

# Additional Value of Susceptibility Weighted Imaging in the Evaluation of Acute Ischemic Stroke Patients

## Akut İskemik İnmeli Hastaların Değerlendirilmesinde Duyarlılık Ağırlıklı Görüntülemenin İlave Değeri

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**ABSTRACT Objective:** The aim of our study was to prove susceptibility weighted imaging (SWI) as a useful adjunct to routine magnetic resonance imaging (MRI) in the evaluation of acute ischemic stroke patients. **Material and Methods:** We performed a prospective study of 65 patients presenting with acute ischemic stroke in whom the diagnoses were based on clinical findings and diffusion weighted imaging (DWI). All patients were referred to computed tomography (CT) and complete brain MRI examinations within 24 hours of stroke onset. **Results:** SWI was able to detect hemorrhage in 12 out of 65 patients (18%) as either macrohemorrhages or petechial microhemorrhagic forms which were later not seen on CT or routine MRI sequences. Out of these 12 patients, 6 (50%) showed macrohemorrhages and the remaining 6 (50%) had petechial microhemorrhages. SWI was able to detect all microhemorrhages (100%) which otherwise would not be picked up by other imaging modalities. A prominent vessel sign was detected in 53 out of 65 (82%) patients in the vicinity of the acute ischemic brain territory. Hyperdense artery sign on CT in 31 (48%) patients and hyperintense artery sign on fluid attenuated inversion recovery (FLAIR) sequence in 21 (32%) patients were present. However, on SWI sequences, susceptible vessel sign (SVS) was present in 55 out of 65 (85%) patients with different major intracranial artery locations. **Conclusion:** SWI has been proven to provide invaluable additive information which otherwise would not be able to be picked up by other imaging modalities in the evaluation of acute ischemic stroke patients.

**Keywords:** Ischemia; magnetic resonance imaging; stroke; susceptibility weighted imaging

**ÖZET Amaç:** Bu çalışmadaki amacımız, duyarlılık ağırlıklı görüntüleme (DAG)'nin akut iskemik inmeli hastaların değerlendirilmesinde rutin manyetik rezonans görüntüleme (MRG)'ye ilave fayda sağlayan bir yöntem olduğunu kanıtlamaktır. **Gereç ve Yöntemler:** Prospektif özellikteki çalışmamızda akut iskemik inme ile prezante olan ve tanıları klinik bulgular ve diffüzyon ağırlıklı görüntüleme (DifAG)'ye dayanan 65 hastayı inceledik. Tüm hastalar inme başlangıcını takip eden 24 saat içerisinde beyin bilgisayarlı tomografi (BT) ve beyin MRG'ye gönderildi. **Bulgular:** DAG ile 65 hastanın 12 tanesinde (%18) daha sonra BT veya rutin MRG sekanslarında görülemeyen makrohemoraji veya peteşial mikrohemoraji formundaki kanamaları saptamayı başardık. Bu 12 hastanın 6 tanesi (%50) makrohemoraji ve kalan 6 tanesi ise (%50) peteşial mikrohemorajiye sahipti. DAG, diğer görüntüleme modaliteleri ile saptanması mümkün olmayacak tüm mikrohemorajileri (%100) saptama yeteneği gösterdi. Belirgin damar işareti, 65 hastanın 53 (%82)'ünde akut iskemik beyin bölgesi yakınında gösterildi. Hastaların 31 (%48)'inde BT'de hiperdens arter işareti ve 21 (%32)'inde "fluid attenuated inversion recovery (FLAIR)" sekansında hiperintens arter işareti saptandı. Bununla birlikte, DAG sekansında 65 hastanın 55 tanesinde (%85) farklı majör intrakraniyal arter lokasyonlarında duyarlılık damar işareti mevcuttu. **Sonuç:** DAG'nin akut iskemik inmeli hastaların değerlendirilmesinde, diğer görüntüleme modaliteleri ile saptanması mümkün olmayacak çok değerli ilave bilgilerin elde edilmesini sağlayan bir yöntem olduğu kanıtlanmıştır.

