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Acquired Hepatocerebral Degeneration: MR and Pathologic Findings

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Summary: Acquired (non-Wilsonian) hepatocerebral degeneration (AHD) is a rare irreversible neurologic syndrome that occurs in patients with chronic liver disease associated with multiple metabolic insults. The pathophysiology and the locations of the cerebral injuries are incompletely understood. We describe a patient with fatal hepatic cirrhosis and AHD in whom MR images showed abnormalities in the brachium pontis bilaterally. Neuropathologic evaluation disclosed multiple regions of subcortical spongiform white matter changes.

Depending on their severity and chronicity, liver diseases have variable neurologic manifestations. Encephalopathy (hepatic encephalopathy) is most common, but, rarely, repeated episodes of hepatic encephalopathy lead to a progressive, generally irreversible extrapyramidal syndrome termed acquired hepatocerebral degeneration (AHD). Neurologic signs of AHD include those seen in hepatic encephalopathy, and may also include abnormal movements, dysarthria, rigidity, intention tremor, ataxia, and impairment of intellectual functions (1).

Pathologic examination of hepatic encephalopathy reveals diffuse proliferation of Alzheimer type-II cells and spongiform changes in the gray matter. Some patients with AHD also have cortical gliosis, laminar neuronal necrosis, atrophy of lenticular nuclei, and polymicrocavitation of the corticomedullary junction, striatum, and cerebellar white matter. The extent and degree of these pathologic changes do not always correspond well with the clinical course (1, 2).

Magnetic resonance (MR) imaging of the brain in patients with chronic hepatic failure stemming from a variety of causes reveals hyperintense signal on T1-weighted sequences, primarily in the lenticular nuclei (3–6). The cause of this signal change is unknown. Experience with MR imaging in AHD is much more limited, and pathologic correlation is generally not available. We describe a patient with AHD associated with striking MR findings, predominantly in the deep cerebellar white matter, and discuss these findings in light of their associated histopathologic features.

Case Report

A 65-year-old man with alcoholic hepatic cirrhosis, diagnosed 15 months earlier, presented with ascites and liver failure. An infectious pathogenesis for the cirrhosis was not identified. A liver biopsy specimen revealed micronodular cirrhosis and increased iron stores, but the quantity of iron was less than is typically present with hemochromatosis. Laboratory studies at the time of our examination revealed normal electrolytes. The hematocrit was 28.5%; white blood cell count, 8.5; platelets, 29 000 (normal, 150 000 to 450 000); prothrombin time, 20.2 seconds (normal, 11.2 to 14.4 seconds); total bilirubin was 6.9 mg/dL (normal, 0.3 to 1.5 mg/dL); aspartate aminotransferase, 216 IU/L (normal, <40); alanine aminotransferase, 178 IU/L (normal, <40); serum ammonia, 32 μmol/L (normal, 9 to 33 μmol/L); γ-glutamyltransferase and ferroxidase were normal. An electroencephalogram revealed mild generalized slowing of the background rhythm. Imaging studies also revealed portal vein thrombosis. Aside from a mild decline in memory, the patient's neurologic status was normal until 2 months before the present examination, when he contracted hepatic encephalopathy precipitated by subacute bacterial peritonitis. Serum ammonia was approximately 80 to 100 μmol/L (normal, 9 to 33 μmol). With treatment of the infection, the patient became alert and attentive, with intact memory and language function. Subsequently, there were periodic episodes of encephalopathy that accompanied metabolic disturbances, such as hyponatremia and bleeding from esophageal varices. Thereafter, and unassociated with encephalopathy, abnormal movements appeared and progressed over the next 2 months, including truncal ataxia, facial grimacing, and choreiform tongue movements with tongue biting. Speech was hypophonic and severely dysarthric, and eye movements were saccadic. There was a mild increase in axial tone in addition to a mild postural tremor. Asterixis appeared occasionally. Dysmetria was not noted. The movement disturbances also worsened during periods of infection or electrolyte imbalance.

MR imaging was performed on a 1.5-T unit a week before the patient died (Fig 1A–C). Punctate regions of mildly increased signal were identified on T2-weighted images in the region of the putamen and globus pallidus bilaterally. No abnormal T1 signal was evident in the basal ganglia.

