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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During the first half of the 20th century, considerable attention has been dedicated to central nervous system manifestations related to advanced cirrhosis.1-5 Mainly focused on clinicopathological studies of single cases or small series, this literature culminated in the seminal article by Victor et al in 1965, who established the generic term “acquired type of chronic hepatocerebral degeneration” that was intended to make a clear distinction from the genetically determined Wilson disease. From this early material, several aspects were delineated that were confirmed later: (1) a variety of chronic neurological and cognitive abnormalities are associated with chronic liver failure, which are clinically distinct from the more acute and transient episodes of hepatic encephalopathy (HE);1-3, (2) most of these symptoms involve basal ganglia (BG) dysfunction and include abnormal involuntary movements, such as choreoathetosis, tremor, myoclonus, dystonia, rigidity, and dystarthis, less frequently ataxia, pyramidal tract signs, and dementia;4-6; (3) paradoxically, neuropathological features are rather uniform and similar to those seen in Wilson disease, including neuronal loss and dysmorphic astrocytes in cortex and subcortical white matter, the BG, and the cerebellum, presence of numerous Alzheimer type 2 astrocytes in cortex and sub-
cortical gray matter, periodic acid–Schiff-positive nuclear inclusions, and Opalski cells; (4) later age of patients, absence of Kaiser-Fleischer rings, and normal copper metabolism allow Wilson disease to be reasonably ruled out; and (5) appearance of neurological symptoms is unrelated to the cause of liver failure, but seems to parallel the degree of portosystemic shunting, the number of HE episodes, and the levels of ammonia.

Little has been added to this view over the following decades, but recently cirrhosis-related BG abnormalities have been the subject of renewed interest, in relation to further radiological and biochemical findings. First, it has been demonstrated that more than 75% of the patients who have cirrhosis have bilateral pallidal hyperintensities on a T1-weighted magnetic resonance imaging (MRI) scan, irrespective of the presence or absence of neurological symptoms. The degree and extension of these changes seem to correlate with the severity of the liver disease as evaluated by the Child-Pugh score, the plasma ammonia level, the presence of either spontaneous or surgical portosystemic shunt, and the presence of some neurological signs such as postural tremor, rigidity, akinesia, and primitive reflexes. Second, several lines of evidence suggest that abnormal manganese (Mn) deposition in the BG may play a pivotal role in the processes leading to both clinical and neuroradiological abnormalities exhibited by patients with cirrhosis. In particular, the demonstration of a severalfold increase in Mn concentration in the pallidum of patients who died while in a hepatic coma has suggested a decreased D2 dopamine receptor density, an altered glutamate- or γ-aminobutyric acid–mediated neurotransmission, and reduced glucose consumption have been found in the BG of patients who have cirrhosis. Fourth, proton magnetic resonance spectroscopy of the cirrhosis-affected brain has revealed diffuse metabolic abnormalities, including an increased glutamine-glutamate peak in the BG compared with other brain regions. Together, these changes suggest a profound impairment of BG circuitry that may provide a physiological basis for the predominantly extrapyramidal symptoms found in these patients.

Many questions remain unanswered and, surprisingly, the spectrum of chronic central nervous system manifestations related to chronic liver failure still remains poorly defined as does the evolution over time of these symptoms, the degree of functional impairment, and the response to treatment. The present study is an attempt to resolve some of these issues.

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 movements 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.

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%.

RESULTS

In a cohort of 51 patients with cirrhosis prospectively assessed during a 1-year period, we found 11 patients...
(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, stooped posture, and falls. Other symptoms at onset included micrographia, dystartria, 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 frontolimb 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

| Table 1. Main Clinical Features in 11 Patients With Cirrhosis-Related Parkinsonism |
|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Variable        | 1      | 2      | 3      | 4      | 5      | 6      | 7      | 8      | 9      | 10     | 11     |
| Sex             | M      | M      | M      | F      | M      | M      | M      | F      | F      | M      | F      |
| Age, y          | 69     | 54     | 51     | 60     | 60     | 54     | 70     | 62     | 68     | 69     | 64     |
| Duration of symptoms, mo | 6      | 6      | 3      | 10     | 5      | 6      | 18     | 4      | 5      | 2      | 14     |
| Symmetry/asymmetry | R L   | R L   | R L   | R L   | R L   | R L   | R L   | R L   | R L   | R L   | R L   |
| Tremor at rest | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | +      | 0      | 0      |
| Postural tremor| +++    | +++    | +      | ++     | +      | +      | +      | +      | +      | +      | +      |
| Rigidity        | +++    | ++     | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    |
| Akininesia     | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    |
| Hypopomimia   | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | 0      | +++    | +++    |
| Micrographia  | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    |
| Dysarthria    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    |
| Stooped posture| +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    |
| Cogwheeling   | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    |
| Postural instability| +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    | +++    |
| Dystonia, affected area | Face | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      |
| Purdue Pegboard Test* | NP | 9-8-6 | 10-10-8 | 2-0-1 | 7-6-4 | 10-8-7 | NP | NP | 10-8-7 | NP | 3-3-0 |
| UPDRS score† | 60    | 28.5   | 20.5   | 47    | 21    | 37    | 53    | 32    | 28    | 24.5   | 61     |
| Response to levodopa treatment | NP | NP | NP | NP | NP | NP | Improvement | NP | NP | Improvement | NP |

*The numbers correspond to the pegs placed in the holes during a 30-second period with the right, left, and both hands successively (R-L-both).
†The maximum score for motor function (part III of the UPDRS) is 108.