**Anahtar Kelimeler:** İskemi; manyetik rezonans görüntüleme; inme; duyarlılık ağırlıklı görüntüleme

Susceptibility weighted imaging (SWI) is a relatively new magnetic resonance imaging (MRI) sequence providing information about any substance that has a different susceptibility than its surrounding

structures. Magnetic susceptibility can be defined as the magnetic response of a substance when it is placed in an external magnetic field. These magnetic susceptibility changes can be induced by different

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substances including deoxyhemoglobin, hemosiderin, iron and calcium.<sup>1</sup> SWI is based on a three dimensional (3D), high resolution, long TE (time to echo), fully velocity compensated gradient echo (GE) imaging technique and has superiority to T2\* GE sequences. Because, it uses both magnitude and phase information and by combining these data an enhanced contrast magnitude image (i.e. SWI processed image) is produced that is especially sensitive to hemorrhage, iron, calcium and slow venous blood.<sup>2</sup> Furthermore, these data are also reconstructed with a minimum intensity projection algorithm (minIP) using thin slices that enables visualization of small veins while suppressing the signal from the normal brain parenchyma. Deoxyhemoglobin is a paramagnetic substance which is used as an intrinsic contrast agent by SWI. It causes a reduction of T2\* and leads to a phase difference between the vessel and its surrounding parenchyma.<sup>3</sup> The SWI has been found to be helpful in the imaging of acute ischemic stroke patients and some authors have even postulated that it can also predict outcome in these patients. In this study, we would like to emphasize the utility of SWI sequence in acute ischemic stroke patients in many aspects. First of all, it is very sensitive to even petechial microhemorrhages which can easily missed by computed tomography (CT). As we know, it is an initial crucial step to discriminate an infarcted area as hemorrhagic versus non-hemorrhagic. On the other hand, these cerebral microbleeds can be a clue of a possible development of later hemorrhagic transformation. Secondly, by performing this sequence, we can demonstrate visualization of draining veins within the areas of impaired brain regions and this represents ischemic penumbra in a different way from the Perfusion weighted imaging (PWI). Nevertheless, this motivates us to perform PWI in order to evaluate potential vascular reserve. Thirdly, susceptibility vessel sign (SVS) is an important finding in terms of revealing the presence of intra-arterial thrombus and its location can help us to evaluate the extent of infarct region and to decide treatment strategies. Based on that, in this article, by demonstrating SVS on SWI sequence in most of the acute ischemic stroke patients, we can obtain useful information in the management of these patients. Besides, we aimed to prove this finding as far superior to hyperintense

vessel sign on fluid attenuated inversion recovery (FLAIR) and hyperdense artery sign on CT. Therefore, in this prospective study, we tried to reveal additional information by using SWI in the imaging evaluation of acute ischemic stroke patients. For this purpose, we investigated the presence of macro- and microhemorrhages, prominent veins in the effected ischemic brain region and SVS in major intracranial arteries on this sequence. We also sought hyperdense artery sign on CT and hyperintense artery sign on FLAIR images in these patients and evaluated the CT and conventional MRI sequences for detection of hemorrhages.

## MATERIAL AND METHODS

A consecutive group of 65 patients were included in our prospective study between January 2015 and April 2017. This study was approved by Institutional Research Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (28/11/2017, No: 874) and informed consents were obtained from all patients. The study was performed according to Helsinki Declaration principles. Our patient cohort consisted of 30 women (46%) and 35 men (54%) and their mean age was  $67.69 \pm 15.6$  years (range 26-92 years).

All 65 consecutive patients included in this study were admitted to our hospital with clinical symptoms of acute stroke and following careful neurological evaluation, they were referred to diffusion weighted imaging (DWI) within 24 hours from the onset of symptoms. Based on clinical and DWI findings, these patients with acute ischemic stroke also underwent computed tomography (CT) and routine brain MRI, including SWI sequence for further comprehensive evaluation in less than a 3-day period. All CT and MR images were interpreted by the consensus of three neuroradiologists who were blinded to the clinical findings of the patients. All images in our study were obtained using a 12-channel phased array head coil on a 1.5 tesla clinical scanner (Avanto-SQ Engine, Siemens, Erlangen, Germany). The SWI sequence parameters are as follows: TR (repetition time), 49 ms; TE (echo time), 40 ms; NEX (Number of excitations), 1; Flip angle (FA), 15°; bandwidth, 80 kHz; slice thickness, 4 mm; Gap, 0.8; matrix size, 256 X 142. A

