Neurologic Spectrum of Chronic Liver Failure and Basal Ganglia T1 Hyperintensity on Magnetic Resonance Imaging

Probable Manganese Neurotoxicity

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Background: An atypical form of parkinsonism has been described in patients with chronic liver disease, associated with increased T1 signal in the basal ganglia on magnetic resonance imaging. The magnetic resonance imaging signal changes are characteristic of manganese accumulation, which has been neuropathologically confirmed. Manganese neurotoxicity may result in additional neurologic findings besides parkinsonism.

Objective: To fully characterize patients with chronic central nervous system symptoms and chronic liver failure associated with basal ganglia T1 hyperintensity.

Design: Prospective and retrospective case study.

Setting: Mayo Clinic, Rochester, Minn.

Participants: Eight patients referred for neurologic evaluation and studied prospectively, and 7 additional retrospectively identified patients who had been examined by Mayo Clinic neurologists.

Main Outcome Measures: Neurologic syndromes identified.

Results: Three syndromes were recognized in these 15 patients with liver failure and basal ganglia T1 hyperintensity on magnetic resonance imaging: (1) isolated parkinsonism, (2) gait ataxia plus other neurologic findings (ataxia-plus), and (3) cognitive impairment with psychiatric features. All but 1 patient had elevated blood manganese levels. Ammonia levels were normal in most, and the neurologic syndromes did not appear to reflect the well-known toxic-metabolic encephalopathy of liver disease.

Conclusions: Chronic liver failure may result in heterogeneous neurologic syndromes that cut across a variety of liver diseases. We selected cases on the basis of evidence of brain manganese accumulation, and this may be a crucial component of these syndromes. Further studies are necessary to explore this issue.

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METHODS

The inclusion criteria consisted of chronic liver failure, chronic neurologic symptoms (symptoms persistent for ≥1 month), basal ganglia T1 hyperintensity on MR brain images, and evaluation by Mayo Clinic neurology staff. The onset of neurologic symptoms was determined by patient report. The patients were identified from...
among those prospectively studied (8 patients between January 1, 2000, and December 31, 2004) by 1 of us (J.E.A.) and from a review of similar patients identified via the Mayo Clinic electronic database (by K.J.K.) during the same period (7 patients). All patients had extensive evaluations performed to exclude other causes of their neurologic syndromes. Serum and urine heavy metal analysis was performed by means of standard coupled plasma mass spectrometry for essential and trace elements. Magnetic resonance imaging of the brain was performed by means of standard imaging sequences on 1.5-T scanners.

All patients were followed up in the Gastroenterology or Liver Transplantation Division. Clinical evaluations, laboratory studies, and liver biopsy were performed to establish the cause of liver failure in all cases. The liver failure was sufficiently severe to place all patients on the liver transplantation list.

### RESULTS

The demographic features of the 15 patients (8 women and 7 men) who met our inclusion criteria are summarized in Table 1. The initial neurologic examination findings (before initiation of levodopa therapy) are summarized in Table 2. The mean age at onset of the neurologic symptoms was 56 years (range, 42-73 years). The mean duration of neurologic symptoms before first neurologic evaluation was 1.6 years (range, 6 months to 5 years). Follow-up clinical examinations and laboratory testing were performed on all 15 patients up to 7 years after their first neurologic evalu-

## Table 1. Demographic Features of Patients With Chronic Liver Failure With Increased T1 Signal in the Basal Ganglia

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Classification</th>
<th>Liver Disease</th>
<th>Latency From Liver Disease to Neurologic Symptoms, y</th>
<th>Liver Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/66</td>
<td>Parkinsonism</td>
<td>Primary biliary cirrhosis</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td>2/M/52</td>
<td>Parkinsonism</td>
<td>Primary sclerosing cholangitis</td>
<td>23</td>
<td>Yes</td>
</tr>
<tr>
<td>3/F/63</td>
<td>Parkinsonism</td>
<td>Primary biliary cirrhosis</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>4/F/57</td>
<td>Parkinsonism</td>
<td>Primary biliary cirrhosis</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>5/M/65</td>
<td>Parkinsonism</td>
<td>Primary biliary cirrhosis</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>6/F/73</td>
<td>Parkinsonism</td>
<td>Alpha-1-antitrypsin deficiency</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>7/M/52</td>
<td>Parkinsonism</td>
<td>Autoimmune hepatitis</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>8/M/64</td>
<td>Parkinsonism</td>
<td>NASH</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>9/F/52</td>
<td>Parkinsonism</td>
<td>NASH</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>10/M/44</td>
<td>Gait ataxia-plus*</td>
<td>Hepatitis C</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td>11/F/65</td>
<td>Gait ataxia-plus</td>
<td>Alcohol cirrhosis</td>
<td>17</td>
<td>No</td>
</tr>
<tr>
<td>12/M/55</td>
<td>Gait ataxia-plus</td>
<td>Alcohol cirrhosis</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>13/F/43</td>
<td>Cognitive and psychiatric</td>
<td>Primary biliary cirrhosis</td>
<td>15</td>
<td>Yes</td>
</tr>
<tr>
<td>14/F/42</td>
<td>Cognitive and psychiatric</td>
<td>Primary biliary cirrhosis</td>
<td>11</td>
<td>No</td>
</tr>
<tr>
<td>15/M/47</td>
<td>Cognitive and psychiatric</td>
<td>Hepatitis C</td>
<td>29</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviation: NASH, nonalcoholic steatohepatitis.
*Gait ataxia plus other neurologic findings.

