


White Matter Microsusceptibility Changes in Patients With Hepatic Encephalopathy

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Radiology Case. 2011 Aug; 5(8):1-7 :: DOI: 10.3941/jrcr.v5i8.393

ABSTRACT

We report a new radiological finding in two patients with hepatic encephalopathy. A new susceptibility-weighted (SWI) magnetic resonance imaging sequence revealed multiple bilateral microsusceptibility changes in the corpus callosum and white matter, while the conventional T1 and T2 weighted images were unremarkable. We postulate that the etiology of the microsusceptibility changes may be related to hepatic coagulopathy and other factors, such as impaired cerebral blood flow and brain edema.

CASE REPORT

INTRODUCTION

Hepatic encephalopathy is a serious clinical complication of acute liver failure and end-stage liver disease, as well as an important prognostic factor in the course of the disease. Previously described cerebral abnormalities associated with hepatic encephalopathy include edema and impaired cerebral blood flow. Brain edema may result from hyperammonemia and can be detected by CT (1). MRI studies in patients with hepatic encephalopathy have also shown signs of edema in the white matter and cortico-spinal tracts (2). The resultant intracranial hypertension is the main cause of mortality in patients with fulminant hepatic failure. The pathophysiology of brain edema may be linked to increased uptake of ammonia by the brain, which leads to osmotic disturbance in the astrocytes (3) and also alterations in cerebral blood flow (CBF). Impaired CBF may result from defective metabolism and dilation of cerebral arterioles (4). Another common radiological finding in hepatic encephalopathy is hyperintense signals in the globus pallidi, putamen and internal capsules on MRI T1-weighted images and this may result from increase manganese and copper deposition (5). Hepatic coagulopathy, which relates to our study, is mainly due to decreased liver production of coagulation proteins. In advanced cases, this can result in consumption coagulopathy and disseminated intravascular coagulopathy, which can lead to petechial hemorrhages in various organs in the body.

In this case-report study we present a new MRI finding in two different patients with hepatic encephalopathy, one who recovered and one who didn't. The conventional T1 and T2 weighted images were unremarkable, but a new high resolution susceptibility-weighted (SWI) magnetic resonance imaging sequence revealed multiple microsusceptibility (1-2 mm) foci in the corpus callosum and white matter (Fig. 1,3). We are postulating that white matter microsusceptibility change may be due to either intravascular coagulopathy or microhemorrhages. We are also proposing that its etiology might be associated with hepatic coagulopathy, as well cellular changes in brain edema and alterations in cerebral blood flow.

CASE REPORT

CASE REPORT 1

A 72 y/o female was transferred to our institution after a fall due to severe lower extremity edema secondary to long-standing cryptogenic cirrhosis. In addition, she developed altered level of consciousness after aggressive dehydration. At the time of admission, the patient was lethargic and confused, with a GCS of 11 (eyes: 4, vision: 2, motor: 5). She had asterixis and 2+ peripheral edema. Four years ago, she had a history of esophageal variceal hemorrhage and TIPS placement.

The patient's laboratory results included increased PT (35.8 sec, normal 9-12 sec), PTT (49.0 sec, normal 20-36 sec), and INR (3.97, normal 0.9-1.2) increased D-dimer (3.5 ug/mL, normal < 0.2 ug/mL), decreased fibrinogen (100 mg/dL, normal 200-400 mg/dL) as well as thrombocytopenia (72 bil/L, normal 100-450 bil/L) and macrocytic anemia. She also had decreased total protein (5.5 g/dL, normal 6.0 - 8.5 g/dL) and albumin (2.7 g/dL, normal 3.2 -5.0 g/dL), and markedly increased total bilirubin (4.9 mg/dL, normal 0.1 - 1.2 mg/dl). Towards the end of her hospitalization, the coagulopathy worsened, with platelets in the 40-60 bil/L range. On the day of her death, her platelets dropped to 19 bil/L. Other terminal values included D-dimer of >20 ug/mL and fibrinogen of 80 mg/dL.