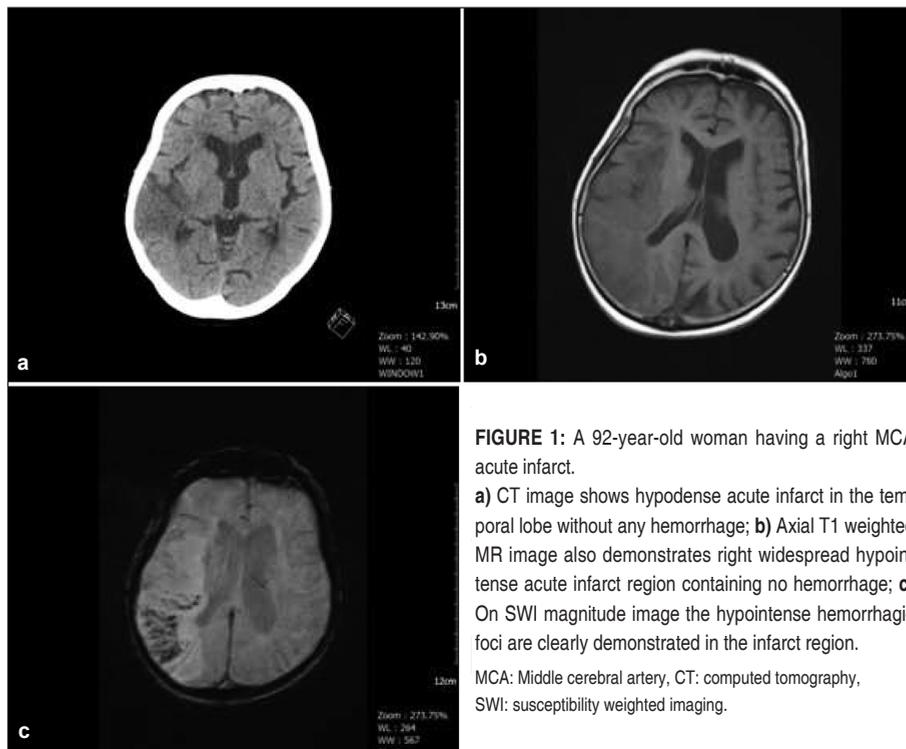
TE of 40 ms was chosen to avoid phase aliasing and a flip angle of  $15^\circ$  was used to avoid nulling of the signal from pial veins located within the cerebral spinal fluid (CSF). The acquisition time was 1.36 min. with the use of iPAT factor-3. After post-processing, 9 to 12 mm. thick minIP slabs were generated.

Hemorrhage in acute stroke patients were categorized into macrohemorrhage and petechial microhemorrhage based on the infarct size on DWI. Where the hemorrhage was more than 50% of the restricted diffusion area on DWI, it was considered as macrohemorrhage, and was otherwise classified as petechial microhemorrhage. On CT images and routine MRI sequences, whether macro- or microhemorrhages present in the brain parenchyma were investigated. Additionally, hyperdense artery sign on CT and hyperintense artery sign on FLAIR images were sought. Then, SWI was carefully scrutinized for the detection of macro- or microhemorrhages, presence of cortical or intramedullary veins in the vicinity of the infarct region and investigation of SVS in the territory of major intracranial arteries. We then compared the findings obtained with CT and routine MRI sequences to the SWI findings of acute ischemic

stroke patients and investigated the potential benefits of SWI sequence in these patients.

## RESULTS

All 65 patients had restricted diffusion on DWI. Among these patients, 53 (82%) had no hemorrhage on CT, conventional MRI and SWI. In the remaining 12 (18%) patients, CT images revealed macrohemorrhage in 6 and conventional MRI sequences in 6 patients. SWI was able to detect hemorrhage in all of the 12 patients which ultimately were not detected by the former studies. Of the 12 patients with hemorrhage, 6 (50%) patients showed macrohemorrhage and 6 (50%) patients had petechial microhemorrhage. The SWI detected all petechial microhemorrhages (100%) which were not detected by the other imaging modalities (Figure 1). This finding is important in terms of differentiating hemorrhagic versus non-hemorrhagic stroke which have completely different treatment strategies. Also, being able to show the presence of petechial microhemorrhages only on SWI sequence carries a crucial importance. It represents increased microvascular vulnerability and alerts us to develop a potential hemorrhagic transformation in the later period.



