Blood in the Brain on Susceptibility-Weighted Imaging

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Abstract

Intraparenchymal brain hemorrhage is not uncommon and results from a wide variety of causes ranging from trauma to tumor. Many a time, it is not possible to determine the exact cause of non-traumatic hemorrhage on conventional magnetic resonance imaging (MRI). Susceptibility-weighted imaging (SWI) is a high-resolution (3D) gradient-echo sequence. It is extremely sensitive to the inhomogeneity of the local magnetic field and highly useful in identifying the small amount of hemorrhage, which may be inapparent on other MR pulse sequences. In this review, we present different pattern of an intra-parenchymal brain hemorrhage on SWI with emphasis on differential diagnosis.

Keywords
► susceptibility-weighted imaging
► hemorrhage
► microhemorrhage
► brain hemorrhage
► magnetic resonance imaging

Introduction

Intraparenchymal brain hemorrhage is a frequently detected finding in magnetic resonance imaging (MRI) examination. Extensive parenchymal hemorraghes resulting from stroke and other causes are obvious on routine MRI sequences. However, difficulty arises in diagnosing microhemorrhages, which is a commonly associated finding with a wide variety of infective and noninfective conditions and may remain occult on conventional MRI sequences. Susceptibility-weighted MRI (SWI) sequence being sensitive to inhomogeneity of the local magnetic field can easily detect microhemorrhages, hence, offer added advantage over conventional MRI sequences.

SWI is a high-resolution 3D gradient-echo MRI sequence, which accentuates the difference between paramagnetic substances (e.g., deoxyhemoglobin, hemosiderin, and ferritin) and brain parenchyma, thereby making this sequence sensitive to detect even microhemorrhages. Moreover, it also contains inherent phase information, which is utilized in various MRI based flow-quantification (e.g., CSF flow, flow velocity in vessels). A typical SWI sequence yields four sets of images—magnitude, filtered phase, mIP (minimum intensity projection), and SW (susceptibility-weighted) image (►Fig. 1). The SWI is generated by creating a phase mask by combining the magnitude and phase images. To improve contrast to noise ratio, multiplication of the phase mask with the original magnitude image is done, which yields the final SWI image. The mIP image is generated by processing images with a 3 to 10 mm slice thickness and applying a minimum intensity projection algorithm. Paramagnetic substances such as hemosiderin, deoxyhemoglobin, and ferritin appear dark on magnitude images and bright on phase images on a left-handed MRI system relative to the surrounding tissue and calcium will look bright (positive phase) because calcium is diamagnetic relative to the brain tissue.4
Diamagnetic susceptibility effect. Whereas other calcium deposits such as choroid plexus or dural calcium may exhibit a diamagnetic calcium. Yamada et al demonstrated that all basal ganglia calcium cations show a paramagnetic susceptibility effect, whereas other calcium deposits located outside the basal ganglia (such as choroid plexus or dural calcium) exhibit exclusively a diamagnetic susceptibility effect.5

Another issue with SWI imaging is problem of dipole artifact, which is due to imperfect dipole inversion of paramagnetic susceptibility. This artifact seen with bleed equal and/or larger than 3 mm. In left-handed system the upper and lower slices of hematomas will show hyperintense signal, while a right-handed system will show the opposite hypointense signal on the phase images. The stages of intracranial hemorrhage are hyperacute, acute, late subacute, and chronic. The differentiation between different stages could be achieved with the combination of T1, T2, and SWI images. Ideally, the evolution of intracranial bleed should result in higher susceptibility, and resultant increase signal on sequential signal-phase images. However, the inhomogeneous distribution of blood products often results in heterogeneous mixed hyper-, iso-, and hypo-signal intensities in the acute and early subacute stages. In the late subacute stage, the signal intensity on phase images will be more homogenous corresponding to the homogeneity in the extracellular distribution of methemoglobin. In contrast, chronic bleed will appear as volume loss of the affected cerebral parenchyma surrounded by hemosiderin staining.9

The intracranial bleed appears hyperintense on T1 during the late subacute stage, which is due to shortening of T1 relaxation time much more than T2 relaxation. This same mechanism explains the hyperintense signal produced by blood products on SWI at times. Although intracellular methemoglobin in early subacute hemorrhage also shortens T1 due to proton-electron dipole-dipole interactions, it is prone to susceptibility effects and appear hypointense on SWI, while extracellular methemoglobin in late subacute hemorrhage is not prone to significant susceptibility effects, allowing it to appear hyperintense on SWI.7

