Chronic Parkinsonism Associated With Cirrhosis

A Distinct Subset of Acquired Hepatocerebral Degeneration

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Context: The clinical, neuroradiological, and biological characteristics of the so-called acquired hepatocerebral degeneration have not yet been fully determined and its frequency remains largely uncertain.

Objectives: To prospectively study the prevalence of extrapyramidal symptoms in patients with moderate to severe cirrhosis of various causes, to delineate the main neurological features of the condition, and to establish correlations with neuroradiological and biological findings.

Patients and Methods: During a 1-year period, all consecutive patients with cirrhosis who were potential candidates for liver transplantation were screened for extrapyramidal features. When extrapyramidal features were present, further workup included a detailed neurological examination, magnetic resonance imaging of the brain, a comprehensive battery of neuropsychological tests, extensive blood tests, and, in some cases, cerebrospinal fluid analysis.

Setting: A community-based hospital.

Results: From 51 patients screened, 11 (21.6%) exhibited moderate to severe parkinsonism sometimes associated with focal dystonia. Typical features included rapid progression over months, symmetric akinetic-rigid syndrome, postural but not resting tremor, and early postural and gait impairment. Neuropsychiatric manifestations were minimal. Some patients were responsive to levodopa therapy. In all patients, magnetic resonance imaging scans showed striking hyperintensities on T1-weighted images typically involving the substantia nigra and the globus pallidus bilaterally. Whole blood and cerebrospinal fluid manganese concentrations were severalfold above the reference range.

Conclusions: Cirrhosis-related parkinsonism may represent a unique, consistent, and common subset of acquired hepatocerebral degeneration, whose features are permanent and entirely different from acute hepatic encephalopathy episodes. This form of parkinsonism can be clearly distinguished from other forms of parkinsonism of middle to advanced age, based on a suggestive association of clinical, neuroradiological, and biological abnormalities. Our findings support the concept of the toxic effects of manganese being the major determinant of basal ganglia dysfunction leading to the predominantly extrapyramidal central nervous system manifestations of cirrhosis observed in these patients.

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Results in Mn concentration in the pallidum of patients in particular, the demonstration of a severalfold increased dopamine receptor density, an altered glutamate-nobutyric acid–mediated neurotransmission, and, for some patients, a computed tomographic scan; and extensive blood tests, in particular, copper metabolism evaluation and whole blood Mn levels determined by a standard method using graphite furnace atomic absorption spectroscopy. In addition, 3 patients had a lumbar puncture and the concentration of cerebrospinal fluid (CSF) Mn was determined using the same method.

MRI of the Brain

Magnetic resonance imaging scans were performed on a 1.5-T Picker Eclipse System (Marconi, Cleveland, Ohio) using standard axial, sagittal, and coronal spin-echo, T1-weighted images (repetition time, 400 milliseconds; echo time, 18 milliseconds) with a field of view of 22 mm, a matrix size of 256 × 256 pixels, and a slice thickness of 4 mm, with an interslice gap of 0.5 mm. Axial fast spin-echo T2-weighted images were also obtained using dual echo spin (16 and 80 milliseconds with a repetition time of 3400 milliseconds).

Magnetic resonance imaging was interpreted by a single neuroradiologist (J.D.) blinded to the patients’ clinical and biological data and compared with MRI scans obtained from 10 age-matched healthy subjects. Hyperintensities observed on T1-weighted images of BG and other structures were quantitatively graded using a scale considering the extension and the degree of the abnormalities (0 indicates none; 1, mild; 2, moderate; and 3, severe hyperintensity).