Owing to the patient's portal vein thrombosis and medical condition, he was not a transplant candidate, and he died of liver failure and intervening sepsis. Postmortem examination revealed an adult brain weighing 1380 g with no external abnormalities. The cross-sectional image of the gross specimen is shown in Figure 1D; histopathologic findings are shown in Figure 1E. Bielschowsky and Luxol fast blue stains showed relative axonal preservation as compared with the degree of myelinolysis. Similar microscopic lesions were found in the internal capsule, the white matter bundles connecting the globus pallidus and putamen, and the cerebral peduncles at the level of the midbrain. No myelinolysis was present in the cere-

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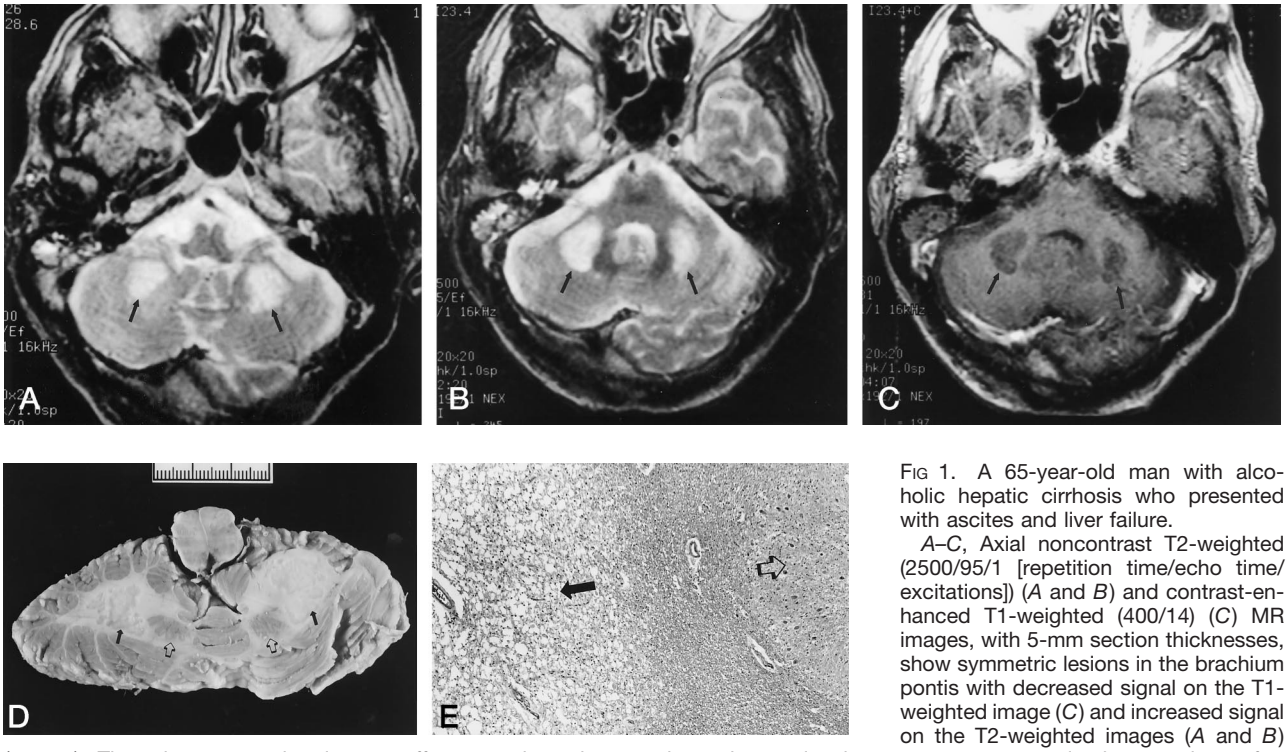

FIG 1. A 65-year-old man with alcoholic hepatic cirrhosis who presented with ascites and liver failure.

A–C, Axial noncontrast T2-weighted (2500/95/1 [repetition time/echo time/excitations]) (*A* and *B*) and contrast-enhanced T1-weighted (400/14) (*C*) MR images, with 5-mm section thicknesses, show symmetric lesions in the brachium pontis with decreased signal on the T1-weighted image (*C*) and increased signal on the T2-weighted images (*A* and *B*) (*arrows*). There is no associated mass effect or volume loss, and no abnormal enhancement was seen in these regions after administration of contrast material (*C*).

D, Axial anatomic section at the level of the dentate nuclei of the cerebellum (*open arrows*) shows the areas of friable grayish discoloration with discrete lobulated margins (*solid arrows*) in the deep cerebellar white matter. These did not involve the dentate nuclei or the cerebellar cortex. There was no evidence of hemorrhage or cyst formation associated with these lesions.

E, Histologic section shows the lateral margin of dentate nucleus (*open arrow*), which is separated from the area of spongiform white matter degeneration (*solid arrow*) by a thin rim of normal-appearing white matter (hematoxylin-eosin, original magnification ×250).

bral white matter, pons, medulla, or lateral geniculate body. The only notable finding at microscopic examination was Alzheimer type-II astrocytosis throughout the cerebral cortex and deep nuclei and in the dentate nuclei of the cerebellum.