Scheid et al in their comparative analysis of 1.5 and 3 Tesla MRI for the evaluation of traumatic microbleeds found approximately two-fold increase in the total number of microbleeds on the 3T MRI system due to superior T2-weighted gradient echo MRI at high field strengths. However, despite the heightened sensitivity of 3 T MRI, the vast majority of cases of probable diffuse axonal injury can be diagnosed by routine MRI at 1.5 T.8

Intraparenchymal hemorrhages are broadly divided into two subtypes—macrohemorrhage (>10 mm) and microhemorrhage (5–10 mm).

Cerebral Macrohemorrhages or Macrobeeds
Cerebral macrohemorrhages or macrobleeds are defined as bleed of more than 10 mm in size and commonly visible on conventional MRI sequences. Cerebrovascular pathologies such as hypertensive vasculopathy, cerebral amyloid angiopathy are the common non-traumatic causes of macrobleeds. Other causes are anticoagulant medications, vascular malformations, and aneurysmal rupture.

Cerebral Microhemorrhages or Microbleeds
Cerebral microhemorrhages or microbleeds are small foci of marked loss of signal intensity on T2*-weighted or SWI. The majority of studies define microhemorrhages as being smaller than 5 mm in diameter with an upper limit of 10 mm. However, recent studies have suggested that the size also depends upon magnetic field strength and pulse sequence.9 Likewise, no separate consensus definition of more fine hemorrhages had been developed.

For the ease of differentiation, we proposed to divide bleed smaller than 10 mm size into two categories—microbleed or microhemorrhage (5–10 mm) and petechial hemorrhage (<5 mm).

Microbleeds
Cerebral microbleeds are more common in older individuals as a part of aging. However, several other diseases such as Alzheimer’s dementia, chronic hypertensive encephalopathy, cerebral amyloid angiopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), radiation therapy and trauma also reveal microbleeds.10,11

Petechial Hemorrhage
Diffuse petechial hemorrhages are commonly detected in various infectious conditions, which may or may not be associated with thrombocytopenia such as malaria, dengue, scrub typhus, and idiopathic thrombocytopenic purpura.
Linear or Streaky Hemorrhage

Linear or streaky hemorrhage are commonly seen in subarachnoid hemorrhage (SAH) and vasculitis such as primary CNS angiitis. In vasculitis, it may be either due to vascular/perivascular inflammation or SAH.

Depending on the site of involvement, two distinct types of intraparenchymal hemorrhage are central and peripheral. The central type affects thalamus, brain stem, and basal ganglia, while peripheral type involves cerebral and cerebellar cortical and subcortical regions. However, wide overlap exists as various conditions involve both peripheral and central parts such as CADASIL, hypertensive encephalopathy, and viral encephalitis (Table 1).

In this review, we would be discussing the various causes of cerebral bleeds such as infection, vasculitis, or other miscellaneous etiologies with an emphasis on the pattern of blooming on SWI.

Table 1 Causes and distribution of various types of hemorrhages (CADASIL-cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, PRES-posterior reversible encephalopathy syndrome, PACNS-primary angiitis of central nervous system)

<table>
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<tr>
<th>Central Hemorrhage</th>
<th>Peripheral Hemorrhage</th>
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<td>Micro</td>
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<td>Hypertension</td>
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<td>Amyloid angiopathy</td>
<td>Sinus Thrombosis</td>
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<td>Encephalitis</td>
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Infections

Cerebral Malaria

It is a fatal neurological complication of *Plasmodium* infection particularly associated with *Plasmodium falciparum*. The plugging of small-caliber blood vessels by *Plasmodium* may result in intracranial hemorrhage. Malaria should be suspected in cases with acute-onset fever with associated chills and rigors in endemic regions. Drowsiness may suggest cerebral involvement MRI in cerebral malaria demonstrates diffuse petechial hemorrhages throughout the cerebral hemisphere in peripheral distribution, predominantly at the gray–white matter junction. SWI is extremely useful in the detection of these diffuse petechial hemorrhages. Besides, involvement of the corpus callosum is quite common and characteristic of this entity, which appears hyperintense on T2/FLAIR due to white matter edema and may also have petechial hemorrhages as well (Figs. 2, 3).

