Cerebral Microbleeds: Imaging Patterns, Interpretation and Relevance

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Learning objectives

1. To discuss in brief physics of susceptibility-weighted imaging (SWI)

2. To discuss the various causes of cerebral microbleeds (CMBs) and discuss their clinical significance.
Background

With the advent of MRI techniques that are exquisitely sensitive to paramagnetic blood products, such as T2*-weighted gradient-recalled echo (GRE) and susceptibility-weighted sequences (SWI), cerebral microbleeds (CMBs) have been detected in ever increasing numbers of patients. CMBs are defined as small, rounded, homogeneous, hypointense foci on T2*-weighted gradient-recalled echo (T2*-GRE) or susceptibility-weighted imaging (SWI) MRI sequences.

CMBs are very common in the general elderly population and their prevalence increases with age. The clinical significance remains elusive. We retrospectively studied MRI brain of 1200 patients from PACS system. Axial T2, T1 and SWI images were compared and then were correlated with the clinical and final diagnosis of the patient. The incidence of CMBs was highest with prior history of trauma, and intracerebral hemorrhage. Second and third most common causes were in patient with prior history of stroke/hypertensive encephalopathy, and neurodegenerative diseases such as amyloid angiopathy, Alzheimer disease. Various other causes found on our study include CADASIL, CARASIL, CMBs due to cardiac (endocarditis, myxoma and cardiac valve), Fabry's, vasculitis, post RT, moyamoya, PRES, and blood disorders.

We discuss in brief the physics of SWI sequence and its role in detection of cerebral microbleeds. We give an algorithmic approach in evaluation and mapping of CMBs with respect to their clinical significance.
PRINCIPLES of SWI

Susceptibility-weighted imaging (SWI) is a 3D, flow-compensated, radiofrequency spoiled gradient-recalled echo sequence that takes advantage of susceptibility variations between tissues. SWI combines magnitude and phase images to detect these differences (Fig. 1 on page 10).

Magnetic susceptibility is a natural property of tissues, which reflects the magnetic response of a substance to an external magnetic field. The susceptibility differences between substances lead to local magnetic field inhomogeneity, resulting in faster T2* relaxation which leads to signal loss on MR sequences sensitive to T2* effects.

T2*-GRE sequence is very sensitive to this susceptibility effect and is far superior to T2-weighted spin-echo sequence in the detection of blood products. The extent of the 'blooming effect' is influenced by MRI parameters. In particular, a longer echo time detects more microbleeds (and makes them appear larger) than a shorter one. This is due to an increased dephasing of the local MR signal.

Electrons and paramagnetic effects

SWI is very sensitive to hemorrhage, calcium, iron storage and slow venous blood, thus allowing a significant improvement compared with T2* GE sequences. Signal loss on SWI is directly proportional to the amount of unpaired electrons present in the tissue (Fig. 2 on page 10).

- Visualization of the cerebral veins relies on paramagnetic properties of deoxyhemoglobin, in which the iron atom contains four unpaired electrons

- In subacute Hg, SWI exploits paramagnetic properties of methemoglobin. Iron atom in the ferric oxidation state contains five unpaired electrons

- Old Hg lesions, T2* signal degradation shown by SWI is due to the superparamagnetic properties of hemosiderin which contains large numbers of unpaired electrons
- Calcium, is a diamagnetic substances, devoid of unpaired electrons, which causes a phase shift. Phase images are sensitive to changes in the magnetic field caused by different components in tissues.

