

Chronic Acquired Hepatic Failure: MR Imaging of the Brain at 1.5 T

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The results of MR imaging of the brain at 1.5 T in 42 adults with non-Wilsonian chronic hepatic failure are reported. T1-weighted images demonstrated increased signal in the globus pallidus in 30 patients and in the putamen in 21, while T2-weighted images demonstrated no corresponding alteration in signal intensity. Symmetric low intensity in the central portion of the globus pallidus on spin-density and T2-weighted images in two patients correlated with regions of calcification on CT scans. Increased intensity on T1-weighted images also occurred in the mesencephalon surrounding the red nucleus (17/42) and in the quadrigeminal plate (4/42). Three patients demonstrated increased intensity in the pons on T2-weighted images unassociated with clinical brainstem dysfunction. Increased intensity on T1-weighted images was seen in the anterior pituitary in 28 of 35 patients. Alterations in signal intensity were not demonstrated in the cerebral cortex or cerebellum. MR findings did not correlate with laboratory indices of hepatic or thyroid function, with histologic liver diagnosis, or with neurologic status at the time of MR evaluation.

Increased signal intensity in the basal ganglia, pituitary gland, and mesencephalon surrounding the red nuclei is characteristic of chronic hepatocellular dysfunction. Deposition of an as yet unidentified paramagnetic substance or altered intracellular water relaxation associated with the proliferation of astrocyte cytoplasmic organelles is postulated as the likely mechanism for this previously undescribed MR manifestation of chronic acquired hepatic failure.

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Histologic alteration occurring in the CNS of patients with chronic non-Wilsonian hepatocellular dysfunction has been well described [1-3]. Characteristic findings include the appearance of type II Alzheimer astrocytes within gray matter of the cortex and basal ganglia, the occurrence of nerve cell degeneration or loss, and the presence of laminar or pseudolaminar necrosis of the cerebral cortex with polymicrocavitation at the gray-white junction.

Neuroradiologic alterations occurring in association with chronic hepatic failure have been less well characterized. Early in the course of hepatic dysfunction, at a time when the presence of clinical hepatic encephalopathy may be detectable only on the basis of formal neuropsychological testing, CT imaging may demonstrate cortical atrophy, cerebral edema, or be entirely normal [4]. Similar CT changes occurring in patients with chronic liver failure due to processes other than alcohol toxicity have been described [5, 6]. MR findings in the brain associated with chronic hepatic failure, other than Wilson disease, have only briefly been reported [7, 8]. Our purpose is to describe the results of MR imaging of the brain in a prospective series of patients with chronic, severe non-Wilsonian hepatic failure and to correlate these findings with the etiology of the hepatic failure and with laboratory indices of hepatic function at the time of imaging. We also correlate these MR alterations with anatomic regions of known neuropathologic alteration occurring with chronic non-Wilsonian hepatocellular dysfunction.

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Subjects and Methods

Our study population consisted of 42 patients undergoing evaluation (including MR imaging of the brain) preparatory to possible orthotopic liver transplantation. Laboratory studies obtained within 2 weeks of the time of MR imaging were available for each of the 42 patients and included determination of serum direct bilirubin (42/42 patients), total bilirubin (41/42), alkaline phosphatase (41/42), GCTP (39/42), SGPT (39/42), SGOT (41/42), NH_3 (41/42), phosphorus (33/42), magnesium (23/42), serum albumin (31/42), total protein (26/42), ceruloplasmin (34/42), iron (36/42), total iron binding capacity (36/42), ferritin (37/42), zinc (29/42), PT (40/42), PTT (40/42), T4 (36/42), T3 resin uptake (34/42), and TSH (30/42). A history and physical examination documenting the presence or absence of encephalopathy at the time of MR imaging were available in all patients. The presence or absence of indicators of portacaval shunting—including splenomegaly, ascites, or endoscopic evidence of varices—was recorded in 38 patients.