Fig. 2 Cerebral malaria, axial SWI image (A) shows diffuse petechial hemorrhages in bilateral fronto-temporo-parietal regions, internal and external capsule and splenium of the corpus callosum. Axial DWI images (B) shows hyperintense signal in the splenium of corpus callosum, axial FLAIR image (C) shows hyperintense signal bilateral cerebral hemispheres in the cortical-subcortical region and also in the splenium of corpus callosum. However, both DWI and FLAIR images fail to demonstrate petechial hemorrhages (Malarial parasites were detected on microscopic examination of peripheral blood smear).
Dengue

Dengue is a febrile viral illness, transmitted by Aedes mosquito. The causative agent is a dengue virus, an arbovirus RNA virus, belonging to the Flaviviridae family with four serotypes (NS1–NS4) known. Although considered a non-neurotropic virus, neurological manifestations may rarely (4–5% of cases) be seen with NS2 and NS3. These complications are usually an immune-mediated phenomenon that may lead to acute demyelinating encephalomyelitis (ADEM), Guillain–Barre syndrome (GBS), neuritis, myelitis, hypokalemic paralysis, and opsoclonus myoclonus.

Hemorrhagic fever is a severe complication of dengue fever. It can result in severe thrombocytopenia and coagulopathy, which can result in intracranial hemorrhage, if left untreated. Dengue hemorrhagic encephalitis is, in fact, a hemorrhagic variant of ADEM, a severe form with a rapid downhill course.

Imaging findings may be normal or may show various types of intracranial hemorrhage (parenchymal, subarachnoid, subdural, or extradural) occurring due to thrombocytopenia or from increased vascular permeability. The hemorrhages are usually larger than those of malaria, and sometimes large intraparenchymal hematoma is also seen. Various studies have shown frequent involvement of brain parenchyma with features of diffuse cerebral edema and signal alteration in the deep gray nuclei. In fact, signal alteration in the basal ganglia–thalamus complex is the most common abnormality on MRI. This leads to symmetrical T2/FLAIR hyperintensity in the thalami and pones. Additionally, there may be signal abnormalities in the medial temporal lobe, midbrain, or cerebellum. These may have diffusion restriction and post-contrast enhancement. Multiple blooming foci suggestive of microhemorrhages may be seen within the affected areas. These microhemorrhages are most likely due to perivenular inflammation and demyelination resulting from immune-mediated necrotizing vasculitis of venules. These portend a poor prognosis and may lead to cognitive and other functional impairments in survivors.

In endemic regions, dengue hemorrhagic fever (DHF) usually spreads post-Monsoon season, corresponding to increased mosquito breeding due to water logging. Onset is acute with fever, bone, and retro-orbital pain and may be associated with petechial rash. The presence of multiple microhemorrhages in the brain increases the likelihood of DHF as similar imaging findings may be seen in other viruses of the Flaviviridae family such as Japanese encephalitis and West Nile virus. However, the timeline of seasonal variation coupled with endemicity is a clue to the diagnosis.

Scrub Typhus

Scrub typhus is an acute febrile illness caused by gram-negative bacteria, Orientia tsutsugamushi, which is transmitted by trombiculid mites. It can involve multiple organs, including the central nervous system. Because of associated vasculitis and perivasculitis, it may result in intracranial hemorrhage. Similar to many other viral illnesses, thrombocytopenia is a frequent finding, which in addition to vasculitis and encephalitis can also contribute to the development of intracranial hemorrhages.
Diffuse petechial hemorrhages are frequently reported in scrub typhus. However, other MRI findings such as meningoencephalitis/encephalopathy, T2/FLAIR hyperintensities in white matter, and microhemorrhages may also present (Fig. 5). The affected regions may show restricted diffusion. Imaging findings involving subcortical white matter may be indistinguishable from posterior reversible encephalopathy syndrome (vide infra). However, febrile presentation in an endemic region favors the diagnosis of Scrub typhus. The diagnosis of scrub typhus is confirmed by demonstrating raised antibody titer by Weil–Felix agglutination test or indirect immunofluorescence test.