On day 2 of hospitalization, the patient had a MRI scan of the head, as well as an MRA and MRS. Her brain MRI showed T2 hyperintensities in the superficial portion of the white matter and in the corpus callosum. (Fig. 1, A-C, Fig.2, B) The SWI sequences showed multiple microsusceptibility changes in the corpus callosum and throughout the superficial portion of the white matter. (Fig. 1, D-E) The MRA study showed normal cerebral vessels. MR spectroscopy showed markedly decreased myo-Inositol peak and large lactate peak, likely due to increased glycolysis. These findings were consistent with hepatic encephalopathy (Fig 2, C).

The patient's mental status continued to deteriorate, despite aggressive medical management and two attempts to close the TIPS. On day 22 of admission, she could no longer follow commands. Two days later, she became comatose and unresponsive and expired on day 37 of hospitalization.

CASE REPORT 2

A 40 y/o woman presented to the emergency room with altered level of consciousness and right-sided facial droop, as well as multiple bruises secondary to a fall. On physical exam, the patient was sleepy, not oriented to time and had amnesia of recent events. She had lower extremity clonus and hyper-reflexia. Her abdominal exam was remarkable for right upper quadrant pain on palpation.

The patient's blood studies were positive for microcytic anemia (Hb: 8.3 g/dL, normal > 12 g/dL ; Hct: 27.4%, normal > 36%), increased liver enzymes (AST: 556 IU/L, normal 0-20 IU/L; ALT: 397 IU/L, normal 0-35 IU/L), decreased albumin (3.4g/dL, normal 3.2 -5.0 g/dL) and abnormal coagulation markers (PT: 17.3sec, PTT 38.8sec, INR 1.29, D-dimer: 3.8 ug/mL). Platelets were normal at 384 bil/L. A hepatitis panel revealed reactive HBsAg and negative HBsAb.

A CT of the head was ordered for cerebral hemorrhage, but it was normal. MRI of the head revealed multiple punctate foci of decreased intensity in the corpus callosum on the SWI sequence. (Fig. 3) The conventional T1- and T2-weighted images showed no abnormalities. An abdominal ultrasound study showed hepatomegaly and splenomegaly, enlargement of portal vein and diffuse gall bladder wall thickening consistent with portal hypertension.

The patient's level of consciousness and facial droop improved by day 5 of hospitalization and the patient was

discharged. Her clinical findings were believed to be due to a minor stroke secondary to hypovolemia combined with hepatic encephalopathy.

DISCUSSION

Hepatic encephalopathy has several brain findings. Some of them, like cerebral edema and hyperintense T1 signal in the globus pallidi have been extensively studied. In our first case report, the conventional MRI sequences showed T2 hyperintensities in the superficial portion of the white matter and in the corpus callosum, as has been previously shown. In the second case report, the T1- and T2-weighted images showed no abnormalities. However, a new MRI technique, SWI, detected microsusceptibility changes in corpus callosum and peripheral white matter.

SW imaging was originally developed to enhance the detection of deoxyhemoglobin within vessels. More recently, this technique has been used for better detection of extravascular deoxyhemoglobin and methemoglobin present in areas of hemorrhage in patients with diffuse axonal injury (6). It is a relatively new technique and is the only technique that images phase changes. The SW images are created by amplifying the phase images by a factor of four and then combining them with appropriate magnitude images. Therefore, the SWI technique is approximately five times more sensitive to susceptibility changes in the brain compared to conventional gradient echo. Please refer to the articles by Tong et al. and Reichenbach et al., which have more detailed description of the technique (6, 7).

The etiology of these white matter microsusceptibility changes is currently unknown, but may be associated with the accompanying hepatic coagulopathy. Both patients presented in this study had coagulopathy and DIC. Previous clinical studies in patients with DIC have described similar MRI findings of white matter microhemorrhages. Lesions consistent with multiple cerebral infarctions have been found in the paraventricular white matter in a patient with blue-rubber-bleb-nevus syndrome and chronic DIC (8) and in the pons region in a patient with DIC due to obstetric complication (9). It is likely then that the white matter hemorrhages described in our study were produced through a similar process generated by the systemic coagulopathy.