CT studies of the abdomen were available in all 42 patients. Data utilized for this study included the presence or absence of ascites or varices. Liver volume calculated from contiguous axial CT images through the liver was available in 36/42 patients.

Spin-echo MR images of the brain at 1.5 T utilized T1-weighted images at 600/20 (TR/TE) and long TR sequences at 2500/25, 100. Images were 5 mm thick with a 1-mm gap or were contiguous. The matrix was 128×256 or 256×256 , with two excitations and a 20-cm field of view in coronal and axial planes. MR images were graded perceptually, with scoring of alterations in intensity and volume of anatomic regions, which included cerebral cortex, globus pallidus, putamen, caudate, thalamus, mesencephalon, pituitary gland, pons, cerebellum, and lateral and third ventricles. The size of subarachnoid spaces over the cerebral and cerebellar convexities was also scored. In 35/42 patients, coronal T1-weighted images were obtained through the anterior lobe of the pituitary with slice placement satisfactory for characterizing signal intensity without partial volume effect from the neurohypophysis. Alterations in MR signal were graded 0, +1, or +2, respectively, for normal intensity or mildly or markedly increased intensity. Alterations in volume were graded 0, -1, or -2, respectively, for normal volume or mild or marked volume loss. CT studies of the brain obtained within 4 weeks of MR imaging were available for correlation in 38 patients.

Statistical evaluation was done to correlate the laboratory data, etiologic diagnosis, liver volume, and MR findings. A two-way cross tabulation of data was completed by using the Fisher exact test for data sets divided into four groups consisting of normal and abnormal imaging and laboratory data. A chi square test was used to compare normal vs abnormal imaging data with laboratory data, etiologic diagnoses, or liver volume when grouping into more than two fields was required.

Results

T1-weighted images in 30/42 patients demonstrated symmetrically increased signal intensity throughout the globus pallidus, which was mild (24/42) or marked (6/42) in severity (Figs. 1–4). Signal intensity in the putamen was mildly (17/42) or markedly (4/42) increased and was bilaterally symmetric (Figs. 1, 3, 4). Increased signal in the putamen only occurred when there was increased signal intensity in the globus pallidus. No patient with increased signal in the globus pallidus or putamen on T1-weighted images demonstrated altered intensity in a similar distribution on T2-weighted sequences. In two patients focal regions of low intensity in the globus pallidus

on T1- and on T2-weighted images correlated with calcification shown on CT scans (Fig. 2).

T1-weighted images demonstrated increased signal intensity surrounding the red nuclei in 17/42 patients (Figs. 1 and 3). This pattern, with one exception, occurred when there was increased intensity in both the globus pallidus and putamen. T1-weighted images demonstrated increased intensity in the quadrigeminal plate in four patients (Fig. 3). One patient who had mildly increased intensity in the caudate nuclei (Fig. 4) also had markedly increased signal intensity in the globus pallidus, putamen, and mesencephalon surrounding the red nuclei. This patient was one of three who had increased signal intensity on long TR short TE sequences in the globus pallidus, putamen, and caudate (Fig. 4).

Increased intensity of the anterior pituitary was seen in 23/35 patients (Fig. 1). In 6/28 this alteration was unassociated with increased signal intensity on T1-weighted images in other scored anatomic regions. Thyroid function was normal in all 35 of these patients.

Cortical volume loss manifested by prominence of cerebral sulci was seen in 19/42 patients involving frontal (18/19), parietal (14/19), temporal (6/19), and occipital (3/19) lobes. Severe volume loss was demonstrated only in frontal (8/18) and parietal lobes (2/14). Cerebellar volume loss occurred in 9/42 patients, with five of the nine occurring in the eight patients with Laennec cirrhosis. In no patient was altered signal intensity demonstrated in the cerebral or cerebellar cortex. There was prominence in size of the lateral ventricles in 8/42 (3/8 severe), of the third ventricle in 5/42 (2/5 severe) and of the fourth ventricle in 1/42 patients. Increased intensity in the central pons was seen on T2-weighted images in 3/42 patients. Three had increased signal in the globus pallidus and two in the putamen on T1-weighted images. None had symptoms of brainstem dysfunction.

