thrombosis (CVT), the sensitivity of conventional MRI sequences to detect clot in the sinuses or veins is incomplete and largely depends on the time elapsed since thrombus formation. Little is known concerning the corresponding diagnostic value of fluid-attenuated inversion recovery (FLAIR), echo-planar T2* susceptibility-weighted imaging (T2*SW) or diffusion-weighted images (DWI).

Methods—We performed a retrospective analysis of 114 MRI examinations from 39 patients with CVT using a structured assessment. The time course of sensitivity in the detection of clot (n=166 clots) was analyzed for different MR sequences using a multilevel logistic model. The sensitivity of different MR sequences for diagnosis of cortical venous thrombosis was tested separately (n=38 clots).

Results—The sensitivity of T2*SW and T1-weighted spin echo image (T1SE) sequences to detect clot in the sinuses or veins was estimated at 90% and 71% between day 1 and day 3, which was much higher than that of T2SE, FLAIR or DWI during the first week of clinical onset. The sensitivity of T2*SW was stable in the first week. After this period, the sensitivity of T2*SW decreased less than that of T1SE. Thrombosed cortical veins, even in the absence of visible occlusion on magnetic resonance venography, were detected more frequently with T2*SW (97%) and T1SE (78%) than with FLAIR or DWI (<40%).

Conclusions—T2*SW imaging appears to be of additional diagnostic value in CVT. The T2*SW sequence may be particularly useful during the acute phase of CVT when the sensitivity of the other sequences is incomplete and for the diagnosis of isolated cortical venous thrombosis. (*Stroke*. 2006;37:991-995.)

Key Words: cerebral thrombosis ■ echo planar imaging ■ magnetic resonance imaging ■ sensitivity

Cerebral venous thrombosis (CVT) is a rare condition which is notoriously difficult to diagnose because of its variable modes of onset and its wide spectrum of signs and symptoms.^{1,2} Brain imaging by itself is of little diagnostic value in CVT because it usually shows nonspecific lesions, such as hemorrhage, infarct or edema, and can be normal in up to 25% of cases.³ The clue to the diagnosis is the imaging of the venous system, which may show either the intravascular thrombus or the occluded vessel. Although CT-scan is still often performed as first line investigation on an emergency basis, it is now well established that the best diagnostic tool is the combination of T1-weighted spin echo (T1SE) and T2SE MRI sequences to show the hyperintense thrombosed vessel and magnetic resonance venography (MRV) to detect the nonvisualization of the same vessel.³ However, both MRV and conventional MRI sequences are of incomplete sensitivity and specificity. MRV, as all other angiographic techniques, does not differentiate thrombosis and hypoplasia, a frequent diagnostic dilemma for the lateral sinuses. Furthermore, these techniques are usually insufficient for the diag-

nosis of isolated cortical venous thrombosis, which still often requires conventional angiography. The 2 main limitations of MRI are flow artifacts (which may result in false-positives) and the absence of hyperintense signal on T1SE-weighted images at the onset of acute thrombosis. During the first 3 to 5 days of CVT, the thrombus is isointense on T1SE and hypointense on T2SE,⁴ and thus extremely difficult to differentiate from normal veins.⁵ Favrole et al recently suggested that the increased signal of the venous clot on diffusion-weighted imaging (DWI) images may have a predictive value for recanalization.⁶ The potential of echo-planar T2* susceptibility-weighted imaging (T2*SW) sequences for the diagnosis of CVT has been illustrated in 2 recent studies.^{7,8} However, little is known concerning the sensitivity of T2*SW, fluid-attenuated inversion recovery (FLAIR) or DWI images in the diagnosis of CVT. In this retrospective study of 114 MRI examinations obtained in 39 patients, the sensitivity of signal modifications as detected on T1SE, T2SE, FLAIR, DWI or T2*SW at the site of thrombosis was analyzed according to the time elapsed since clinical onset.