Our two cases and other studies show lesions in specific areas of the brain, mainly the white matter and sometimes the basal ganglia and pons. These are the areas supplied by small perforating blood vessels and are often associated with hypertensive disease or other angiopathies. In hepatic encephalopathy, these small cerebral blood vessels may be preferentially affected. Susceptibility changes were especially prominent in the corpus callosum, which may be due to the fact that the callosal white matter fibers are closely packed together, so that the penetrating vessels have even smaller diameters and less compliance, therefore may be at increased risk of developing intravascular thrombi or microhemorrhages. There is also alteration in cerebral blood flow, which may also

be responsible in part for brain hyperemia, resulting in cerebral edema. The lack of autoregulation of CBF in liver failure patients is believed to be due to brain hyperammonemia, in combination with dilation of cerebral arterioles and cerebral vasoparalysis. (4) These changes in microvasculature could also be the reason that small arterioles are more susceptible to injury and create the hypointensities which can be detected by SWI.

TEACHING POINT

This article describes a new finding of white matter and corpus callosum microsusceptibility changes by using a new MRI technique, susceptibility-weighted imaging (SWI) in two patients with hepatic encephalopathy. The etiology of these lesions is probably related to the presence of hepatic coagulopathy, but other factors, such as impaired cerebral blood flow and brain edema may also play a role.