## Table 2. Clinical Features of Patients With Chronic Liver Failure With Increased T1 Signal in the Basal Ganglia at Time of Initial Consultation*

*Abbreviations: NP, not performed; plus sign, present; minus sign, absent.
*Examination findings were from initial consultation before levodopa therapy.
ation. Median follow-up was 2.5 years (range, 1-7 years). In all cases, the family history was negative for neurologic disease.

Three clinical syndromes were evident to all authors, on the basis of the predominant symptoms and neurologic findings: (1) parkinsonism, 9 patients; (2) gait ataxia plus other features (gait ataxia-plus), 3 patients; and (3) cognitive impairment with psychiatric symptoms, 3 patients.

**PARKINSONISM SYNDROME**

Parkinsonism developed in 9 patients with a median age at onset of 62 years (range, 52-73 years). Some of the clinical features were reminiscent of idiopathic PD, including absence of early gait instability and falls as well as the age at symptom onset. Overall, 5 of the 6 patients treated with levodopa demonstrated some clinical improvement. Two patients improved markedly, similar to patients with idiopathic PD, and the other 3 patients had only partial improvement. Two patients showed no improvement despite mean dosages of 625 mg of levodopa per day (with carbidopa; range, 300-1200 mg of levodopa per day). However, several distinctive differences emerged in comparison with idiopathic PD. First, an action hand tremor (5 of the 9 patients) was more common than rest tremor (3 patients). Second, mild cognitive impairment was common in this group at the time of presentation (7 patients). Third, the parkinsonian signs were symmetric in 5 of the 9 cases. Finally, the parkinsonism developed subacutely, coinciding with worsening of the primary liver disease (Table 1 and Table 2).

**SYNDROME OF GAIT ATAXIA-PLUS**

Three patients presented with a mixed syndrome characterized primarily by gait ataxia plus cognitive impairment and other neurologic impairments, including seizures (patient 10), dystonia (patient 11), or tremor (patient 12). Brain imaging, cerebrospinal fluid examination, and blood studies effectively ruled out other causes. Although 2 of the 3 patients had a history of alcoholic cirrhosis, both patients had been abstinent from alcohol for a mean of 4 years and had had no gait symptoms during this abstinence until the subacute development of gait ataxia and cognitive impairment. Neither patient had midline cerebellar atrophy on brain MR images. The cognitive impairment consisted of short-term memory loss and inattention. None of the patients fulfilled DSM-IV criteria for dementia.6

**SYNDROME OF COGNITIVE IMPAIRMENT WITH PSYCHIATRIC SYMPTOMS**

Prominent cognitive and psychiatric symptoms were present in 3 patients. In 2, the cognitive and psychiatric symptoms developed concurrently with a subacute time course. The third patient developed psychiatric symptoms 1 year before the cognitive symptoms (patient 13). The median latency from documentation of liver failure to onset of neurologic symptoms was 15 years (range, 11-29 years). All 3 patients reported loss of short-term memory, difficulty concentrating, and inattention. One patient reported episodic confusion. Examples of cognitive symptoms included forgetting conversations, appointments, when to eat meals, and how to perform their tasks at work. Activities of daily living were preserved in all patients.

Characteristic abnormalities on the Kokmen short test of mental status included impairment in attention and immediate recall. One patient underwent neuropsychometric testing. These results were summarized as demonstrating mild cognitive impairment consistent with a subcortical pattern. The impairment consisted of difficulty with sustained attention and concentration (best observed on the Stroop color and word test), immediate and delayed recall, executive function (as determined by the Wisconsin Card Sorting Test), and visuospatial dysfunction (Rey-Osterrieth Complex Figure). None of these patients had evidence of florid confusion, fluctuating or reversible cognition, myoclonus, asterixis, or elevated ammonia levels as seen in toxic-metabolic hepatic encephalopathy.