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Materials and Methods

Patients

From our computerized stroke database, we selected all patients with confirmed CVT seen in our institution between April 2002 and August 2004. Only patients who had at least 2 MRI examinations including the T2*SW sequence (first MRI obtained at time of diagnosis) were included. In all of them the diagnosis of CVT was based on the following criteria: (1) history and clinical manifestations compatible with or suggestive of CVT; (2) presence of a partial or complete venous occlusion on MRV, CT-angiography or conventional angiography; and (3) typical signal changes highly suggestive of the presence of intraluminal thrombosis in sinuses or veins on T1SE (iso- or hyperintensity) or T2SE (iso- or hyperintensity), on at least 1 MRI examination during the follow-up.^{2,6-10}

MRI Data

All MRI examinations were performed on a 1.5-Tesla Signal Imager (GE Medical System) using the following parameters: T1SE (TR, 500 ms; TE, 14 ms; 20 slices, sagittal with or without axial slices; 5 mm thickness; matrix size, 256×192; field of view, 24×24 cm; acquisition time, 1.44 minutes; 1 excitation), T2SE (TR, 5200 ms; TE, 102 ms; 20 slices; axial slices; slices thickness, 5 mm; matrix size, 256×320, field of view, 24×24 cm; acquisition time, 1.20 minutes; 2 excitations), FLAIR (TR, 8400 ms; TE, 145 ms; 20 slices; axial slices; 5 mm thickness; matrix size, 256×192; field of view, 24×24 cm; acquisition time, 3.48 minutes; 1 excitation; TI, 2100), DWI (TR, 10 000 ms; TE, 100 ms; 20 slices; axial slices; slice thickness 7 mm; matrix size, 128×128; field of view, 24×24 cm; acquisition time 32 seconds, b value, 1000 s/mm²; diffusion gradient, G=22 mT/m; duration, 32 ms; separation time, 39 ms), T2*SW (TR, 560 ms; TE, 15 ms; 20 slices; slice thickness 5 mm; matrix size, 256×192; field of view, 24×24 cm; acquisition time 1.09 minutes;), 2-dimensional time-of-flight sequence (TR, 24 ms; TE, 4.9 ms; interleaved section, 121×1.5 mm slices; matrix size, 256×128; field of view, 24×18 cm; flip angle, 20°; bandwidth, 16 kHz; acquisition time, 4.54 minutes; 1 excitation).

All sequences obtained at each MRI examination were reviewed retrospectively by a neuroradiologist (M.B.) blinded to the subject's clinical condition. First, the sites of venous occlusion were systematically assessed by the reader on each MRI examination (based on all available data) at the following locations: superior sagittal sinus (SSS), left lateral sinus (LLS), right lateral sinus (RLS), deep venous system (DVS; vein of Galen, internal cerebral veins or straight sinus), right cortical veins (RCV) or left cortical veins (LCV). At each site of thrombosis, the presence of a normal flow-void, isointense signal or hyperintense signal on T1SE, T2SE, DWI, and FLAIR images were recorded. In addition, the presence or absence of a typical magnetic susceptibility effect on T2*SW was noted (MSE; only a strong and obvious hypointense signal encompassing the vessel lumen was considered in this category). A second observer performed the same task in a subset of patients (n=46 sites). The intra- and interobserver agreement was good or excellent (for each parameter, weighted κ coefficients were between 0.851 and 1 for the intra-observer agreement and between 0.768 and 0.939 for the inter-observer agreement).

Data Analysis

Descriptive statistics were first used for the main clinical and MRI data. The results were presented as counts (percents) for categorical variables and as means (SD) or medians (range) for continuous variables.