**TABLE 1:** Distribution of acute ischemic infarct cases.

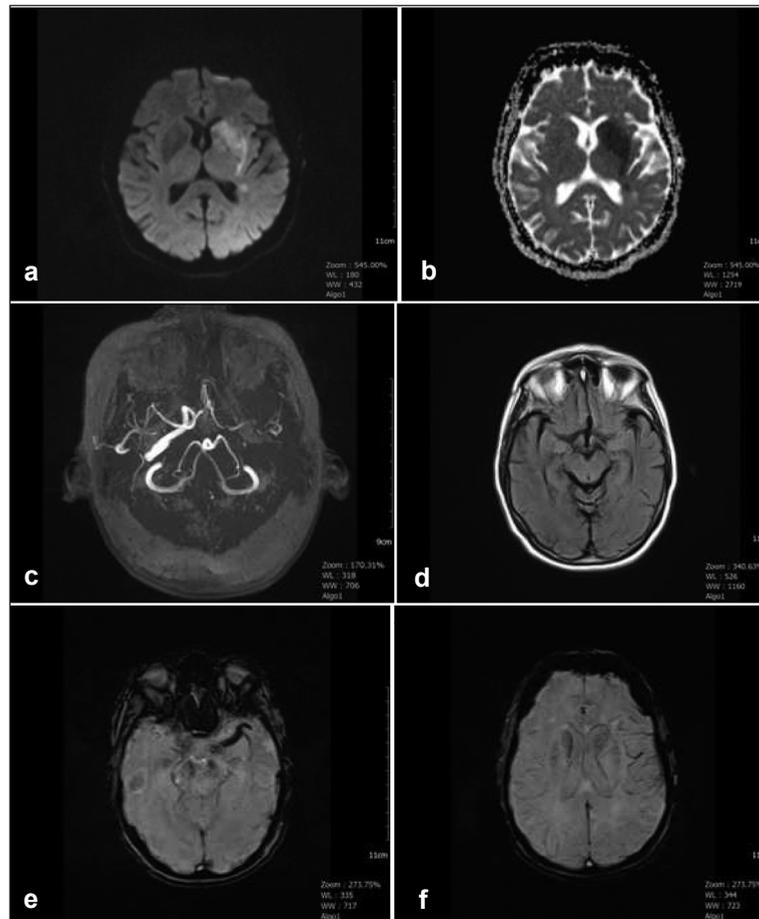
Territories	Number
MCA	43
PCA	12
ACA	2
SCA	1
AICA	1
PICA	6

MCA: Middle cerebral artery, PCA: Posterior cerebral artery,  
 ACA: Anterior cerebral artery, SCA: Superior cerebellar artery (SCA),  
 AICA: Anteriorinferior cerebellar artery, PICA: Posterior inferior cerebellar artery.

Territories of these acute ischemic infarcts were as follows: Middle cerebral artery (MCA), 43 patients; posterior cerebral artery (PCA), 12 patients;

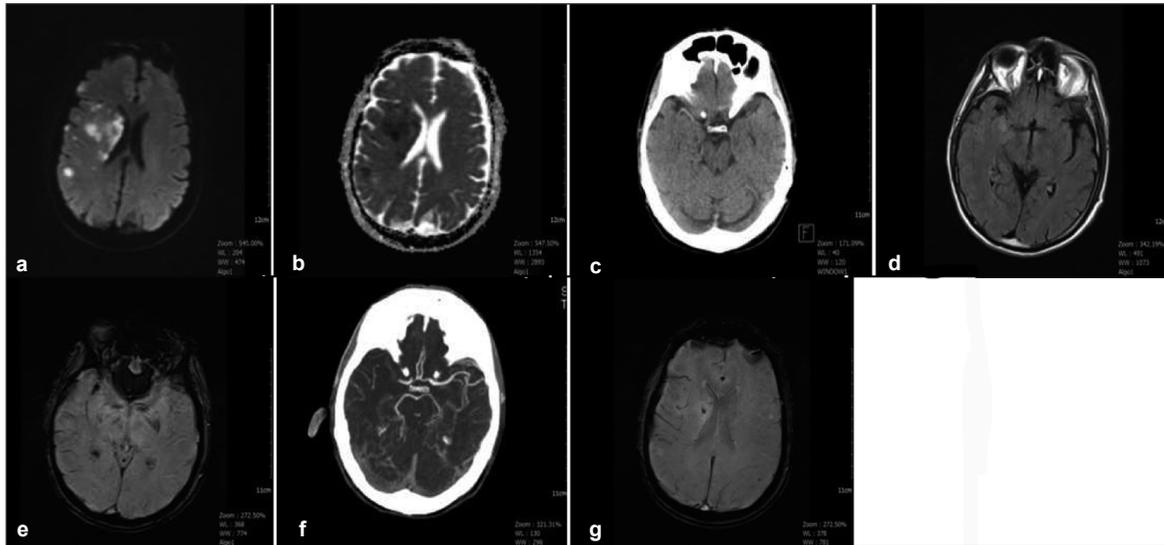
anterior cerebral artery (ACA), 2 patients; superior cerebellar artery (SCA), 1 patient; anterior inferior cerebellar artery (AICA), 1 patient; and posterior inferior cerebellar artery (PICA), 6 patients. In 2 patients both MCA and PCA, and in 1 patient both vertebral and PCA simultaneous occlusions were detected (Table 1).