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FIGURES

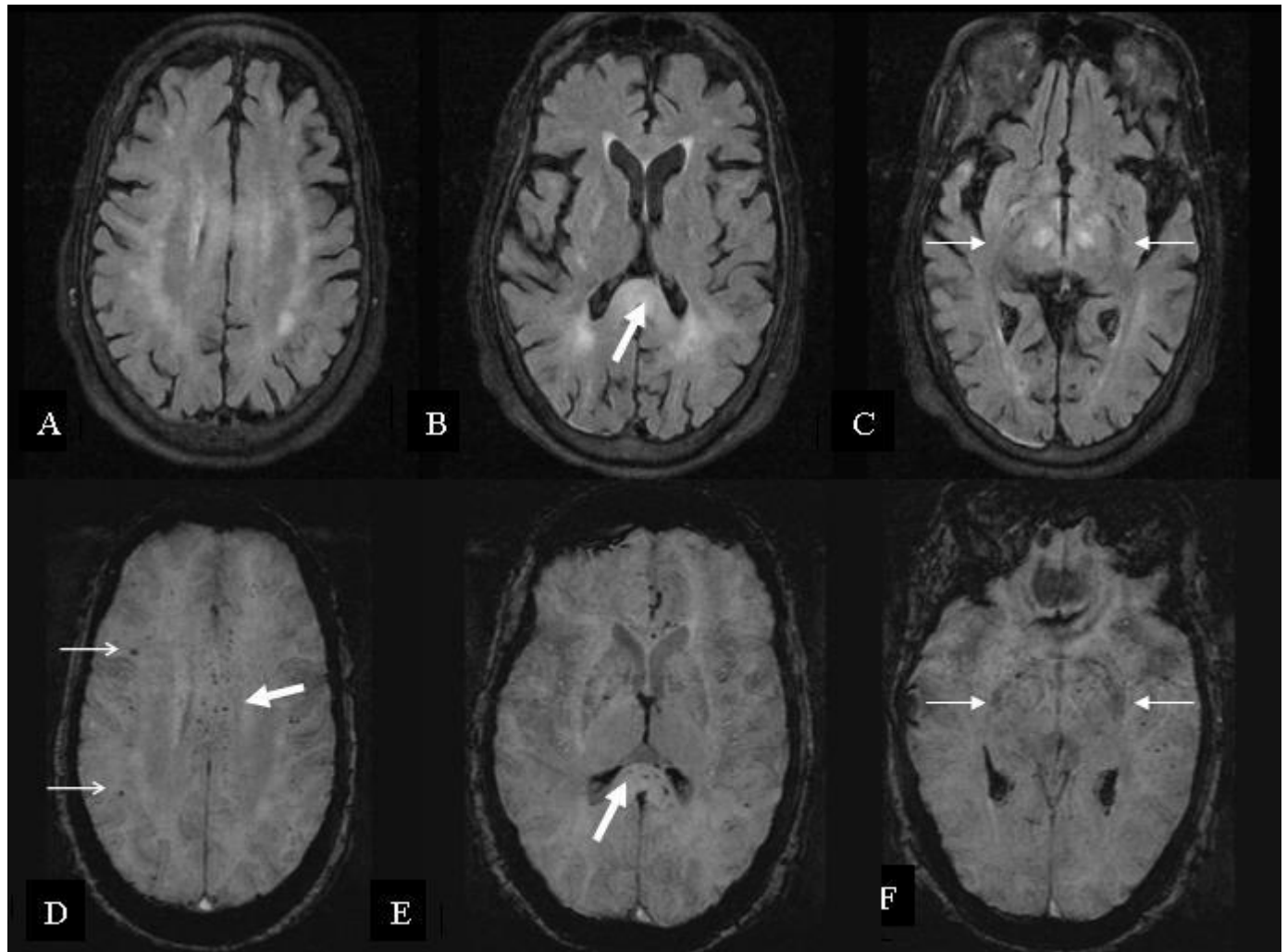


Figure 1. Case 1: 72 year-old female with end-stage liver disease and hepatic encephalopathy. Comparison of FLAIR (1.5 Tesla, TR: 9999, TE: 110) and SWI (1.5 Tesla, TR: 57, TE: 40) sequences. A, The FLAIR sequence shows diffuse edema in the peripheral portion of the white matter and in the corpus callosum. B, on a lower slice through the ventricles, the FLAIR sequence shows edema in the splenium of the corpus callosum (arrow). C, FLAIR shows hyperintensity in the red nuclei (arrows). D, SWI, which corresponds to A and shows microsusceptibility changes in the corpus callosum (thick arrows) and in the peripheral white matter (thin arrows). E, SWI corresponds to B and shows multiple microsusceptibility changes in the splenium of corpus callosum (arrow). F, SWI corresponds to C and demonstrates no microsusceptibility changes in the red nuclei (arrows).