The cause of chronic hepatic failure was determined in all patients (Table 1). Increased intensity on T1-weighted images occurred with cholestatic disease (12/13), chronic active hepatitis (13/21), and Laennec cirrhosis (5/8). The difference was not statistically significant. Laboratory indices of hepatic function and the presence or absence of varices or ascites did not correlate at a statistically significant level with the occurrence of regions of altered signal intensity. Altered liver volume did not statistically correlate with altered intensity in the basal ganglia on T1-weighted images when the sample of 36 patients was examined simultaneously. All eight patients with liver volumes less than 1000 cm^3 , however, had increased signal in the globus pallidus on T1-weighted images and six had increased intensity in the putamen.

Discussion

Hepatic encephalopathy may initially be subclinical, may be manifested as altered mental status, or may present as a combination of tremor, asterixis, incoordination, rigidity, myoclonus, seizures, or incontinence [9]. These findings occur with hepatocellular insufficiency of any cause, and may relate to either hepatocellular disease or to portasystemic shunting where portal blood bypasses the hepatocyte. In hepatic encephalopathy, ingested toxic agents and substances pro-

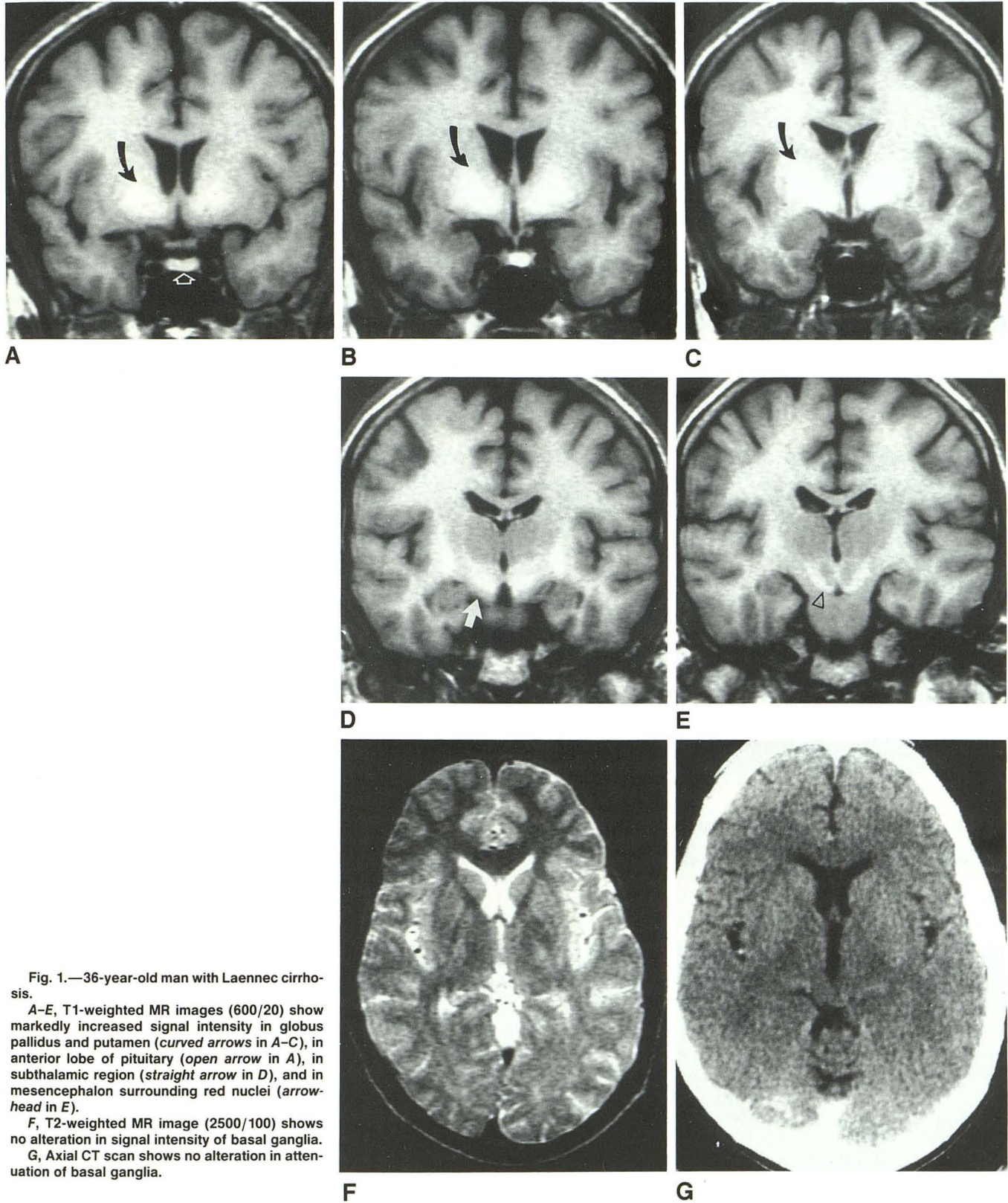


Fig. 1.—36-year-old man with Laennec cirrhosis.
A-E, T1-weighted MR images (600/20) show markedly increased signal intensity in globus pallidus and putamen (*curved arrows in A-C*), in anterior lobe of pituitary (*open arrow in A*), in subthalamic region (*straight arrow in D*), and in mesencephalon surrounding red nuclei (*arrowhead in E*).
F, T2-weighted MR image (2500/100) shows no alteration in signal intensity of basal ganglia.
G, Axial CT scan shows no alteration in attenuation of basal ganglia.

duced by intestinal bacteria enter the systemic circulation to alter cerebral metabolism, neuron membrane function, or neurotransmitter concentration. Major factors responsible for the development of hepatic encephalopathy appear to be

elevated levels of ammonia, gamma-aminobutyric acid, and aromatic amino acids [9, 10].

Neuropathologic findings in chronic non-Wilsonian liver failure are characteristic but not specific. Their severity varies

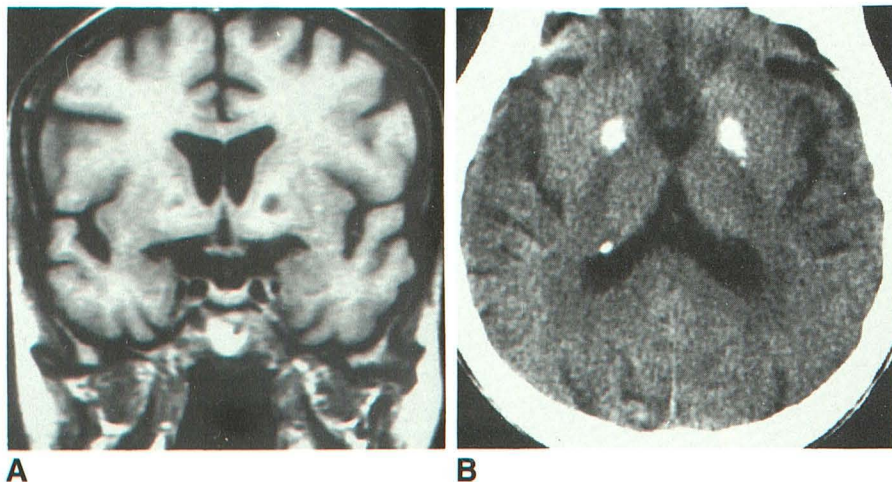


Fig. 2.—65-year-old man with primary biliary cirrhosis.