Because the main objective of the present study was to investigate the signal changes occurring with time in venous clots, only MRI results at the sites of venous occlusion were considered for statistical analysis. Given the variable delays between the repeated MRI examinations and clinical onset and the different venous sites of thrombosis included in the analysis, the course of the sensitivity for the different MRI sequences was analyzed using a multilevel logistic model. This model accounted for correlations between the repeated observations during the follow-up for each venous occlusion through random effects.^{11,12} Additionally, a second level of correlation was

considered using random patient effects. From the observed data, a piecewise linear model for time was first assumed, with an additional quadratic effect of time after 30 days. In a second step, the detailed structure of both fixed and random effects best fitting the data were selected using Schwartz's Bayesian Information Criterion (BIC) model selection criterion.¹³ Once the final model was fitted, specific hypotheses regarding fixed effects were tested.¹⁴ When performing 2×2 group comparisons, Hochberg's correction for multiple testing was used.¹⁵

The comparisons across groups outside this model were performed using the χ^2 test or the Student t test. All tests were 2-sided, and a probability value under 0.05 was considered significant. Analyses were performed using R.2.0.1 software (The R Development Core Team).

Results

Patients

Thirty-nine patients were included (4 males, 35 females) in the study. The median age was 32 years (range: 14 to 62.5). Clinical onset was acute (first neurological symptoms or signs since <48 hours) in 6 cases, subacute (48 hours to 1 month) in 31 cases, and chronic (>1 month) in 2 cases (33 days and 45 days). At the time of diagnosis, all patients complained of headache, which was the only symptom in 7 cases. Seven patients had papilledema. Other clinical manifestations at onset included focal neurological deficits (n=15), seizures (n=10) and drowsiness (n=4). All patients were treated with heparin immediately after the diagnosis. In 2 patients, mechanical endovascular treatment was also performed because of clinical worsening despite anticoagulation. In 26 patients, the total duration of anticoagulation (heparin, switched-over to vitamin K antagonists) varied from 6 (n=11) to 12 months (n=15). Two patients voluntarily stopped their treatment at 4 and 5 months. One patient was treated for 18 months. In 9 patients, anticoagulation is still ongoing (follow-up <1 year: 7 patients; underlying coagulopathy or systemic thrombotic disease: 2 patients). Complete neurological recovery occurred in 31 patients. Four patients had focal neurological sequelae (modified Rankin Scale score <2 in all of them), and 4 others had recurrent epileptic seizures.

The number of examinations performed in each patient ranged from 2 to 4 (average: 3). One hundred and fourteen examinations corresponding to 650 MR sequences (T1SE, n=113; T2SE, n=102; FLAIR, n=113; T2*SW, n=103; DWI, n=108; MRV, n=111) were analyzed. MRV was not obtained at follow-up in 3 MRI examinations.

Main MRI Features at Time of Diagnosis

The presence of a thrombosed sinus or vein was detected on MRV combined with MRI at the site of SSS in 20, LLS in 21, RLS in 18, DVS in 10, LCV in 2, and RCV in 3 patients. A single venous site, as defined previously, was involved in 19 patients, 2 venous sites in 13 patients, 3 in 2 patients, 4 in 5 patients, and 1 patient had an extensive CVT involving 5 different sites. At the time of diagnosis (first MRI examination), 75 different clots were identified at these different sites.

At the 75 sites of thrombosis (Figure 1), the clot appears on the first MRI examination as hyperintense on T1SE in 83% of sites, on T2SE in 27%, on FLAIR in 28% and on DWI in 21%. A typical MSE was detected on T2*SW at 93% of the sites of thrombosis (illustrative case shown in Figure 2).