H1N1 Encephalitis

H1NI virus, which is a novel influenza A virus may involve cerebral parenchyma. The spectrum of neurological manifestations in H1N1 encephalitis vary from acute necrotizing encephalopathy, encephalitis, meningitis/meningoencephalitis, and opportunistic fungal infection. Acute necrotizing encephalitis is a fulminant condition, which is characterized by bilateral symmetric involvement of thalamus with the hyperintense signal on T2/FLAIR sequences and restricted diffusion. Other regions such as basal ganglia, brainstem, cerebellum, and periventricular white matter may also be involved. Neuronal and glial necrosis characteristically leads to peripheral diffusion restriction. These lesions are frequently associated with microbleeds/petechial bleeds. SWI is a useful technique in the detection and better characterization of the extent of hemorrhage, which may be inapparent on other MR pulse sequences (Fig. 6). Meningoencephalitis may involve subcortical white matter in frontal and parietal lobes, bilateral thalami, and corpus callosum. Some case reports also suggest the involvement of the perirolandic region with leptomeningeal enhancement.

Primary Angiitis of Central Nervous System

Primary angiitis of central nervous system (PACNS) is a single organ vasculitis exclusive to the CNS in the absence of any systemic involvement. It is a medium- to small-vessel vasculitis, usually affecting the individuals of 40 to 50 years age group. The inflammation of the blood vessel wall with resultant stenosis and obstruction of the vessel lumen is a predominant pathology behind the development of intracranial hemorrhage.
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MR findings are nonspecific, which include infarcts, white matter lesions, and confluent lesions with a pseudo-mass-like appearance mimicking demyelination or even neoplasm. MR angiography may demonstrate vascular abnormalities in large and medium vessel vasculitits. Small vessel vasculitits, in contrast, may have no abnormality on conventional MRI, the diagnosis of which may be suspected only by a demonstration of microbleeds on gradient-echo images. SWI better demonstrates the extent of hemorrhagic lesions and also reveals inapparent subarachnoid hemorrhage, parenchymal, and microhemorrhages.21–24

This entity should be suspected in middle-aged individuals presenting with history of headache and recurrent stroke-like symptoms. MRI findings of recurrent bleed with multiple linear/streaky perivascular blooming with adjacent T2/FLAIR hyperintensity and linear/punctate or lace-like enhancement, is highly suggestive of PACNS (Fig. 7). Linear or lace-like blooming with irregular margins in PACNS is attributed histopathologically to perivenular inflammation with leucocytic infiltration in Virchow–Robin spaces. Lace-like enhancement in the adjacent parenchyma may be suggestive of contrast extravasation secondary to the breach in the blood–brain barrier.

Miscellaneous

Idiopathic Thrombocytopenic Purpura

The most common cause of cerebral microbleeds is age-related macroangiopathy, which gets exacerbated by risk factors such as hypertension followed by amyloid angiopathy. Besides these, other causes of cerebral microbleeds are cerebral small vessel diseases, including both familial amyloid and nonamyloid angiopathies and hematological disorders.

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune hematological disorder characterized by increased destruction of platelets in the reticuloendothelial system. Marked thrombocytopenia can result in clinically apparent intracranial hemorrhage, which may be intraparenchymal, intraventricular, or subdural. The presence of various types of hemorrhages such as microbleeds, intraparenchymal hematoma, and the subdural hematoma in a single MRI scan should prompt the search for this entity or other coagulopathies (Fig. 8).

Nonetheless, even asymptomatic patients may have occult microhemorrhages, which may be better detected by SWI. Such microhemorrhages may be a harbinger of future macro-hemorrhagic events in such patients, thereby identifying the at-risk population.25–27

Fig. 7 Case of primary angiitis of the central nervous system, axial FLAIR images (A, B) abnormal areas with the hyperintense signal in right temporoparietal region predominantly involving subcortical white matter. Axial SWI images (C, D) show multiple microhemorrhages and linear streaky peri-vascular hemorrhages in involved areas. Axial contrast images (E, F) shows multiple linear and punctate enhancement in the right frontoparietal and left parietal region (diagnosis confirmed at brain biopsy).