A, T1-weighted MR image (600/20) shows focal regions of low signal intensity in globus pallidus surrounded by a more diffuse slightly increased signal intensity.

B, CT scan shows foci of dense calcification in globus pallidus correlating with regions of low intensity on the MR image.

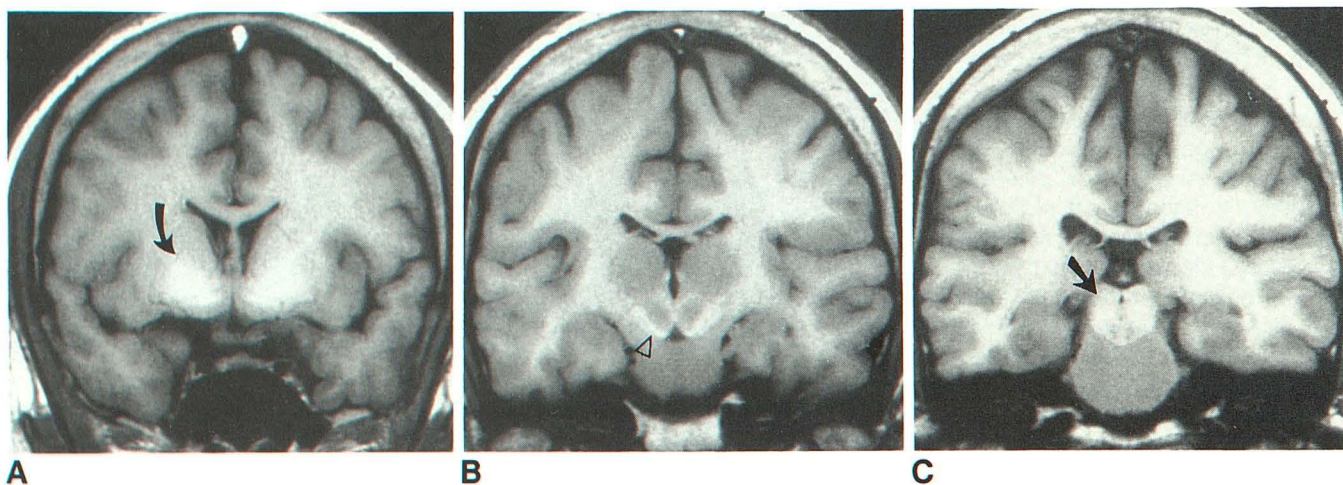


Fig. 3.—27-year-old man with chronic hepatitis.

A-C, T1-weighted MR images (600/20) show markedly increased signal intensity in globus pallidus and putamen (curved arrow in A), in mesencephalon surrounding red nuclei (arrowhead in B), and in quadrigeminal plate (straight arrow in C).

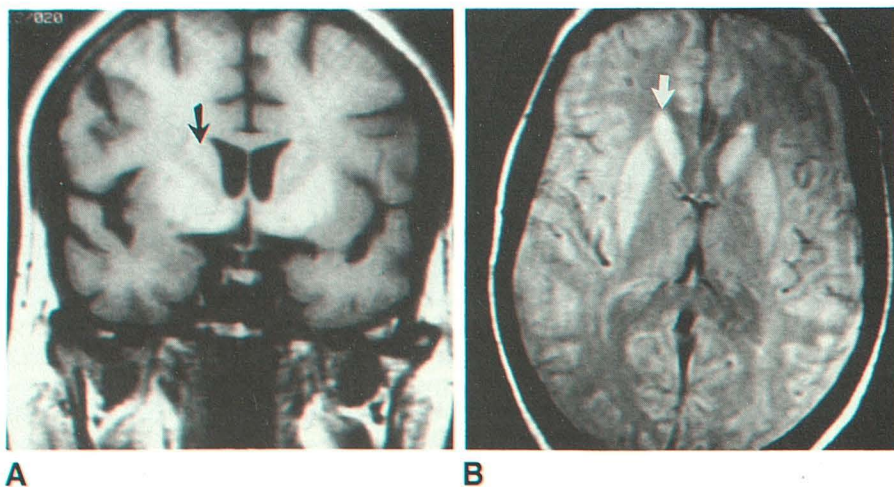


Fig. 4.—53-year-old man with postoperative biliary obstruction.