Prominence of cortical and intramedullary veins were found in 53 (82%) acute ischemic stroke patients in the vicinity of the ischemic brain region (Figure 2 and Figure 3). This finding could only be visualized on SWI (particularly on minIP images) and could not be detected by CT and conventional MRI sequences. It shows ischemic penumbra region which represents the salvageable brain tissue with impaired



**FIGURE 2:** A 75-year-old woman with acute left lenticulo-striate infarct, **a)** and **b)** DWI and ADC map images show restricted diffusion in the left caudate nucleus head and lentiform nucleus, **c)** MRA MIP image demonstrates loss of flow in the left ICA and MCA vessels, **d)** Axial FLAIR image reveals hyperintense vessel sign along the left MCA, **e)** SWI minIP image shows blooming artifact consistent with SVS along the left MCA. **f)** SWI minIP image, clear prominence of the vessels in the left cerebral hemisphere.

DWI: Diffusion weighted imaging, ADC: Apparent diffusion coefficient, MRI: Magnetic resonance imaging, MRA: Magnetic resonance angiography, MIP: Maximum intensity projection, ICA: Inferior cerebral artery, MCA: Middle cerebral artery, FLAIR: Fluid attenuated inversion recovery, SVS: Susceptibility vessel sign, SWI: Susceptibility weighted imaging.



**FIGURE 3:** A 58-year-old man presenting with acute right MCA infarct **a)** and, **b)** DWI and ADC map images demonstrate restricted diffusion along the right fronto-parietal and periventricular regions, **c)** CT image shows hyperdense vessel sign along the right MCA, **d)** Axial FLAIR image also shows hyperintense vessel sign, **e)** SWI minIP image, SVS is detected along the right MCA, **f)** Axial cranial CT angiography MIP image reveals absence of flow along the right MCA consistent with total occlusion, **g)** SWI minIP image shows prominent vessels close to the infarct area and also reveals microhemorrhagic focus which are not detected on CT and conventional MR sequences.

DWI: Diffusion weighted imaging, ADC: Apparent diffusion coefficient, MIP: Maximum intensity projection, ICA: Inferior cerebral artery, MCA: Middle cerebral artery, FLAIR: Fluid attenuated inversion recovery, SVS: Susceptibility vessel sign, SWI: Susceptibility weighted imaging, CT: Computed tomography, MR: Magnetic resonance.

perfusion but not yet become infarcted. This finding should motivate us to immediately perform PWI in order to evaluate vascular reserve.

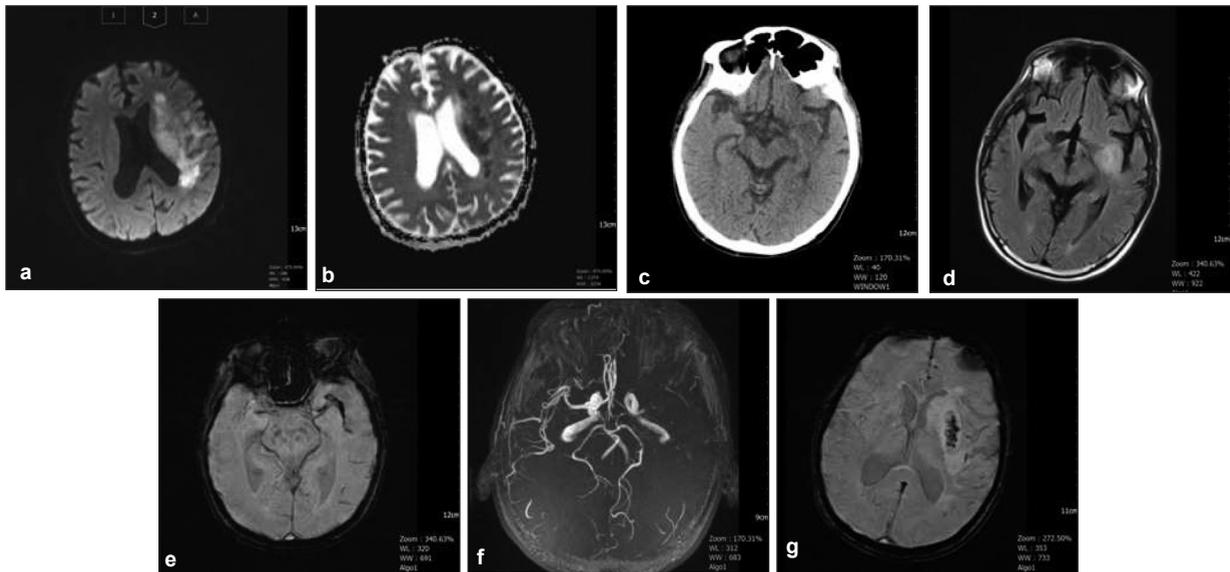
Hyperdense artery sign on CT images was found in 31 (48%) patients with acute ischemic stroke with 29 cases located to the MCA, 1 to the vertebral artery and 1 to the PCA territories. Hyperintense artery sign on FLAIR images was seen in 21 (32%) patients with all detected in the MCA territory. However, SVS was present in 55 out of 65 (85%) patients with 38 MCA, 9 PCA and 8 vertebral artery territories. All patients showing hyperdense artery sign on CT and hyperintense artery sign on FLAIR images were detected by SWI owing to SVS (Figure 4 and Figure 5). The SVS was found to be far superior to hyperintense artery sign on FLAIR images and hyperdense artery sign on CT. These findings are summarized in Table 2.