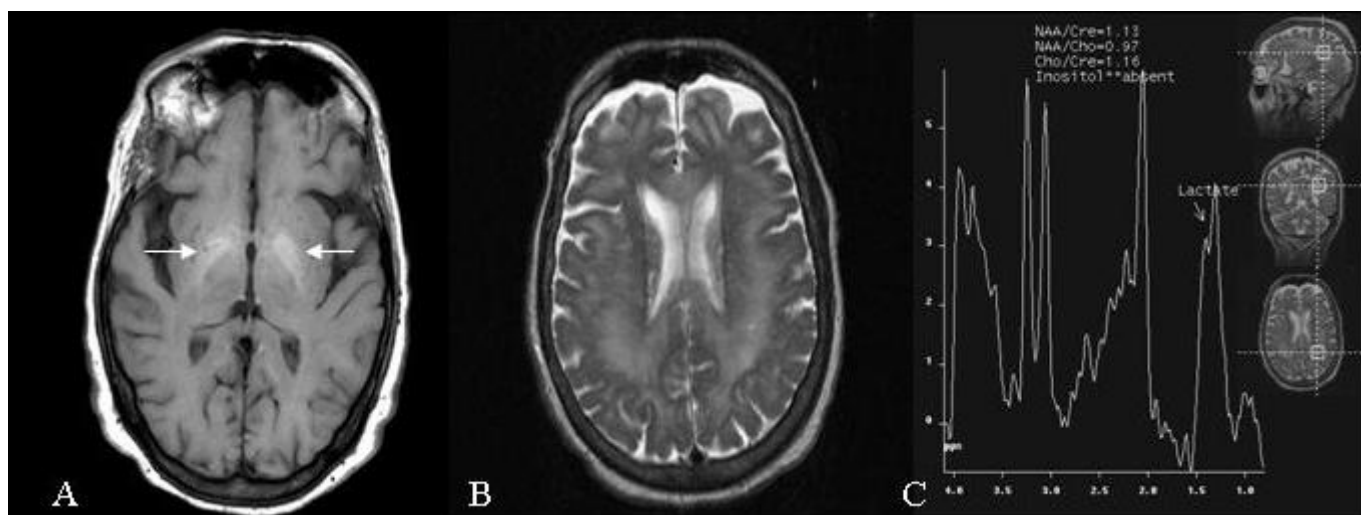


Figure 2. Case 1: 72 year-old female with end-stage liver disease and hepatic encephalopathy. A, axial T1 weighted image (1.5 Tesla, TR: 770, TE: 14) shows increased signal in the basal ganglia bilaterally (arrows). B, axial T2 weighted images (1.5 Tesla, TR: 4000, TE: 120) show increased signal in the peripheral white matter corresponding to Fig.1, FLAIR images A and B. C, MR spectroscopy in the left occipital white matter corresponding to image B shows markedly decreased myo-Inositol peak and large lactate peak, likely due to increased glycolysis, consistent with hepatic encephalopathy.

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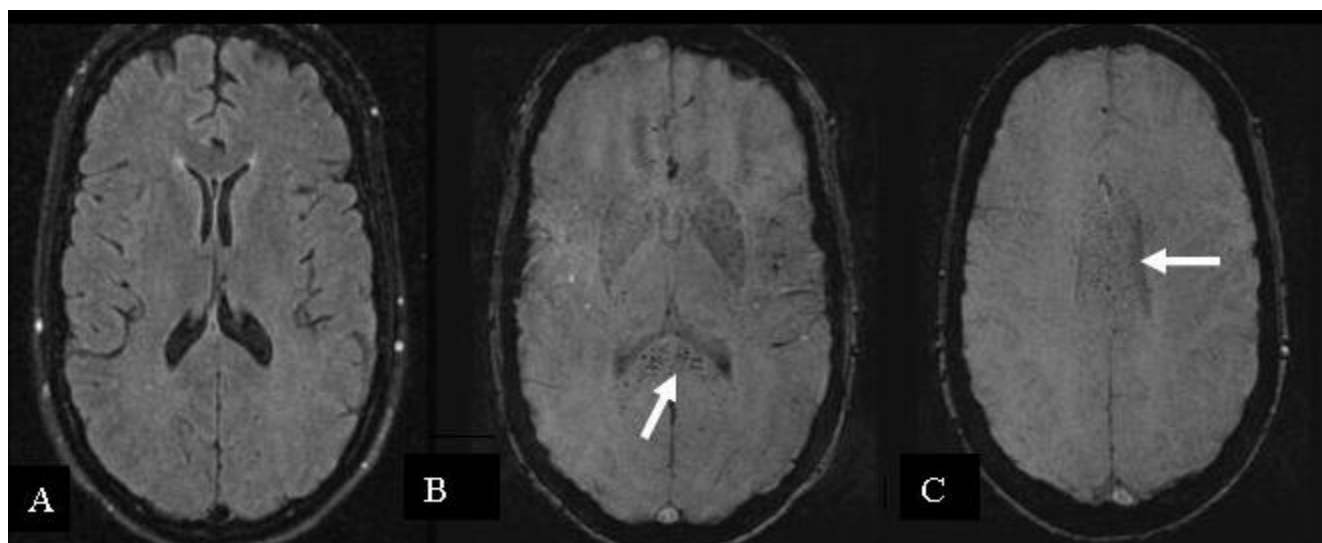


Figure 3. Case 2: 40 year-old female with cirrhosis and likely hepatic encephalopathy. Comparison of FLAIR (1.5 Tesla, TR: 9999, TE: 110) and SWI (1.5 Tesla, TR: 57, TE: 40) sequences. A, A FLAIR image shows normal findings. B, SWI, which corresponds to A, shows multiple microsusceptibility changes in the splenium of corpus callosum (arrow). C, SWI close to the vertex shows microsusceptibility changes in the body of the corpus callosum (arrow).