<table>
<thead>
<tr>
<th>Stage of thrombosis &amp; approximate duration</th>
<th>Status of hemoglobin</th>
<th>Magnetism</th>
<th>T1 shortening (Hyperintense)</th>
<th>T2 &amp; T2* Shortening (Hypointense)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (0-3 days)</td>
<td>DeoxyHb</td>
<td>T2 Paramagnetic</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Early subacute (&lt;1 week)</td>
<td>Intracellular MetHb</td>
<td>T1&amp; T2 Paramagnetic</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Late subacute (1-2 weeks)</td>
<td>Extracellular MetHb</td>
<td>T1 Paramagnetic</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Chronic (&gt;2 weeks)</td>
<td>Hemosiderin</td>
<td>T2 Paramagnetic</td>
<td>-</td>
<td>++++</td>
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</tbody>
</table>

**Differentiating Calcification v/s Iron Deposits on SWI**

SWI provides a window of opportunity to detect calcium and iron deposits in brain tissue using high-pass-filtered phase images, due to local tissue susceptibility effects. Calcium is diamagnetic and devoid of unpaired electrons but generates weak local field inhomogeneity leading to phase change. The phase shift induced by calcium shows negative phase (in left-handed MR systems), so it causes calcium to appear hypointense on phase images (Fig. 3 on page 11).

Similarly, SWI can detect nonheme iron deposition in the brain, predominantly in the form of ferritin and transferrin, using filtered phase images. The paramagnetic nonheme iron shows a positive phase shift and thus appears hyperintense on phase images.

**DIFFERENTIAL DIAGNOSIS OF CEREBRAL MICROBLEEDS**

- Sporadic cerebral small vessel diseases: **Hypertensive arteriopathy**

Patients with microhemorrhages were significantly older and had a higher frequency of hypertension. A strong correlation between the white matter hyperintensity and the number of microhemorrhages was also observed. Because hypertension is a well-
An established cause of small-vessel disease and extensive white matter hyperintensity has been reported to represent microangiopathy-related tissue damage. These microhemorrhages were most frequently located in lentiform nucleus, thalamus, and cortical-subcortical regions, where symptomatic hematomas are commonly observed (Fig. 4 on page 12).

- Sporadic cerebral small vessel diseases: Sporadic cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is characterized by the presence of homogenous eosinophilic deposits in the cortical and meningeal vessels which leads to luminal stenosis and fibrinoid necrosis. This makes vessels fragile and increases the tendency to bleed. CAA has no correlation with hypertension, diabetes or atherosclerosis. Imaging: may show superficial lobar hematomas, commonly with subcortical or subarachnoid extension. Focal or patchy/confluent WM disease (70%), and/or nonhemorrhagic diffuse encephalopathy. GRE and T2WI may show multifocal black dots (Fig. 5 on page 13).

- Neurodegenerative diseases: Alzheimer's disease

Increased iron deposition is found in Parkinson's disease, Huntington's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis and pantothenate kinase-associated neurodegeneration (PKAN). The capability to measure the amount of non-heme iron in the brain will facilitate a better understanding of the disease progression and will also help in predicting the treatment outcome. Lobar CMBs are reported in more than 20% (ranging from 15 to 32%) of patients with sporadic AD. By contrast, CMBs are substantially less prevalent in other causes of dementia, such as frontotemporal dementia, corticobasal degeneration, dementia with Lewy bodies and progressive supranuclear palsy. Their distribution suggests that lobar CMBs in Alzheimer's disease reflect underlying CAA.

- Inherited cerebrovascular disorders: CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited stroke disorder, which results from a mutation in the NOTCH3 gene, mapped onto chromosome 19q12. Typically, patients present with progressive cognitive decline, migraine with aura, mood disturbances and small vessel infarcts. MR imaging features include white matter changes on T2-weighted images, lacunar infarcts on T1-weighted images, and CMBs. The white matter changes are found in a periventricular distribution and involve characteristically the anterior temporal lobes, corpus callosum and external capsule (Fig. 6 on page 13). Lacunar infarcts are usually seen in the capsulostriatal region, thalami and central pons. CMB
burden and location, as well as lacunar infarcts and brain atrophy, are associated with decline in cognitive function.

- Cerebral microbleeds associated with cardiac disorders

Various cardiac conditions can act as major source of emboli which may present either as TIA, ischemia or bleeds in the brain. Common conditions which can cause microbleed includes infective endocarditis, atrial myxoma, and prosthetic valves. CMBs are not uncommon with community acquired infective endocarditis (57 % in the endocarditis group compared with only 15 % in the control group)( Fig. 7 on page 14 ). CMBs tended to occur in the cortical sulci, which may be explained by the fact that some of the lesions may have been mycotic aneurysms.