## DISCUSSION

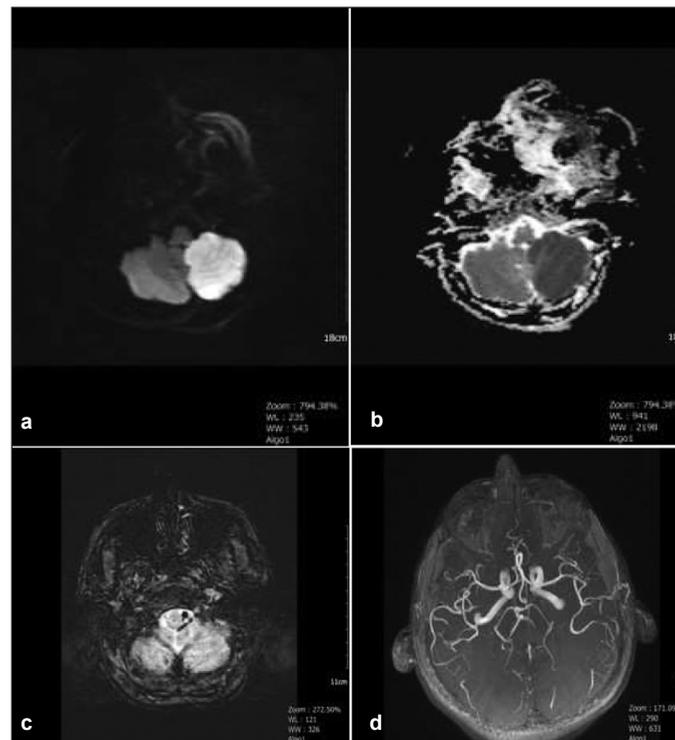
In recent years, SWI has become a useful imaging tool in the evaluation of acute stroke patients. Although DWI is regarded as the gold standard for detecting acute cerebral ischemia, SWI can surely

provide further valuable information about the affected vascular territory. Acute infarction arises from vascular occlusion due to thromboembolism or stenosis of the vessel and causes decreased arterial flow and an increased pool of deoxygenated blood. This results in an increase of deoxyhemoglobin concentration and depending on its paramagnetic properties, susceptibility changes occur which can be detected by SWI. In acute ischemic stroke patients, SWI has the ability to show macro- and microhemorrhages, presence of prominent veins in the vicinity of ischemic brain region and can also detect intra-arterial thrombus by revealing SVS in major intracranial arteries. Therefore it can be considered as a useful imaging tool in the evaluation of stroke severity, prognosis and treatment.<sup>4,5</sup>

SWI is helpful in detection of calcification and microhemorrhages, which are both characterized by low signal. Here, the evaluation of phase images allows for the differentiation between these two substances. In left handed MR systems, hemorrhage appears bright due to a positive phase shift, whereas calcification exhibits low signal depending on opposite shift effect.



**FIGURE 4:** A 67-year-old man with acute left lenticulo-striate infarct, **a)** and, **b)** DWI and ADC map images reveal left lenticulo-striate acute infarct, showing restricted diffusion, **c)** CT image demonstrates hyperdense vessel sign along the left MCA, **d)** Axial FLAIR image shows hyperintense vessel sign, **e)** SWI minIP image clearly demonstrates SVS of the left MCA. **f)** MRA MIP image, no flow is detected along the left MCA consistent with total occlusion, **g)** SWI minIP image also demonstrates prominent vessels and microhemorrhagic foci in the infarct area which were not possible to be detected on CT and conventional MR sequences. DWI: Diffusion weighted imaging, ADC: Apparent diffusion coefficient, MRA: Magnetic resonance angiography, MIP: Maximum intensity projection, MCA: Middle cerebral artery, FLAIR: Fluid attenuated inversion recovery, SVS: Susceptibility vessel sign, SWI: Susceptibility weighted imaging, CT: Computed tomography, MR: Magnetic resonance.