A, T1-weighted MR image (600/20) shows increased signal intensity in caudate (arrow), globus pallidus, and putamen.

B, At 3000/25 there is increased signal intensity in the heads of the caudate nuclei (arrow) and in putamen. T2-weighted images were normal.

TABLE 1: Causes of Hepatic Failure in 42 Patients

Finding (No. of Cases)
Laennec cirrhosis (8)
Cholestatic liver failure (13)
Sclerosing cholangitis (7)
Primary biliary cirrhosis (5)
Congenital biliary atresia (1)
Hepatocellular dysfunction (21)
Chronic active hepatitis (18)
Hemochromatosis (1)
Cryptogenic (1)
Alpha-1 antitrypsin deficiency (1)

with the duration and extent of hepatocyte dysfunction or portasystemic shunting [1-3], but not with the cause. With chronic hepatic failure the predominant finding is the conversion of protoplasmic astrocytes into Alzheimer II cells. This most likely relates to the astrocyte's function as the site of cerebral NH₃ metabolism to glutamate and glutamine [10, 11]. Alzheimer II cells have large pale nuclei with prominent nucleoli and marginated chromatin. The cytoplasm, relative to that of the astrocyte from which it is derived, is markedly distended by membrane-bound vacuoles, by a three- to fourfold increase in mitochondria, and by an increase in rough endoplasmic reticulum and lysosomes. Alzheimer II cells are found in the lenticular nuclei, caudate nuclei, thalamus, substantia nigra, red nucleus, dentate nuclei, pontine nuclei, and deep layers of the cerebral cortex [1-3].

In our series of 42 patients with chronic hepatic failure, T1-weighted images demonstrated symmetrically increased intensity in the globus pallidus in 30, in the putamen in 21, and in the mesencephalon surrounding the red nucleus in 17. Increased intensity was seen in the anterior pituitary in 28 of 35. In no patient was intensity alteration demonstrated in the cerebral cortex.

The cause of the increased intensity on T1-weighted images remains undetermined. The deposition of a paramagnetic substance that has bypassed the detoxification mechanisms of the liver due to portacaval shunting or hepatocyte dysfunction can be postulated but has not been demonstrated. In previous studies the presence of high signal intensity on T1-weighted images has been demonstrated in association with cerebral parenchymal calcification, possibly reflecting the incorporation of paramagnetic ions or altered effects of hydration [12]. Although CT studies in our patients demonstrated no change to correlate with regions of high MR signal intensity, the presence of increased calcium or other metal ions cannot be excluded. Analysis of postmortem tissue, not available in our series of patients, would have been useful in evaluating these possibilities.

Biologic membranes and macromolecules accentuate water proton relaxation both by the exchange of protons between water and the macromolecule and by a cross relaxation between water protons and protons within the membrane. These membrane effects appear to be responsible for the high signal intensities of myelin and of the posterior pituitary on T1-weighted images [13, 14]. They are also most likely responsible for the increased signal intensity seen within the basal ganglia on T1-weighted images in patients with

neurofibromatosis [15]. The abundant mitochondria and cell organelles of Alzheimer II cells may, by increasing intracellular membrane content, similarly promote relaxation of intracellular water protons, accounting for the increased signal intensity on T1-weighted sequences seen with chronic hepatocellular dysfunction. Saturation transfer techniques are being developed in our laboratory to test this hypothesis [16].