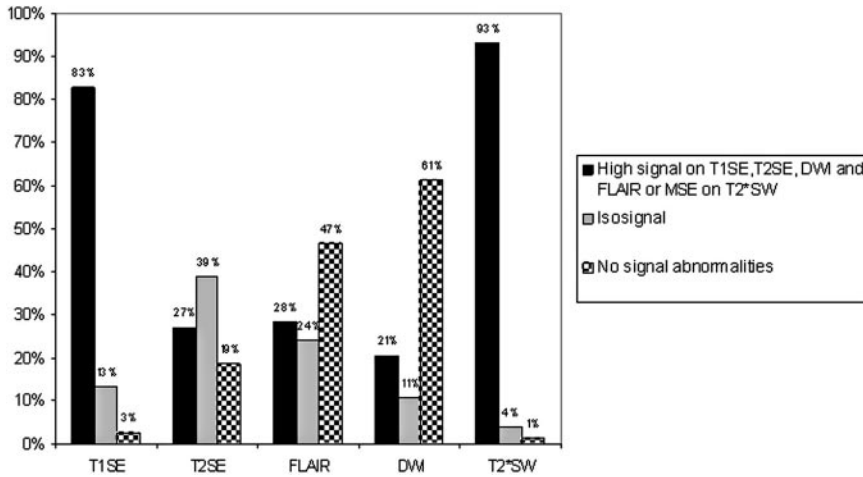


Figure 1. Frequency of different MRI aspects of the thrombus on the first MRI examination (75 sites).

MRI was performed within 3 days of the onset of symptoms in 7 patients. Eleven sites of thrombosis were identified in these subjects with the clot appearing on T1SE as hyperintense in 5/7 clots and isointense in 2/7; on T2SE as hyperintense in 1/7 clots, and isointense in 4/7 (T1SE and T2SE data were not available in 1 patient who had 4 sites of venous occlusion). With FLAIR and DWI, hyperintensity was detected at 1/11 sites, and on T2*SW a typical MSE was detected at 10/11 sites.

Time-Related Sensitivity of Hyperintense Signal on T1SE, T2SE, FLAIR and DWI and of the Presence of a MSE on T2*SW

All MRI data were included for this analysis corresponding to 166 sites of thrombosis located in the SSS (n=37), LLS (n=53), RLS (n=46), DVS (n=16), LCV (n=5) and RCV (n=9).

The model estimates of sensitivity for the hyperintense signal of the clot as observed on T1SE, T2SE, FLAIR and DWI and

for the presence of a MSE on T2*SW are presented in Figure 3. The model showed that the sensitivity of the different MRI sequences significantly differed at the first day of clinical onset ($P < 0.0001$). The sensitivity of both T1SE and T2*SW were found higher than the sensitivity of the other sequences ($P = 0.00012$ after adjustment for multiple testing). However, the difference in sensitivity between the hyperintense signal of the thrombus on T1SE (87.0%) and the presence of the MSE on T2*SW (94.3%) did not reach statistical significance ($P = 0.51$). Between day 1 and 7, the sensitivity of the corresponding signal modifications varied significantly between the different sequences ($P < 0.0001$). An increase in sensitivity was observed for all sequences (significant positive slopes), except for the MSE on T2*SW whose sensitivity remained stable (slope in the model = -0.0055 ; standard error (SE) = 0.246 ; $P = 0.83$) and differed from the other slopes ($P = 0.05$). Between day 7 and day 30, no global difference was detected in the variations of sensitivity between the different sequences ($P = 0.11$). However, the decrease in sensitivity was less rapid for the MSE on T2*SW than for the hyperintense aspect on T1SE; slopes: -0.053

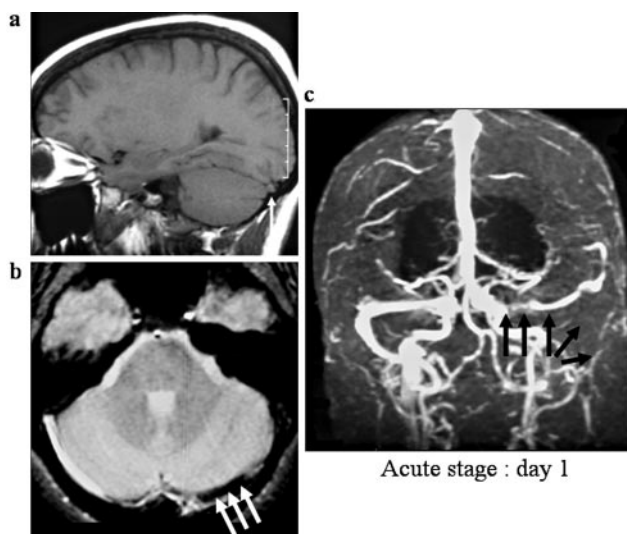


Figure 2. MRI obtained at the first day after clinical onset in patient 29 showing an acute thrombosis of the left LS. An isosignal was observed on parasagittal slices on T1SE MRI (a: arrow) whereas a typical MSE was detected on axial T2*SW (b: arrows). The frontal projection of 2-dimensional time-of-flight MR venography confirmed the occlusion of the corresponding sinus (c: arrows).