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Etiology	Develops in the setting of fulminant hepatic failure which results in brain edema, attributed to increased permeability of the blood-brain barrier, impaired osmoregulation within the brain and increased cerebral blood flow. It is also believed to be a disorder of astrocyte function, which play a role in the blood-brain barrier and detoxification of chemicals, including ammonia. Neurotoxic substances, such as ammonia and manganese may also play a role in causing astrocyte dysfunction. The brain edema may be severe enough to result in increased intracranial pressure.
Incidence	It occurs in nearly 70% of patients with cirrhosis. Symptoms may be debilitating in a significant number of patients and are observed in 24-53% of patients who undergo portosystemic shunt surgery. Approximately 30% of patients dying of end-stage liver disease experience significant encephalopathy, approaching coma.
Gender ratio	No gender predilection, increased incidence of alcoholic hepatitis/liver failure in women.
Age predilection	No age predilection, most common in 20-60 y/o.
Risk factors	Main risk factors are cirrhosis, fulminant hepatic failure, portal hypertension, portosystemic shunting. Precipitating factors include renal failure, gastrointestinal bleeding, infection, constipation, medications (opiates, benzodiazepines, antidepressants and antipsychotic agents), diuretic therapy, high protein diet.
Treatment	Low-protein diet, cathartics (lactulose, lactitol), antibiotics (neomycin and other antibiotics, such as metronidazole, oral vancomycin, paromomycin, rifaximid, and oral quinolones) to decrease bacterial concentration in the colon, zinc supplements, sodium benzoate, sodium phenylbutyrate, sodium phenylacetate to improve ammonia extraction.
Prognosis	Variable, depending on the degree of liver failure; 80% of patients who proceed to coma die.
Imaging findings	CT- diffuse cerebral edema; MRI: increased T1W and decreased T2W in basal ganglia and midbrain; acute: high T2 signal in the cerebral cortex; chronic: generalized cerebral and cerebellar atrophy; MRS: decreased myoinositol/creatine, decreased choline/creatine, increased glutamine/creatine.

Table 1: Summary table for hepatic encephalopathy

Differential	CT	MRI-T1	MRI-T2	DWI	Contrast
Hepatic encephalopathy	Diffuse cerebral edema	Bright signal basal ganglia; cerebral and cerebellar atrophy	Acute: increased signal cerebral cortex	Acute: increased cortical signal	None.
Wilson disease	Widening of the frontal horns	Bright signal basal ganglia; cerebral and cerebellar atrophy	Mixed intensity in the basal ganglia and thalami.	Increased or decreased diffusion in basal ganglia.	None.
Hyperalimantation	None	Bright signal globus pallidus, substantia nigra.	None	None	None
Hyperglycemia	None	Increased signal bilateral basal ganglia	None	None	None
Hypoxic-ischemic injury	Low density basal ganglia and cortex.	Bright signal basal ganglia and cortex.	Increased signal basal ganglia and cortex.	Increased signal if acute	Positive or negative
Neurofibromatosis type I	Sphenoid wing dysplasia, plexiform lesions.	Bright foci in basal ganglia, thalami and white matter	Bright foci in basal ganglia, thalami and white matter	Increased ADC in bright foci.	None.
Basal ganglia calcifications	High density basal ganglia	Increased signal basal ganglia	None	None	None.

Table 2: Differential diagnoses for hepatic encephalopathy

ABBREVIATIONS

ALT - alanine transaminase
 AST - aspartate transaminase
 CBF - cerebral blood flow
 GCS- Glasgow comma scale
 MRA - magnetic resonance angiogram
 MRI - magnetic resonance imaging
 MRS - magnetic resonance spectroscopy
 NAA - N-acetyl aspartate
 SWI - susceptibility-weighted imaging.

KEYWORDS

neuroradiology; hepatic encephalopathy; brain MRI; susceptibility-weighted imaging

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