**FIGURE 5:** A 54-year-old woman with left acute cerebellar infarct **a)** and, **b)** DWI and ADC map images show restricted diffusion in the left cerebellar region, **c)** SWI magnitude image, SVS is seen involving both the left vertebral and PICA arteries. **d)** MRA MIP image reveals absence of flow along the proximal left vertebral and PICA arteries.

DWI: Diffusion weighted imaging, ADC: Apparent diffusion coefficient, MRA: Magnetic resonance angiography, MIP: Maximum intensity projection, SVS: Susceptibility vessel sign, SWI: Susceptibility weighted imaging, PICA: Posterior inferior cerebellar artery.

**TABLE 2:** Demonstration of findings obtained with imaging modalities.

	CT	MRI	SWI
Macrohemorrhage	5	6	6
Petechial microhemorrhage	–	–	6
Prominent vessel sign	–	–	53
Hyperdense artery sign	31	–	–
Hyperintense artery sign	–	21	–
SVS	–	–	55

CT: Computed tomography, MRI: Magnetic resonance imaging, SVS: Susceptibility vessel sign, SWI: Susceptibility weighted imaging.

In acute stroke patients, one of the most important determinants of thrombolytic therapy is the presence or absence of intraparenchymal hemorrhage. Although CT is regarded as the main imaging modality to rule out hemorrhage in acute stroke patients, MRI using GE sequences has traditionally been performed to detect hemorrhage in these patients. SWI is reported to be as accurate as CT in detection of hyperacute hemorrhage and superior to CT for the detection of chronic hemorrhages and SWI is also regarded as 3-6 times more sensitive than GE sequences in depicting hemorrhages and has also successfully been used in diffuse axonal injury cases to improve visualization of microhemorrhages.<sup>6,7</sup> Microhemorrhages represent small hemosiderin deposits adjacent to the small vessels seen as punctate hypointense foci on SWI.<sup>8</sup> The presence of multiple microhemorrhages may represent increased vascular vulnerability in stroke patients. Hemorrhagic transformation in acute stroke patients occur in 20-40% of the patients within the first week of stroke onset and could be a devastating complication.<sup>9</sup> Presence of microhemorrhages in acute stroke patients has been shown to be significantly associated with later hemorrhagic transformation.<sup>10</sup> In our study, SWI was able to detect petechial microhemorrhages in 6 patients, which were otherwise not picked up by CT or conventional MRI sequences.

SWI can also demonstrate prominent vessels. These multiple, hypointense prominent veins in the vicinity of acute infarct region are considered to be due to increased oxygen extraction and pooling of deoxyhemoglobin concentration in the vessels near the infarcted area and in the penumbra.<sup>11,12</sup> Therefore, the

presence of these vascular structures are hypothesized to represent the penumbra and are also considered to be a presentation of collateralization. Several studies have showed that the detection of these prominent veins on SWI could be a signature of salvageable ischemic tissue that will become infarcted if prompt blood perfusion is not established.<sup>6,13,14</sup> Given the fact that, the extent of prominent vessel sign indicates the extent of penumbra, patients showing more extensive prominent vessel sign can be expected to have a larger volume of salvageable tissue to be rescued. However, Huang et al. reported no correlation between the prominent vessel sign and prognosis, presence of later hemorrhagic transformation and edema and clinical outcome.<sup>10</sup> It is reported that prominent vessel sign on SWI could be a marker of an increased risk of hemorrhagic transformation in patients receiving thrombolytic therapy.<sup>8</sup> If SWI reveals prominent veins in the vicinity of ischemic brain region, this finding could be used to predict tissue at risk in the penumbra. Therefore additional imaging studies especially dynamic contrast perfusion study using relative cerebral blood flow (rCBF) and relative cerebral blood volume (rCBV) should be performed in order to evaluate vascular reserve.<sup>8</sup> In our study, we demonstrated prominent vessel sign in 53 out of 65 (82%) stroke patients on SWI.