Fig. 8 Idiopathic thrombocytopenic purpura axial SWI image (A) shows multiple microhemorrhages in bilateral frontal lobes and left subdural hematoma (arrow). Axial FLAIR image (B) fails to demonstrate microhemorrhage, however, left subdural hematoma is seen (arrow). (diagnosis confirmed at bone marrow study).
Hypertensive Microangiopathy and Hypertensive Intracerebral Hemorrhage

Acute hypertensive bleed frequently occurred in the central part of the brain, i.e., basal ganglia thalamus and brain stem. However, there may be involvement of the cerebral and cerebellar hemispheres as well.

Microbleeds are the reasonably common manifestation of chronic hypertensive encephalopathy, which is often missed on the conventional MRI sequences. SWI being sensitive sequences to paramagnetic substances can very well demonstrate the extension of acute intracranial bleed as well as microbleeds of chronic hypertensive encephalopathy, predominantly involving the basal ganglia, thalamus, and brain-stem (Figs. 9, 10).

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome, resulting from accelerated blood pressure that exceeds the auto-regulatory capacity of the brain vasculature. This syndrome also associated with preeclampsia/eclampsia, renal decompensation, and immunosuppressive drugs.

MRI findings in typical cases are fairly characteristic with bilateral symmetrical T2/FLAIR hyperintensity in the region supplied by posterior circulation, e.g., parietal, occipital, posterior temporal, and cerebellar hemispheres. Atypical imaging findings include the presence of hemorrhage,
diffusion restriction or contrast enhancement. Intracranial hemorrhage is not uncommon, seen in around 15% of cases, which include microhemorrhages, subarachnoid hemorrhage, and focal hematoma (►Fig. 11).^{21,29}

Cerebral Amyloid Angiopathy (CAA)
Amyloid angiopathy is a small vessel disease that occurs due to the deposition of β-amyloid in the vessel wall. Cerebral amyloid angiopathy (CAA) is an age-related disorder with a prevalence of 75% in patients aged 90 years or older and also associated with aging, dementia, and Alzheimer’s disease.

Intracranial hemorrhage in CAA commonly manifests as microbleeds centering on the cortical-subcortical junction with lobar and cortical siderosis. The microbleeds predominantly affect the peripheral part of the brain (►Fig. 12).^{3,21}

Histopathologically, microbleeds result from damage to the elastic lamina of the arteries consequential to the amyloid deposition. The presence of superficial parenchymal hemorrhage involving both cortex-subcortical white matter, frontal and parietal lobes should raise the suspicion of CAA. Detection of microbleeds and their subsequent follow-up help in risk stratification for future hemorrhagic events besides monitoring therapeutic response.

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
CADASIL is an autosomal dominant arteriopathy manifesting at 40 to 50 years of age. Recurrent transient ischemic attacks (TIAs), strokes in multiple vascular territories, and migraine are the most common presenting symptoms.

MRI shows bilateral symmetrical T2/FLAIR hyperintensity in the periventricular and deep white matter involving subinsular white matter, external capsule, frontal, and anterior temporal lobes. Superficial white matter is less commonly affected with relative sparing of the cerebral cortex and arcuate fibers. Lacunar infarcts and dilated Virchow–Robin spaces at the gray–white matter junction and basal ganglia are also commonly seen. Microbleeds are the well-known features of this condition and seen in various parts of the brain with a preference for cortical-
subcortical regions. Cerebral white matter, thalamus, and brainstem are less frequently involved. However, Lesnik Oberstein et al found that thalamus is the most common site for microbleeds (→ Fig. 13). The typical location of microbleeds is outside the ischemic areas. These microbleeds may be present in both symptomatic as well as asymptomatic cases. These patients have a remote risk of intracranial hemorrhage of which cerebral microbleeds may be a predictor.

The diagnosis of this condition based on characteristic MRI findings of white matter hyperintensities, lacunar infarcts, and cerebral microbleeds in an appropriate clinical backdrop. Confirmation is by the demonstration of NOTCH3 mutation on genetic analysis. The involvement of anterior temporal lobe helps in differentiating this entity from other small vessel arteriopathies.

**Conclusion**

SWI is a sensitive MRI sequence helpful in detecting brain hemorrhage and can also help in identifying the underlying cause or narrowing down the differential diagnosis based on various patterns.

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None.

**Conflict of Interest**

None declared.

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