- Cerebral microbleeds associated with hematological disorder

Various hematological disorders can increase the risk of ischemic stroke or ICH. This increase could be due disturbances in the blood counts or damage to the vessel wall or combination of the two. Intracranial bleeds are commonly seen with leukemia, and thrombocytopenia due to consumption of the coagulations factor or due to blastic phase of the disease. CNS complications are estimated to occur in between 2 and 4% of leukemic patients/month Fig. 8 on page 15 . Involvement of the CNS in leukemia may be direct results from a mass lesion intrinsic to neural tissue, infiltration of neural tissue by tumor cells, or external compression of neural tissue by an extrinsic mass, directly affecting the blood vessels, resulting in vascular occlusion and end-organ ischemia or indirect due to infection, drug- and radiation-induced neurotoxicity, and electrolyte disturbance

- Posterior reversible encephalopathy syndrome (PRES)

PRES describes a neurotoxic state associated with a wide range of conditions, though is usually associated with hypertension, eclampsia or cyclosporine use after organ transplantation. Patients usually present with a combination of headache, altered mental status, visual loss and seizures. On MR imaging, focal areas of symmetric hemispheric hyperintensities are seen on fluid attenuation inversion recovery (FLAIR) sequences, most commonly in parietal and occipital lobes, which reflects vasogenic edema Fig. 9 on page 16 . It used to be thought that hemorrhage was an atypical feature of PRES, however hemorrhage may be seen in 17-58 % of patients using SWI. It is proposed that CMBs in the context of PRES is related to endothelial cell dysfunction.

- Renal failure and microhemorrhages
Exact cause of cerebral microbleeds in cases with renal failure is not determined. However, increase incidence of microhemorrhages has been reported in patients with chronic renal failure maintained on haemodialysis. Cho et al. retrospectively studied 152 patients who presented with acute ischaemic stroke and had gradient echo imaging. They found a strong association between impaired renal function and the presence of microbleeds. Ryu et al. has indicated that there is an association of chronic renal disease without diabetes with CMBs, but not in patients with diabetes.

- **Traumatic brain injury (TBI)**

  CMBs in the context of traumatic brain injury are a manifestation of diffuse axonal injury, occurring after the rotational acceleration and deceleration of the brain. Traumatic microbleeds can be usually differentiated from CMBs due to sporadic small vessel disease from history and other imaging features of brain trauma. However, the distribution of traumatic microbleeds is also different from other CMBs, usually occurring at the grey-white matter junction, especially in the frontal and temporal lobes, and in the corpus callosum Fig. 10 on page 17.

- **Cavernomas of the brain**

  Cavernous malformations are well-circumscribed nodules of clusters of dilated endothelial vessels without intervening neural tissue. The typical appearance of a haemosiderin rim with a core of mixed signal intensity representing haemorrhage of different ages gives the characteristic 'popcorn' appearance. Smaller (type IV) cavernomas appear as punctate hypointensive lesions on T2*-GRE images and can be indistinguishable from CMBs (Fig. 11 on page 18). Most cavernomas are believed to be of congenital origin, and have an incidence as high as 0.5%. Radiation (RT) induced cavernoma and capillary telangiectasia have been reported and are hypothesized to be due to hyalinization and fibrinoid necrosis of small arterioles. It is also responsible for mineralizing microangiopathy with dystrophic calcification and often seen in children treated with chemo and RTX. Cavernomas take a longer time to develop after RTX, with latency period ranging from 1 to 26 years.

**CLINICAL SIGNIFICANCE OF MICROHEMORRHAGE**

1. Cognition:
Small vessel disease is thought to be a major cause of vascular cognitive impairment. The role and the incidence of cognition with microbleeds remains uncertain. Experimental studies suggests that CMBs are not clinically 'silent' for cognition. There is documented evidence of the association of CMBs with executive and speed and attention dysfunction. In the Rotterdam Scan Study the presence of multiple (#5) CMBs, especially in a strictly lobar distribution, was associated with worse cognitive performance, even after adjusting for vascular risk factors and other imaging markers of small vessel disease.