The spectrum of psychiatric symptoms ranged from a major depressive disorder with or without suicidal ideation to anxiety symptoms with insomnia. None of these patients had a history of previous psychiatric illness. These cognitive and psychiatric symptoms overlapped with findings in the other 2 groups. All 3 patients in the gait ataxia-plus group and 7 of 9 patients with parkinsonism also reported subjective cognitive impairment. Two patients in the parkinsonism group reported major depression. Thus, cognitive and, to a lesser extent, psychiatric symptoms were common among this entire cohort. However, the 3 patients in this group lacked motor abnormalities and presented with a pure cognitive and psychiatric syndrome.

**LIVER FAILURE HISTORY**

All 15 patients had chronic (nonwilsonian) liver failure. The most common cause was primary biliary cirrhosis (6 patients), while the remaining patients had different causes of the liver disease (Table 1). Six of the 15 patients had impairment of liver synthetic function, as determined by albumin level and prothrombin time. Venous ammonia levels were elevated in 4 of 9 patients in whom this was obtained (Table 3). None of the patients developed symptoms or signs of toxic-metabolic hepatic encephalopathy during the course of neurologic symptoms. Specifically, none of the patients showed signs of fluctuating awareness or delirium, asterixis, or electroencephalographic findings of triphasic waves; a single patient did have myoclonus (patient 4).

Two patients received a liver transplant and had subsequent improvement of the T1 signal on brain MR images (patients 2 and 13). The parkinsonism in patient 2 improved with substantial carbidopa-levodopa therapy (1500 mg of levodopa daily), but the parkinsonism largely persisted at 1 year after transplantation. Patient 13 had cognitive impairment that resolved within 1 week after liver transplantation. The Kokmen short test of mental status returned to a perfect score.
METAL STUDIES

The serum manganese level was elevated in 14 of 15 cases and near the upper limit of normal in the other (patient 4). Urine manganese levels were tested in patients 1, 2, and 12 and were normal in all. Serum copper and zinc levels were also elevated in patient 13, while serum iron level was elevated in patient 14 (Table 3). Patient 2 had serum manganese levels drop to near normal after liver transplantation, correlating with improvement of the T1 signal abnormality on MR imaging.

IMAGING

All 15 patients had bilateral hyperintense signal on T1-weighted sequences in the basal ganglia, apparent on both sagittal and axial images. In most cases, the signal abnormality involved both the globus pallidus and putamen but rarely would isolate to 1 of the 2 locations. The Figure displays 3 representative MR images demonstrating the basal ganglia T1 hyperintensity present in all patients. Two of the 15 patients also had increased T2 signal in the bilateral globus pallidus and putamen and, in 1 of these patients, in the dentate nucleus. Gadolinium, used in 7 of 15 brain MR images, showed no abnormal enhancement. The T1 signal abnormality improved after liver transplantation in patients 2 and 13.

COMMENT

We selected only patients with liver failure who had basal ganglia T1 hyperintensity on MR imaging, recognizing this as a biomarker of brain manganese accumulation.8 Previous authors have proposed brain manganese accumu-

### Table 3. Laboratory Indexes*

<table>
<thead>
<tr>
<th>Value</th>
<th>Patient No.</th>
</tr>
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<tbody>
<tr>
<td>Manganese, ng/mL (0.4-0.85 ng/mL)</td>
<td></td>
</tr>
<tr>
<td>Copper, µg/dL (75-145 µg/dL)</td>
<td></td>
</tr>
<tr>
<td>Ceruloplasmin, mg/dL (22.9-43.1 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Zinc, µg/dL (66-110 µg/dL)</td>
<td></td>
</tr>
<tr>
<td>Iron, µg/dL (35-145 µg/dL)</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL (&lt;50 µg/dL)</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time, s (8.4-12.0)</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, mg/dL (0.1-1.0)</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L (55-142 U/L)</td>
<td></td>
</tr>
<tr>
<td>AST, U/L (12-31 U/L)</td>
<td></td>
</tr>
<tr>
<td>ALT, U/L (9-29 U/L)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; BG, basal ganglia; MR, magnetic resonance; NP, not performed.

**SI conversion factors:** To convert ammonia to micromoles per liter, multiply by 0.587; copper to micromoles per liter, multiply by 0.157; iron to micromoles per liter, multiply by 0.179; manganese to nanomoles per liter, multiply by 18.2; total bilirubin to micromoles per liter, multiply by 17.1; and zinc to micromoles per liter, multiply by 0.153.

*Reference ranges are given in parentheses. Boldface entries represent abnormal values.
mulation to be a substrate for at least some of the neurolologic symptoms in liver failure.1-3 We identified 3 syndromes: (1) predominant parkinsonism, (2) gait ataxia plus other neurologic findings (gait ataxia-plus), and (3) cognitive impairment with psychiatric features. These cut across a variety of liver failure causes.