Assessment of Liver Function

The diagnosis of cirrhosis was biopsy proven in 9 patients; using current clinical, radiological, and biological criteria, cirrhosis was suggested in 2 patients. Liver assessment was performed by the same gastroenterologist (L.S.) in all patients. The cause of liver failure was chronic alcoholism in 6 patients, viral infection in 4, and unknown in 1. Alcoholic patients had quit drinking alcohol for at least 6 months at the time of assessment. Severity of liver disease was graded according to the Pugh modification of the Child classification, which considers clinical factors and biological test results of liver function. This method provides a global prognosis for patients who have cirrhosis. All patients had an upper gastrointestinal tract endoscopy to assess the presence of esophageal varices. Measurement of portal pressure was performed according to a standard invasive method during transjugular liver biopsy. Portal hypertension is present when the gradient between the wedged and free hepatic venous pressure (the hepatic venous pressure gradient) exceeds 5 mm Hg. Finally, an aminopyrine breath test was performed in 5 patients. The aminopyrine breath test is a reliable index of the hepatic microsomal capacity and has valuable prognostic value. In our laboratory, reference values have been established to range between 4.7% and 7.0%.

Methods

Neurological Assessment

During a 1-year period, all consecutive patients who had advanced cirrhosis and were hospitalized as potential candidates for liver transplantation were prospectively and independently examined by 2 neurologists (P.R.B. and R.D.P.) trained in movement disorders as part of the routine transplantation program of University Hospital, Geneva, Switzerland. From 51 patients screened during this 1-year period, 11 had definite parkinsonism and other extrapyramidal symptoms. Parkinsonism was defined by the presence of at least 2 of the following signs or symptoms: tremor at rest, rigidity, and akinesia. Some patients with only mild akinesia or questionable rigidity were excluded because some degree of slowness of movement or rigidity can be seen as part of HE, yet these signs are insufficient to fulfill the criteria for parkinsonism.

These 11 patients then underwent a comprehensive neurological workup that included a detailed history and neurological examination; administration of the Unified Parkinson’s Disease Rating Scale (UPDRS), a Purdue Pegboard Test, and a battery of neuropsychological tests; an MRI of the brain; and, for some patients, a computed tomographic scan; and extensive blood tests, in particular, copper metabolism evaluation and whole blood Mn levels determined by a standard method using graphite furnace atomic absorption spectroscopy. In addition, 3 patients had a lumbar puncture and the concentration of cerebrospinal fluid (CSF) Mn was determined using the same method.

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(21.6%) exhibiting definite parkinsonism. In some of them, parkinsonism was associated with other extrapyramidal symptoms. There were 7 men and 4 women; their mean age was 61.9 years (age range, 51-70 years). None was treated with drugs known to induce neurological symptoms or MRI abnormalities, such as neuroleptic, immunomodulatory, or antiviral agents, with the exception of 1 patient who was receiving low doses of clozapine therapy.

**CLINICAL FINDINGS**

The main characteristics of the parkinsonian syndrome are given in Table 1. Typically, onset of disease was insidious and first symptoms were frequently noticed by the patient's relatives rather than by the patient. In all, duration from onset until maximally severe parkinsonism was short, ranging from 2 to 18 months (mean, 7.2 months). The main initial symptom was global slowness of movements and gait impairment in 10 of 11 patients, characterized by short shuffling steps, unsteadiness, and falls. Other symptoms at onset included micrographia, dysarthria, hypomimia, action and postural but not resting tremor, and postural instability.

On neurological examination, prominent signs included moderate to severe akinesia and lead-pipe rigidity with cogwheeling and reinforcement by the Froment maneuver. Akinetic-rigid syndrome was typically symmetric except in 3 patients in whom a mild side predominance was noted by the patient and the examiner. Rest tremor was notably absent except for patient 10 who exhibited a 5-Hz, pill-rolling tremor in both hands. In contrast, all patients showed a 6- to 10-Hz postural tremor of low amplitude involving upper but not lower limbs bilaterally, which was also present during action in some.

Flapping tremor was absent in all cases at the time of examination. Postural instability and gait impairment were severe, leading to falls in most cases. Patients walked slowly with short shuffling steps, stooped posture, and reduced arm swing, but no freezing episode was seen. Turning around was difficult, if not impossible in some cases, and the pull-test result was positive in 9 patients. Six patients were unable to stand up from a chair without being helped. The motor function score of the UPDRS (part III) ranged from 20.5 to 61.0 (mean [SD], 37.5 [15]), which indicates moderate to severe parkinsonism. The Purdue Pegboard Test score, obtained in 7 patients, was considerably impaired compared with age-matched control subjects and paralleled the UPDRS scores.