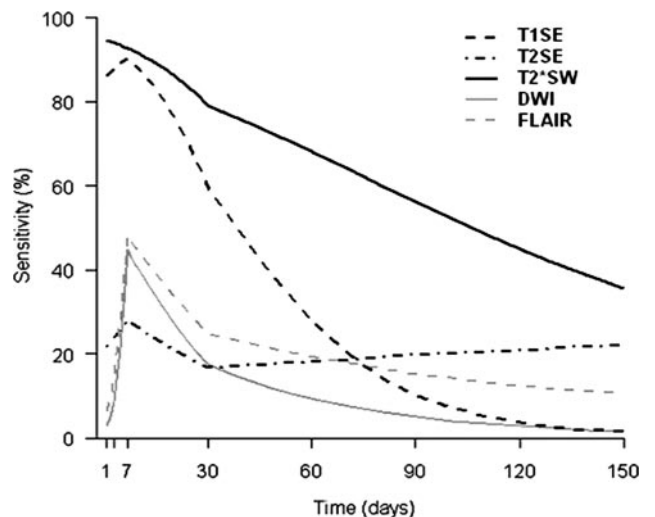


Figure 3. Time course of the sensitivity estimated by the model for the hyperintense aspect of the thrombus on T1SE, T2SE, DWI and FLAIR images and for MSE on T2*SW. Note the high sensitivity of T1SE and T2*SW at the early phase of CVT and the different curves after the first week for these 2 sequences.

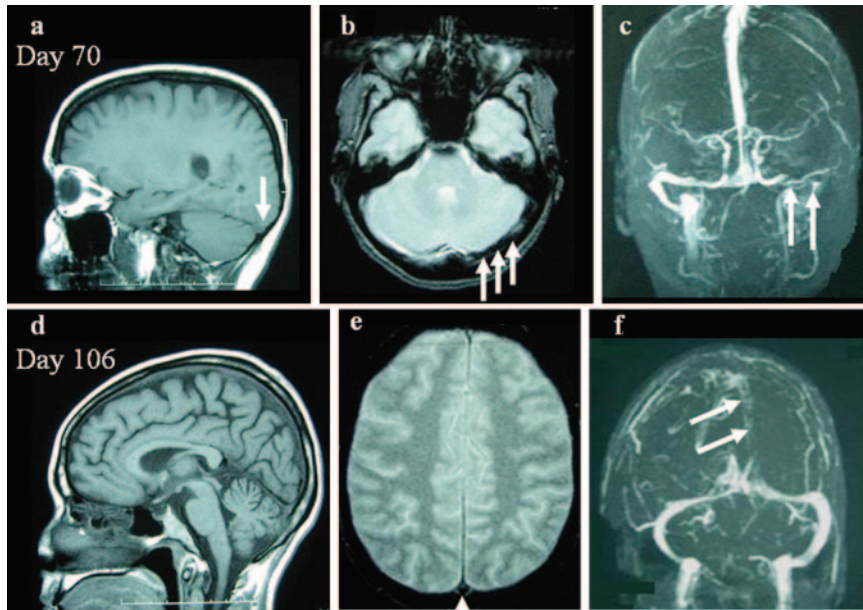


Figure 4. MRI signal modifications in 2 patients at the late stage of CVT. The MRI examination performed 70 days after the clinical onset in patient 7 showed the thrombus as isointense on T1SE (a: arrow), a typical MSE on T2*SW (b: arrows) and the absence of flow in the left lateral sinus and jugular vein on 2-dimensional time-of-flight MR venography (c: arrows). The MRI obtained at 106 days in patient 16 revealed no signal abnormality on midsagittal T1SE MRI (d), a MSE on axial T2*SW within the SSS (e: arrow) and the corresponding interruption of flow on the 2-dimensional time-of-flight MR venography (f: arrows).