As the previous literature would suggest, parkinsonism was common and was the primary finding in 9 of our 15 patients. It differed from idiopathic PD in the following respects. First, a kinetic hand tremor was more common than rest tremor.9 Second, mild cognitive impairment was common at the time of presentation. Third, the parkinsonism was symmetric more often than asymmetric at time of presentation. Fourth, 3 of the 5 patients who responded to treatment with levodopa were not as responsive to the therapy as typical patients with PD. Finally, the parkinsonism developed subacutely, coinciding with worsening of the primary liver disease. These differences suggest that the parkinsonism is not coincidental PD, which is supported by most studies that have reported clinical improvement in parkinsonism after liver transplantation.1,3,5

Other brain nuclei besides the pallidum also accumulate manganese, albeit to a lesser extent. These include putamen, caudate, substantia nigra, mesencephalic tegmentum, and occipital and frontal cortex.10 Elevated cerebrospinal fluid manganese levels have been documented in patients with liver failure, consistent with more widespread manganese accumulation.11 Thus, symptoms beyond parkinsonism might also reflect manganese accumulation.

Classically, parkinsonism resulting from manganese neurotoxicity in miners and welders is unresponsive to levodopa.2 In these patients, positron emission tomographic scans of the brain are normal; thus, it has been suggested that manganese may result in pallidal injury with relative sparing of nigrostriatal projections. However, recently Racette et al12 reported relatively symmetric and severely reduced fluorodopa F 18 uptake on positron emission tomography in the posterior putamen in a patient with manganese due to chronic liver failure and the T1 hyperintensities in the basal ganglia on MR imaging. Thus, patients with chronic liver failure may accumulate manganese in the nigrostriatal projections, allowing for some response from levodopa therapy, as was seen in our patients.

Cognitive impairment was also common, albeit mild, among our 15 patients; it was the predominant finding in conjunction with psychiatric symptoms in 3 patients and has previously been reported.13,14 Moreover, some degree of cognitive impairment was present in 10 other patients (total, 87% with mild cognitive impairment).

A syndrome termed minimal hepatic encephalopathy has been reported previously, consisting of subcortical dysfunction of attention and short-term memory.13,14 The common abnormalities found on bedside testing include deficits in attention, immediate recall, and visuospatial tasks. Psychometric abnormalities are commonly seen in tests of executive function (Wisconsin Card Sorting Test), attention tasks (Stroop color and word test), visuospatial tests (Rey-Osterrieth Complex Figure), and psychomotor speed (pegboard test and finger tapping).13,14 Similar abnormalities were present in 13 of our 15 patients by history and examination and were confirmed by neuropsychometric testing in 3 cases.

Gait instability was the predominant finding in 3 of our patients and was associated with a variety of other features, including cognitive impairment, which was indistinguishable from the other groups. Although 2 of the 3 patients had alcoholic liver disease, the gait ataxia developed long after they had stopped drinking (mean, 4 years). Moreover, the coinciding, subacute development of additional neurologic abnormalities suggests that the gait disorder was not simply due to alcoholism.

We selected patients with T1 basal ganglia hyperintensity on MR imaging. This MR imaging pattern is identical to that in previous reports in patients with chronic liver disease3 and reflects manganese accumulation within the basal ganglia, as previously reported in neuropathological studies.10,15 In fact, there is a correlation between the MR imaging T1 hyperintensity and measured postmortem brain manganese concentrations.13 Patients receiving long-term parenteral nutrition with excessive manganese have also developed the same MR imaging signal abnormalities, which resolve with elimination of manganese from the infusate.16,17

These findings should be considered preliminary and require further confirmation. We cannot be certain that some aspects or symptoms were not coincidental or due to factors other than manganese, although the overlap in these patients and with other series is noteworthy, including series cited earlier with manganese neurotoxicity from other sources.2,17 Some symptoms found in our patients might easily be overlooked and hence have not been consistently recognized; these include polyminimyoclonus observed in 2 patients as well as subtle parkinsonism. Other symptoms might be written off as nonspecific, such as headaches, an unsteady gait, or mild cognitive impairment. In fact, these cases raise many questions that have yet to be addressed: What percentage of patients with liver failure have pallidal T1 hyperintensity on MR imaging? Of these, what fraction have neurologic symptoms or signs? What aspects of liver disease spare certain patients? What fraction of those with the T1 hyperintensity are asymptomatic, and why? Are these same syndromes seen among patients with liver failure without T1 hyperintensity? What are the pathologic underpinnings and what is the neuropathological basis for symptoms not referable to the pallidum (with the T1 hyperintensity)?

Although we cannot be certain that manganese was responsible for all of the clinical symptoms, there is at least circumstantial evidence favoring a major contribution from brain manganese accumulation. Similar symptoms, including parkinsonism, cognitive dysfunction, tremor, and personality change, have been observed in welders2 and patients receiving total parenteral nutrition.15 In both welders and patients receiving total parenteral nutrition who share the overlap of symptoms with our patients, the characteristic T1 hyperintensity in the basal ganglia on MR images is identical.

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REFERENCES