Besides parkinsonism, 6 patients exhibited dystonia involving the face in 3 patients, the face and lower limbs in 2 patients, and the toes in 1 patient. Dystonic features consisted of blepharospasm, oromandibular dystonia, and toe dystonias. No chorea was detectable or other extrapyramidal, pyramidal, or cerebellar features. Kayser-Fleischer rings were notably absent in all.

None of the patients had dementia; neuropsychological testing showed no dysphasia, apraxia, or agnosia. There was, however, some degree of frontal lobe impairment as evidenced, for example, by poor ability at the Trail-Making Test. There were no prominent psychiatric symptoms, except for a mild degree of depression in 2 patients. Although 5 patients had a clear history of 1 to several episodes of HE, there was no evidence of overt HE by the time of examination.

Five patients were followed up over a 24-month period during which several neurological examinations were performed. The last 2 patients included in the study (cases 7 and 11) have been treated with a combination of levodopa and dopa-decarboxylase inhibitor (ie, 200 mg of...
levodopa and 50 mg of benserazide, thrice daily, in both cases). Both patients experienced a significant and sustained response of parkinsonism assessed by an improved UPDRS motor function score by 38.7% in patient 7 (UPDRS scores, 53 before and 32.5 while receiving levodopa therapy) and by 40.2% in patient 11 (UPDRS scores, 61 before and 36.5 while receiving levodopa therapy). After about 1 year of long-term levodopa therapy, no dyskinesia was observed. The parkinsonism remained virtually unchanged over time in the 3 untreated patients.

Mn CONCENTRATIONS IN BLOOD AND CSF

The whole blood Mn level was measured in a fasting state in 9 patients (Table 2). Mean (SD) value was 23.33 (15.26) µg/L (425 [278] nmol/L), ranging from 8.78 to 54.35 µg/L (160-990 nmol/L), all results being above the upper normal limit (reference range, <8.24 µg/L [<150 nmol/L]). The CSF Mn concentration was increased in the 3 cases from which CSF had been obtained (reference range, <1.48 µg/L [<27 nmol/L]). The levels of ceruloplasmin (mean [SD] value, 1.03 [0.35] mg/dL [16.2 (5.5) µmol/L]; study range, 0.56-1.59 mg/dL [8.8-24.5 µmol/L]; reference range, 0.80-1.50 mg/dL [12.5-23.6 µmol/L]) were within the reference range except for patient 1 in whom the serum copper level was slightly elevated. Serum ammonia levels assessed at the time of neurological examination were minimally increased in several patients.

MRI FINDINGS

Magnetic resonance imaging was assessed in 9 of 11 patients owing to inappropriate technique in one and movement artifacts in another. A variable degree of cortical and subcortical homogeneous atrophy was detected in all. In general, the severity of vascular changes, when present, was minimal. Typically, all patients showed, on T1-weighted images, bilateral and symmetrical hyperintensities that were restricted to certain brain areas while others were consistently spared (Table 3). The substantia nigra and the globus pallidus were bilaterally affected in all patients and the changes were graded as severe in most of them. In some, similar hyperintensities were also found in the ventral aspect of the midbrain, the substantia innomi-
nata, and the hypothalamus. In addition, 3 patients showed pallidal calcifications on computed tomographic scan of the brain. The putamen, caudate nucleus, thalamus, the red nucleus, and the cerebellum were spared in all cases. There was no radiological counterpart on T2-weighted images for these abnormalities. Typical examples of these changes are shown in the Figure.