(SE=0.025) versus -0.080 (SE=0.024); $P=0.0076$). After day 30, the variations in sensitivity also differed according to the different MRI sequences ($P=0.021$ on the quadratic term). A significant difference was also found between the slopes of the different sensitivity curves after day 30, particularly between those of T1SE and T2*SW ($P=0.0075$). The frequent persistence of MSE on T2*SW at the very late stage of CVT is illustrated in Figure 4.

Sensitivity of Different MRI Sequences to Detect Cortical Cerebral Venous Thrombosis

MR signal changes related to thrombosis in cortical veins were analyzed separately in the 89 examinations with a complete MRI data set. Thirty-eight cortical venous sites were diagnosed as thrombosed in 12 patients (cases 6, 16, 21, 23, 24, 25, 27, 30, 34, 35, 36 and 39) among whom 10 presented with thrombosis in other venous sites and 2 as isolated cortical venous thrombosis. A typical MSE on T2*SW

was found at 37 cortical venous sites, whereas hyperintensity on T1SE was detected at 30 sites (98 versus 79%; $P=0.01$; illustrative case shown in Figure 5). Hyperintensity corresponding to the clot was detected at only 5 sites on FLAIR images (14%), 1 site on DWI (3%) and was not detected on T2SE. Noteworthy, MRV disclosed an occluded cortical vein in only 14 sites with cortical venous thrombosis (37%).

Discussion

This is the first extensive time-dependent analysis of clot-related MR signal changes in CVT. In the present series, the major female predominance, age of onset, frequency of subacute onset, and different clinical manifestations are those classically reported in large series of CVT.^{1-3,16-19} The frequency of headache (reported by all of our patients) was higher than previously reported figure (80% to 90%).^{1,3} This may be related to some recruitment of patients through the emergency headache center present in our institution.

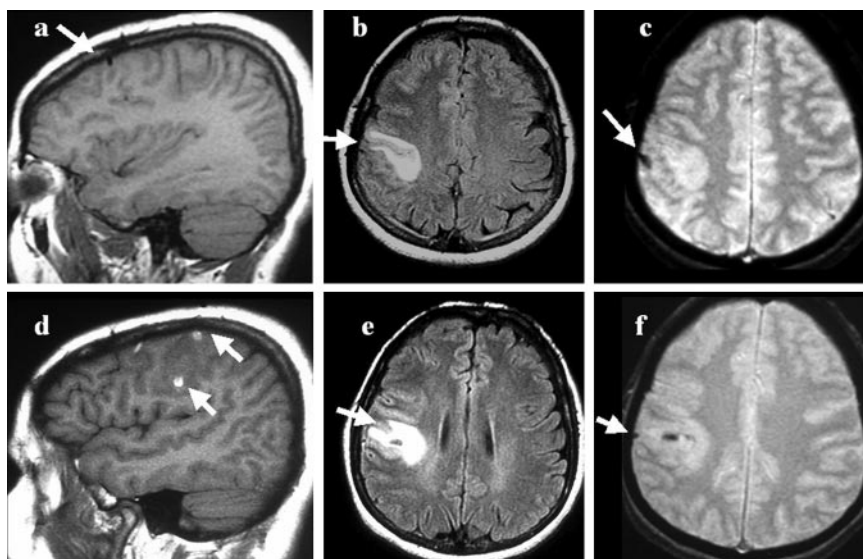


Figure 5. MRI data obtained at day 5 and at day 13 after the onset of symptoms in patient 23 who had isolated CVT. At day 1, parasagittal slices showed on T1SE a normal aspect of flow void in an isolated cortical vein (a: arrow); axial FLAIR images showed a hyperintense parenchymal lesion within the parietal lobe without abnormal vessels (b: arrow); a typical MSE was detected on T2*SW with a tubular aspect consistent with a thrombosed cortical vein (c). The images obtained at day 13 revealed hyperintense thrombosed cortical veins (arrow, up) and the hemorrhagic transformation of the parietal lesion (arrow, down) on T1SE (d); FLAIR images showed the hyperintense parietal lesion with hypointensity at the center corresponding to the hemorrhagic transformation (e). On T2*SW, a thrombosed cortical vein was detected at the surface of the brain as a tubular MSE (f).