In acute ischemic stroke patients, the demonstration of intra-arterial thrombus with an accurate assessment of its location is very helpful for planning thrombolytic treatment.<sup>15</sup> The SVS could be used to detect intra-arterial thrombus and was also found to be useful in assessment of infarct extent and prognosis.<sup>16</sup> SVS on SWI is defined as the presence of hypointensity within the vessel, in which the diameter of the hypointense signal within the vessel exceeds the contralateral vessel diameter. It is considered that SVS mainly results from deoxyhemoglobin within the thrombus. This high concentration deoxyhemoglobin within the thrombus leads to a severe T2 shortening and produces a susceptibility effect. Hyperdense artery sign on CT is well depicted in MCA territory and is rarely seen in other intracranial major arteries. Similarly, hyperintense artery sign on FLAIR images are usually observed in the MCA territory. Unlike these two signs, SVS could be detected in all major intracranial artery locations.

Lingegowda et al. in their retrospective study including 48 patients, found that SVS has a sensitivity of 82% and specificity of 100% for detecting acute intra-arterial thrombus located in all major intracranial arteries.<sup>17</sup> In their series, none of the 10 cases having a chronic thrombus showed SVS. They also concluded that SVS is more sensitive and specific than hyperdense artery sign on CT and hyperintense artery sign on FLAIR images in detecting acute thrombus. In another study performed by Huang P. et al., the SVS showed a significant association with arterial occlusion based on MR angiography.<sup>10</sup> They obtained a 54.5% sensitivity and 90.9% specificity. Radbruch A. et al. have compared the diagnostic accuracies of SVS and time of flight (TOF) MR angiography in 94 patients in terms of detecting vessel occlusion in acute stroke patients.<sup>18</sup> They demonstrated that SWI was significantly more sensitive than TOF MR angiography in detecting peripheral thrombi in these patients.

There is a potential drawback of SWI, because susceptibility artefacts arising from the skull base and paranasal sinuses could hamper the detection of thrombi located in the internal carotid artery territory.

In our study, we were able to show SVS in 55 out of 65 (85%) acute ischemic stroke patients and found it more useful than those of hyperdense artery sign on CT and hyperintense artery sign on FLAIR images in detecting acute intra-arterial thrombus. We assumed that the reason for one third of the cases with missing SVS were probably due to a more peripheral vessel location of the thrombi, because small vessel diameter is an important predictor in appearance of SVS.

The limitations of our study were, firstly, the relatively small sample size where most of the patients were not clinically followed up. Besides, follow up MRI of the patients were not evaluated in terms of temporal evolution of findings detected on SWI. Secondly, although all the patients in our study were referred to MR angiography or digital subtraction angiography (DSA) for a precise location of acute intra-arterial thrombus, we did not use either of these techniques for a reference standard to reveal the accuracy of SVS. Thirdly, we did not also perform per-

fusion MRI studies to evaluate the significance of prominent veins which represent ischemic penumbra. Finally, we could not evaluate occurrence of later hemorrhagic transformation in patients with petechial microhemorrhages due to the lack of follow up studies.

## CONCLUSION

In conclusion, SWI should be included in the evaluation of acute ischemic stroke patients as part of routine MRI sequences. Nowadays, availability of parallel imaging techniques with high gradient field strength MR machines, It only has an acquisition time of 3-5 minutes to image whole brain. This technique is extremely sensitive to even very small amount of hemorrhages that may be missed on CT or conventional MRI sequences. It clearly visualizes petechial microhemorrhages which are not detected otherwise, and may alert clinicians for further possible hemorrhagic transformation. SWI also reveals prominent veins in the vicinity of the infarcted brain region representing ischemic penumbra and encourages to perform perfusion weighted imaging studies for evaluation of vascular reserve. The presence of SVS in SWI can be used for detection and accurate localization of intra-arterial acute thrombus which is very helpful when planning thrombolytic therapy. It is more sensitive and specific than those of hyperdense artery and hyperintense artery signs on CT and FLAIR images, respectively. In summary, SWI provides very useful additional information in evaluation of acute stroke patients and should be included in the routine MRI protocols of patients with suspected acute ischemic stroke.

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### Conflict of Interest

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

**Authorship Contributions**

**Idea/Concept:** Ahmet Mesrur Halefoğlu; **Design:** Ahmet Mesrur Halefoğlu; **Control/Supervision:** Ahmet Mesrur Halefoğlu; **Data Collection and/or Processing:** Alper Demirci, Betül Duran Özel; **Analysis and/or Interpretation:** Ahmet Mesrur Halefoğlu, Alper

Demirci; **Literature Review:** Alper Demirci, Betül Duran Özel; **Writing the Article:** Ahmet Mesrur Halefoğlu; **Critical Review:** Ahmet Mesrur Halefoğlu, Alper Demirci, Betül Duran Özel; **References and Fundings:** Alper Demirci, Betül Duran Özel; **Materials:** Alper Demirci, Betül Duran Özel.

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