**CIRRHOSIS ASSESSMENT RESULTS**

According to the Child classification (grade A indicates mild; grade B, moderate to severe; and grade C, end-stage liver failure), the condition of 1 patient was graded as Child A; 5 were Child B; and 5 were Child C. At endoscopy, all patients had spontaneous portosystemic collaterals demonstrated by the presence of esophageal varices. Patient 2 had had a surgical portosystemic shunt constructed several years earlier. Table 4 lists the results of the liver assessment. Portal hypertension was present in all patients in whom the measurement was performed. In addition, aminopyrine breath test values were consistent with impaired liver microsomal function. Abnormal laboratory results are summarized in Table 2. Variable degrees of anemia, thrombocytopenia, reduced prothrombin time, hypoalbuminemia, hyperbilirubinemia,
and elevated transaminase levels were noted in all of the patients, which is consistent with moderate to severe liver failure.

By the time of publication of this article, no liver transplantation will have been performed in these 11 patients. Three patients have died and the remaining 8 are no longer candidates for the transplantation program for various reasons, including the resumption of alcohol consumption in 3, advanced age in 4, and refusal in 1.

Table 4. Assessment of Liver Function in 11 Patients With Cirrhosis-Related Parkinsonism

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
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<td>Cause of cirrhosis</td>
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<td>A</td>
<td>V</td>
<td>V</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>U</td>
<td>V</td>
<td>A</td>
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<td>Past episodes of HE</td>
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<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
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<td>−</td>
<td>−</td>
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<td>Child classification*</td>
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<td>C</td>
<td>C</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>HVPG, mm Hg†</td>
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<td>29</td>
<td>16</td>
<td>−</td>
<td>19</td>
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<td>21</td>
<td>−</td>
<td>12</td>
</tr>
<tr>
<td>ABT, %‡</td>
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<td>−</td>
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<td>1.3</td>
<td>−</td>
<td>−</td>
<td>0.6</td>
<td>1.2</td>
<td>1.4</td>
<td>−</td>
</tr>
</tbody>
</table>

Abbreviations: A, alcohol related; ABT, aminopyrine breath test; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; U, unknown; V, viral; −, absent or undetermined; +, present.

*The severity of liver disease was graded according to the Pugh modification of the Child classification as follows: A indicates mild; B, moderate to severe; and C, end-stage liver failure.

†The reference range for HVPG is 5 mm Hg or less.

‡The reference range for ABT is 4.7% to 7.0%.

We report detailed clinical, neuroradiological, and biological data from a homogeneous group of patients with cirrhosis and moderate to severe chronic parkinsonism. This association seems to emerge as a distinct entity among parkinsonian syndromes of various causes including Parkinson disease.

Clinically, these patients are initially seen with a rapidly evolving and symmetric akinetic-rigid syndrome, early gait and postural impairment, and, in about half of them, focal dystonia. Resting tremor is notably minimal or absent, but postural tremor is prominent. Oculomotor, cerebellar, pyramidal, or sensory abnormalities are lacking. Cognitive functions are globally preserved except for some degree of frontal lobe dysfunction and, besides mild depression, there is no prominent psychiatric features. Parkinsonian features are conspicuous, as evidenced by elevated UPDRS scores, and lead to major functional disability. Evolution is characterized by insidious onset and rapid progression over months until parkinsonism reaches a plateau, followed by a chronic and more stable course over years. Parkinsonism develops independently of and can be clearly separated from HE episodes, although portosystemic shunting and a history of HE seems to constitute a necessary background for parkinsonism to occur. Because the causes of liver failure were diverse, the appearance of parkinsonism seems more related to the degree of liver failure rather than to a specific cause. These patients, therefore, can clearly be distinguished from alcohol-induced parkinsonism for instance.52 Although reminiscent of Parkinson disease, several features allow Parkinson disease to be reasonably ruled out in these patients, such as rapid evolution, absence of resting tremor, no consistent asymmetry of symptoms, and early gait impairment. Similarly, atypical parkinsonian syndromes, such as multiple systemic atrophy, progressive supranuclear palsy, or corticobasal degeneration seem unlikely. Wilson disease was excluded, as were the most frequent causes of secondary parkinsonism, such as vascular, toxic, and drug-induced parkinsonisms.