**Abbreviations:** L, left side; NP, not performed; R, right side; UPDRS, Unified Parkinson’s Disease Rating Scale; 0, none; +, mild; ++, moderate; ++++, severe.
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] level, 0.339 [0.109] g/L; study range 0.20-0.51 g/L; reference range, 0.22-0.62 g/L) and serum copper (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 innominata, and the putamen.

### Table 2. Relevant Biological Factors in 11 Patients With Cirrhosis-Related Parkinsonism

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range</th>
<th>Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-blood manganese, µg/L</td>
<td>&lt;8.24</td>
<td>1 2 3 4 5 6 7 8 9 10 11</td>
</tr>
<tr>
<td>CSF manganese level, µg/L</td>
<td>0.82-1.48</td>
<td>NP</td>
</tr>
<tr>
<td>Serum copper level, µg/dL</td>
<td>0.80-1.50</td>
<td>NP</td>
</tr>
<tr>
<td>Ceruloplasmin level, g/L</td>
<td>0.22-0.62</td>
<td>NP</td>
</tr>
<tr>
<td>Ammonia level, µg/dL</td>
<td>0.12-0.65</td>
<td>NP</td>
</tr>
<tr>
<td>Erythrocytes, ×10^12/µL</td>
<td>4.4-6.0</td>
<td>NP</td>
</tr>
<tr>
<td>Leukocytes, ×10^9/µL</td>
<td>4.0-11.0</td>
<td>NP</td>
</tr>
<tr>
<td>Thrombocytes, ×10^9/µL</td>
<td>150-350</td>
<td>NP</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>80-120</td>
<td>NP</td>
</tr>
<tr>
<td>Serum albumin level, g/dL</td>
<td>370-530</td>
<td>NP</td>
</tr>
<tr>
<td>Total bilirubin level, mg/dL</td>
<td>0.29-9.95</td>
<td>NP</td>
</tr>
<tr>
<td>Alkaline phosphatase level, U/L</td>
<td>30-125</td>
<td>NP</td>
</tr>
<tr>
<td>Aspartate aminotransferase level, U/L</td>
<td>14-50</td>
<td>NP</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; NP, not performed.

To convert whole-blood manganese to nanomoles per liter multiply by 18.2; copper to micromoles per liter multiply by 0.1574; ammonia to micromoles per liter multiply by 0.714; and total bilirubin to micromoles per liter multiply by 17.1.

### Table 3. Magnetic Resonance Imaging Brain Scan Findings in 9 Patients With Cirrhosis-Related Parkinsonism*

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 2 3 4 5 6 8 9 10 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperintensities</td>
<td></td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td>Putamen</td>
<td>0 0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Caudate nucleus (head)</td>
<td>0 0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td>Substantia innominata</td>
<td>0 ++ 0 ++ 0 ++ 0 ++ 0 ++</td>
</tr>
<tr>
<td>Atrophy</td>
<td>++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td>Calcifications</td>
<td>0 + 0 + 0 + 0 + 0 + 0 +</td>
</tr>
</tbody>
</table>

**Visual scale of hyperintensity and atrophy severity is as follows:** 0, not detected; +, mild; ++, moderate; ++++, severe; for calcifications, 0, none; +, present.

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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,
Clinical features of patients with cirrhosis-related parkinsonism are inconsistent and often emerge as a distinct entity. These patients usually present with a rapidly evolving and symmetric akinetic-rigid syndrome. Severity of symptoms can vary, but postural tremor is prominent. Oculomotor, cerebellar, and pyramidal dysfunctions are absent, but sensory abnormalities are lacking. Cognitive functions are generally preserved except for mild depression. Parkinsonian features are conspicuous, as evidenced by elevated UPDRS scores, and lead to major functional disability. Evolution is characterized by rapid progression 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. MRI studies of our patients are striking and consistently show hyperintensities involving both substantia nigra and globus pallidus symmetrically and homogeneously. They show, on T1-weighted images only, extensive hyperintensities involving 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. 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-
and neuropathological confirmation. 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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REFERENCES

24. Pujol A, Graus F, Peri J, Mercader J, Rimola A. Hyperintensity in the globus pal-