Discussion

Our patient had many of the clinical features of hyperkinetic extrapyramidal syndrome typically associated with AHD, including limb tremor, chorea of the tongue, ataxia, and dysarthria. The hyperkinetic movement disorders with chorea were thought to be due to a disturbance of the striatal-lateral globus pallidus pathway; in addition, the truncal ataxia suggested a midline cerebellar disturbance. The speech disorder was nonspecific in nature but was compatible with either cerebellar or basal ganglia dysfunction. On examination, we did not note features of brain stem or pyramidal system disease. Although the clinical features were consistent with AHD, the course was somewhat rapid. The portal vein occlusion that led to complete portosystemic shunting of nondetoxified blood may have predisposed the patient to rapid clinical deterioration. Portosystemic shunting has been noted in other patients with AHD (6).

MR imaging findings were consistent with lesions in the lenticular nuclei and the midline cerebellum, thus supporting the diagnosis of AHD; however, there were none of the hyperintense T1 signal changes often seen in the lenticular nuclei in patients with advanced liver disease. Increased signal on T1-weighted images has also been reported in the pituitary gland, quadrigeminal plate, caudate nucleus, subthalamic region, and red nucleus of other patients with liver disease (3–6). Such MR findings are of uncertain origin, but they may be due to an overabundance of mitochondria, rough endoplasmic reticulum, and vacuoles containing lipofuscin pigment in the Alzheimer type-II cells, or they may stem from unidentified paramagnetic substances (6). We did note, however, mildly increased signal in the lenticular nuclei caused by T2 prolongation. In our patient, well-demarcated, relatively symmetrically increased signal caused by T2 prolongation in the brachium pontis bilaterally was the most striking finding, and one that has been noted only rarely in patients with hepatocerebral disturbances. In their review of 42 adults with severe hepatic diseases, Brunberg et al (3) did not find MR signal abnormalities in the cerebellum in any patient. In two patients with severe hepatocerebral diseases (one with AHD and one with Wilson disease), similar MR signal changes were noted in the deep cerebellar hemispheres, but the abnormal signal foci were thought to be in the dentate nuclei (7, 8). A review of the published images from these patients suggests that the signal changes may actually lie outside the dentate nuclei and within the brachium pontis, as they did in our patient. Hitoshi et al (5) attributed the signal changes identified in their patient with portosystemic shunting to lesions of the brachium pontis; however, pathologic confirmation was not available.

In our patient, the increased T2 signal in the brachium pontis correlated with histologic spongiform (myelinolytic) white matter changes. This hyperintense signal was probably due to the presumed increase in extracellular water in these lesions. As anticipated from the MR images, there was no involvement of the dentate nuclei. The large myelinolytic areas in the cerebellum did not reveal any cellular reaction or foamy macrophages to suggest an ischemic or infectious process. The increased signal caused by T2 prolongation in the globus pallidus and putamen correlates well with myelinolysis of small white matter bundles between the putamen and globus pallidus. In AHD, involvement of the white matter manifests as polymicrocavitation and myelinolysis adjacent to the gray mat-

ter. Thus, the deep cerebellar white matter involvement is unusual as compared with the more common white matter damage in the cerebellar folia. The finding of diffuse type-II astrocytosis supported the diagnosis of chronic liver disease. There were none of the necrotic or gliotic areas in the gray matter seen in AHD, which may have been due to the rapid demise of the patient after the clinical symptoms evolved.

The cause of these white matter changes is uncertain. Toxic-metabolic processes related to the liver disease are the most likely suspects. Osmotic changes associated with electrolyte disorders in patients with liver disease could also affect white matter. The white matter changes noted in our patient and in several others with hepatocerebral diseases are not radiographically or pathologically distinguishable from those seen in central pontine and extrapontine myelinolysis. The distribution of lesions in pontine and extrapontine myelinolysis varies greatly. Cerebral and cerebellar white matter, deep nuclei, thalami, and mammillary bodies are variably affected in addition to the pontine involvement. However, in extrapontine myelinolysis, cerebellar deep white matter involvement is very unusual, since the commonly affected area is the cerebellar folia (9). In addition, the most frequently involved extrapontine site is the lateral geniculate body, which was unaffected in our patient. In a dog model of myelinolysis following rapid correction of hyponatremia, the cerebellar white matter was especially affected (10). Interestingly, Weissman and Weissman (11) reported a patient with abnormal signal in both middle cerebellar peduncles and not in the pons following rapid correction of hyponatremia associated with transurethral prostate resection and bladder irrigation. Other investigators (9) have also noted extrapontine myelinolysis in the absence of pontine involvement.

Determining the causes of these white matter changes is further complicated by the fact that central pontine and extrapontine myelinolysis are common in patients with chronic alcoholism, in whom the frequency of hyponatremia and liver disease is relatively high. Thus, white matter changes in the middle cerebellar peduncles are associated with AHD, but they are nonspecific and may be part of a spectrum of radiological and pathologic changes that occur in patients with advanced liver disease (acquired or inherited) and extrapontine myelinolysis, perhaps because of similar, as yet undefined, pathophysiological mechanisms.

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