A few similar patients have been described previously, usually on a single-case basis, suggesting a highly uncommon condition. However, our cohort has been gathered over a short period and represents more than 20% of the patients with cirrhosis who were evaluated for liver transplantation in a community-based program. Thus, we suspect that the frequency of parkinsonism related to cirrhosis is largely underestimated and may be more frequent than suggested by the current scarcity of available articles on the topic. Possible explanations include unawareness of the specific condition described herein and confounding effect of HE episodes, chronic alcoholism, or medications. Further studies are clearly needed to establish the true prevalence of this problem in larger cohorts of patients.

In accord with what has been described in the last 10 years, MRI studies of our patients are striking. They show, on T1-weighted images only, extensive hyperintensities involving both substantia nigra and globus pallidus (Figure) symmetrically and homogeneously. Although pallidal hyperintensities may be found in 71% to 92% of the patients with cirrhosis with no obvious clinical expression, nigral hyperintensities, rarely mentioned thus far, seem to constitute an MRI feature unique to this cohort of patients with cirrhosis-related parkinsonism. Moreover, because of the proximity of these hyperintensities with the red nucleus, they anatomically match the pars compacta of the substantia nigra, suggesting a direct, possibly causal, relationship between nigral extension of MRI lesions and appearance of parkinsonism.

Compelling evidences point toward increased endogenous Mn deposition into the BG as a major determinant of MRI hyperintensities observed in patients with cirrhosis. Arguments favoring the "Mn hypothesis" are the following: (1) blood Mn levels are dramatically elevated in patients who have cirrhosis and palli-
(2) liver transplantation provides normalization of both MRI abnormalities and Mn levels; (3) BG tissue from cases of deceased patients who had cirrhosis contains a severalfold increase of Mn concentration compared with controls; (4) identical MRI features are observed in long-term Mn intoxication and in patients who do not have cirrhosis and in monkeys treated with prolonged total parenteral nutrition containing high concentrations of Mn that resolve after discontinuation of Mn intake; and (5) increased intensity of signal limited to T1-weighted images is caused by compounds with paramagnetic properties such as manganine, methemoglobin, or some heavy metals. Manganine, as opposed to ammonia or bilirubin, has been shown to possess such typical paramagnetic behavior as detected by MRI.

Our study provides further arguments supporting the Mn hypothesis. First, all tested patients had high whole blood concentrations of Mn, in the same range as those reported in patients with symptomatic occupational Mn exposure, assessed by similar dosage methods. Second, CSF Mn levels have been found increased in 3 of our 51 patients. Third, the clinical findings described herein resemble those found in both occupational and nutritional Mn neurotoxic reactions. Notably, the association of an akinetic-rigid syndrome and dystonia in the same patient seems to be of particular interest at differentiating Mn-induced from other forms of parkinsonism. The main difference between our patients and those with manganese lies in the high occurrence of neuropsychiatric manifestations in the latter. Since these patients usually developed neurological symptoms shortly after massive exposure to Mn, it is possible that a more acute profile of Mn intoxication may be necessary for neuropsychiatric dysfunction to become prominent.

Two patients received levodopa therapy for more than 1 year. Both showed a substantial improvement of nearly all parkinsonian features with an average reduction of the UPDRS score by about 40%. None was treated with dopamine agonists. While this apparent levodopa responsiveness needs to be confirmed on larger numbers of patients, dramatic and sustained response to levodopa therapy constitutes a strong argument in favor of a defect in the nigro-striatal pathway (presynaptic parkinsonism) as a major determinant of the akinetic-rigid features in these patients. We, therefore, suspect that Mn deposition into the substantia nigra, consistently observed in our patients, plays a pivotal role in the pathophysiology of this form of parkinsonism. As in Parkinson disease, the reduced dopamine supply to the striatum may lead to inhibition of the direct pathway and disinhibition of the indirect pathway and, ultimately, a decreased activation of the thalamus and the motor cortex via an increased inhibition from the BG output. Concomitant dystonia, as well as hyperkinetic abnormal movements reported by others, may result from Mn deposition in the globus pallidus. These hypotheses need further studies, however, in particular fluorodopa F18 positron emission tomography or single-photon emission computed tomography using dopamine transporter ligands and neuropsychological confirmation.

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