2. Marker of recurrent hemorrhage:

In cases of amyloid angiopathy lobar CMBs predict a high future risk of recurrent symptomatic ICH.

3. Marker for recurrent stroke

Increase risk of recurrence mainly concerned ischaemic events rather than ICH has been found in patients with CMBs especially in the lobar or mixed, but not deep CMBs Fig. 12 on page 19.

4. Anticoagulation therapy and CMB:

Identifying CMBs and ruling out early changes of amyloid angiopathy is important in patient who need to be on long term anti-coagualnt therapy. It has been documented that wish to be . It has been documented that these patients are at higher risk of intracranial hemorrhage as compared to the age matched control group. So reliable detection of CMBs (especially multiple lobar CMBs) could in the future have a direct impact on anticoagulation treatment decisions. A small prospective study showed that aspirin might be associated with recurrent lobar ICH in patients with CAA.
Fig. 1: Steps in generating SWI image: In the first processing step, phase images (Pha) undergo filtration to minimize the background unwanted susceptibility. Next, the filtered phase images are used to generate a phase mask. The phase mask is then multiplied with the original magnitude data (Mag) to obtain SWI magnitude images (SWI). This step enhances the susceptibility effects. In the final processing step, several SWI magnitude images are combined to create thick minimum intensity pixel (mIP) images to further enhance susceptibility effects (Usually #4 images of SWI combined to obtain one mIP image)

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**Fig. 2:** Signal loss on SWI is directly proportional to the amount of unpaired electrons present in the tissue

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**Fig. 3:** On SWI-filtered phase images, calcium carbonate appears with the opposite-sign phase compared to haemosiderin

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**Fig. 4:** Patient with hypertensive arteriopathy shows classical deep cerebral distribution of microbleeds.

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**Fig. 5:** A 76 yr old male patient with amyloid angiopathy presented with acute head and weakness due to right parietal hemorrhages.

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Fig. 6: Images obtained in a patient with biopsy-proved CADASIL display the extensive white matter changes with involvement of the anterior temporal lobe and superior frontal WM. Multiple scattered CMBs are noted. Histopathological slide showing the arteriopathic changes

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Fig. 7: Patient with infective endocarditis presenting with right temporal hemorrhage, with multiple CMBs. On DSA patient had a septic aneurysm in the distal MCA branch.
Fig. 8: Multiple tiny hemorrhages in the cerebral parenchyma seen on CT and MR during the blast crisis of ALL (leukocyte>300,000/mm3)

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Fig. 9: 41 year old female pt with eclampsia shows classical changes of PRES on MR. GRE images also sowed areas of microhemorrhages in the frontal and occipital cortex. PRES changes were also seen in the cerebellar parenchyma.
**Fig. 10:** DWI, SWI and color maps of DTI shows restricted diffusion (red arrow) and microhemorrhages (blue arrow) in the splenium of the corpus callosum and cerebral white matter leading to disruption of the fibers.

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**Fig. 11:** Smaller (type IV) cavernomas appear as punctate hypointensive lesions on T2*-GRE images and can be indistinguishable from CMBs

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Fig. 12: Right thalamic hemorrhage in a patient with multiple CMBs seen on a previous MRI

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Conclusion

- With the development of MRI techniques (gradient-recalled echo and susceptibility-weighted sequences) paramagnetic blood products, microbleeds are commonly encountered on routine brain MRI.

- The incidence of CMBs is highest with prior history of trauma, and intracerebral hemorrhage, followed by prior history of stroke/hypertensive encephalopathy, and; neurodegenerative diseases.

- Though once thought to be nonspecific and benign, microbleeds are seen to be associated with various neurological disorders, particularly in neurodegenerative disorders, recurrent hemorrhage, strokes and anticoagulation therapy.
Personal information

Image contribution: Dr Paul Kalapos, Associate Professor, Department of Neurosurgery and Radiology, Penn State university
References