Oxygen radicals within reactive macrophages have been postulated as the cause of T1 shortening at sites of cerebritis or abscess formation [17]. In chronic hepatic failure significant cerebral macrophage accumulation does not occur and the presence of free radicals would not appear to be a likely explanation.

Since the occurrence of coagulopathy is well described in chronic liver failure, the presence of methemoglobin from recent petechial hemorrhage could theoretically account for the increased intensity on T1-weighted images and for the absence of markedly decreased intensity on T2-weighted sequences [18]. Although sequential studies are not available in our patients, the presence of petechial hemorrhage is thought unlikely because of the focal nature and symmetry of the findings, and because of the frequency of occurrence of the finding in clinically stable patients. The absence of signal loss on T2-weighted sequences also suggests that a prolonged process of petechial hemorrhage with hemosiderin deposition has not occurred.

The second major neuropathologic alteration occurring in chronic non-Wilsonian hepatic dysfunction is neuronal alteration. Changes included patchy pseudolaminar degeneration and loss of neurons deep in the cortex; polymicrocavitation of white matter at the gray-white junction; patchy neuronal degeneration in the basal ganglion, thalamus, and red nuclei; and neuronal degeneration of the cerebellar cortex [1, 3]. Lamellar necrosis is patchy and most evident in the parietal, occipital, and frontal cortex [1]. Cortical neuronal alteration is generally more prominent than that seen in the basal ganglia [3, 19]. MR alterations in signal intensity to correlate with cortical laminar or pseudolaminar necrosis and with polymicrocavitation at the gray-white junction were not demonstrated in this study. We are unable to determine whether our patients, free of symptoms of extensive encephalopathy at the time of imaging, had less severe neuropathologic alteration or whether such changes, though present, were not imaged.

Alterations consistent with cortical volume loss, manifested by prominence of cerebral sulci, were demonstrated in 19/42 patients. Changes were most prevalent in the frontal and parietal regions. Cerebellar cortical volume loss was demonstrated in 9/42 patients with five of these occurrences in the eight patients with Laennec cirrhosis, possibly representing the effect of both ethanol toxicity and chronic hepatic dysfunction.

Although myelinated fibers have demonstrated histologic degeneration with fragmentation of axis cylinders in chronic hepatocellular dysfunction, prominent neuropathologic lesions of the cerebral or cerebellar white matter have not been reported. Other than in one patient with previous infarction, MR imaging in our series did not demonstrate alterations in cerebral or cerebellar white matter. Three patients did dem-

onstrate increased signal intensity limited to the pons on T2-weighted images, consistent with central pontine myelinolysis [20, 21]. Two had Laennec cirrhosis, and one had primary biliary cirrhosis. The possibility that the MR changes relate to spongy degeneration of pontine white matter associated with hepatic encephalopathy cannot be excluded [22]. None of our patients had symptoms of brainstem dysfunction.

Since our recognition of the correlation of T1 shortening within the globus pallidus and putamen in association with hepatic dysfunction, two patients undergoing MR imaging of the brain have been prospectively diagnosed as having underlying hepatic disease on the basis of this MR finding. Increased intensity in the lenticular nuclei on T1-weighted images is not specific for hepatic dysfunction and has been found in three additional patients with systemic lupus erythematosus. Two of these patients have had no clinical or laboratory indices of hepatic dysfunction, although liver biopsies have not been accomplished. The third has been subsequently diagnosed as having lupus hepatitis.

The presence of symmetrically increased intensity on T1-weighted images in the lenticular nuclei, in the mesencephalon surrounding the red nuclei, and in the anterior lobe of the pituitary gland has been found in the majority of our patients with chronic hepatocellular dysfunction. This finding appears to be characteristic of but not specific to chronic liver dysfunction or portasystemic shunting, and should prompt prospective consideration of such diagnoses when it is encountered. It is postulated that this finding may relate to deposition of a paramagnetic substance or may relate to altered intracellular water relaxation associated with the proliferation of astrocyte cytoplasmic organelles.

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