In this series, conventional MRI sequences combined with MRV were used for diagnosis.^{4,9} MRV showed the presence of an occluded vein or sinus in 37/39 patients at the first MRI examination. T1SE showed a hyperintense signal at the site of thrombosis, highly suggestive of a recent thrombosis in 84% of cases. The most important finding of this study is that a MSE was detected at 90% sites of venous thrombosis at the first MRI investigation. Interestingly, a MSE was detected at 6 sites of thrombosis when the clot was only isointense on T1SE-weighted images. Moreover, within the first 3 days of symptom onset, the frequency of MSE on T2*SW images was over 90%, whereas the frequency of a hyperintense signal on T1SE was ≈70%. These data suggest that T2*SW may be helpful for the diagnosis of CVT, particularly during its early phase when the signal of thrombosis on T1SE is not yet hyperintense.

In the present study, the sensitivity of different MRI sequences in the detection of clots in CVT was estimated. The results confirm signal changes reported in T1 and T2SE in the early phase of CVT.⁹ Particularly, we observed that the frequency of hyperintensity at the site of venous occlusion progressively increases during the first week and decreases after this period for T1SE, FLAIR and DWI. Furthermore, we found that after 4 months, a hyperintense signal is no longer present on T1SE or DWI, in contrast to what is seen on T2SE and FLAIR images (20% and 54% respectively). Conversely, the frequency of MSE on T2*SW is high early in the course of clot formation and decreases very slowly with time. The estimated frequency of MSE on gradient echo images remained higher than 30% 4 months after clinical onset. These findings suggest that T2*SW cannot be used in isolation to date the appearance of venous occlusion. However, the combination of different MRI sequences, particularly T1SE and T2*SW, may be helpful to determine the time elapsed since the occurrence of thrombosis.

Thirty-eight sites of venous occlusion involving the cortical veins were identified in 12 patients with CVT in the present series. The sensitivity of T2*SW to detect these cortical venous clots was particularly high. The 98% frequency of MSE at the sites of cortical CVT was higher than the frequency of hyperintensity on T1SE and largely exceeded the diagnostic potential of MRV in these locations. T2*SW thus appears as the most sensitive MRI sequence for the diagnosis of cortical CVT, as already suggested in isolated cases.⁸ Therefore, this sequence should be added to conventional MRI sequences particularly when isolated cortical CVT is suspected.²⁰

There are several limitations in the present study. First, because the analysis was performed retrospectively, data were not always complete for all MRI examinations, which could lead to imprecise estimations of sensitivity. However, only 4.9% of the sequences were unavailable for analysis. Second, the external validity of the present study may be altered by (1) the specific MRI parameters used in our center that may influence the results, albeit slightly, (2) the expertise of the center in CVT, and (3) the review of films in a research setting in cases with an already established diagnosis of CVT. Despite these limitations, the present data are consistent with previous analyses of signal changes caused by clots both *in vitro* and *in vivo*.²¹ Finally, the time-dependent changes in sensitivity observed in the present study resembles the MR signal changes reported in tissue

hemorrhages.²¹ As reported in cerebral hemorrhages, early MSE on T2*SW within the venous thrombus is presumably related to the appearance of deoxyhemoglobin. The persisting decrease in MR signal is attributable to secondary accumulation of methemoglobin after a few days that is replaced by hemosiderin after several weeks. By contrast, the delayed increase of MR signal on T1SE is caused by the transient accumulation of methemoglobin in the clots.

In conclusion, this study shows that T2*SW is of additional diagnostic value for clot detection in CVT in conjunction with conventional MRI and MRV, particularly in the acute phase of thrombosis and in cortical CVT. The results of this study should be helpful for both diagnosis and therapy in CVT.

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