Craniocerebral Magnetic Resonance Imaging Measurement and Findings in Lesch-Nyhan Syndrome

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Objective: To provide the first comprehensive magnetic resonance imaging (MRI) assessment of brain in a series of patients with Lesch-Nyhan syndrome (LNS), with emphasis on basal ganglia measurements.

Design: Routine readings of MRI studies, repeated reading in random order blinded to subject diagnosis, and 3-dimensional volumetric measures of basal ganglia regions.

Setting: The Johns Hopkins Hospital, Baltimore, Md.

Patients: Seven patients with LNS who have hypoxanthine guanine phosphoribosyltransferase levels less than 1.6% and characteristic clinical features of the disorder, which include hyperuricemia, cognitive impairment, and dystonic movement disorder, were compared with 7 age-matched control subjects. Five of the 7 patients demonstrated self-injurious behavior. MRI studies were performed using general anesthesia because of the severity of the movement disorder.

Main Outcome Measures: Measurement of brain regions from MRI-obtained images.

Results: Routine readings described mild cerebral atrophy in 2 of 7 patients, but no caudate or putamen abnormalities were reported. However, on the directed blinded rereading, small caudates were suspected in 5 of 7 cases, and abnormalities in cerebral size and cranium were identified. Volumetric studies of the patients with LNS confirmed a 34% decrease in caudate volume ($P<.001$), a 17% decrease in total cerebral volume ($P<.03$), and a 12% decrease in putamen volume ($P=.19$).

Conclusions: To our knowledge, this is the first demonstration of consistent neuroanatomic abnormalities in LNS. The findings of reduced basal ganglia volume are consistent with the dystonic movement disorder.

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Lesch-Nyhan syndrome (LNS) is caused by the near absence of the purine salvage enzyme, hypoxanthine guanine phosphoribosyltransferase (HPRT). It is a rare sex-linked metabolic disorder with an estimated prevalence of 1:380,000 with an unusual neurologic and behavioral phenotype. It was first described in 1964 in 2 brothers who presented with hyperuricemia, mental retardation, choreoathetosis, and self-destructive biting. Affected individuals may appear to develop normally during the first months of life, although hypotonia may be present. Between 8 and 12 months of age, prominent motor signs suggestive of dysfunction of the basal ganglia become evident. Subsequently, behavioral features including aggression, self-injurious behaviors, and cognitive dysfunction are recognized. Most patients have choreoathetosis or dystonia, and ballismus has been reported. Other patients also display spasticity with hyperreflexia and abnormal extensor plantar reflexes.

Despite the severe motor disturbance, neuropathologic studies have failed to reveal any consistent neuroanatomic abnormalities in the cortex or basal ganglia, even at the electron microscopic level. There are few reported neuroimaging studies, in part due to the rarity of the disease but also due to technical difficulty in obtaining adequate images without general anesthesia. In descriptions of patients that have included neuroimaging studies, no consistent neuroanatomic abnormalities have been identified. In a thorough longitudinal clinical review of 8 patients with LNS, Watts et al described 3 who had computed tomographic (CT) scans. The images were considered within normal limits, including the cortex and basal ganglia. In another study, CT scans were re-
SUBJECTS AND METHODS

SUBJECTS

Subjects included 7 patients with LNS. The diagnosis was based on the demonstration of HPRT enzyme activity of less than 1.6% in erythrocyte lysates and intact fibroblast cultures performed by Theodore Page, PhD, and William Nyhan, MD, PhD, La Jolla, Calif. All patients displayed a characteristic phenotype that included delayed motor development with hypotonia, early-onset choreoathetosis or dystonia, dysarthria, cognitive impairment, aggressive behavior, and hyperuricemia. Five of the patients also demonstrated typical self-injurious behaviors. The other 2 (HPRT levels of 0.9% and 1.4%) were atypical in that self-injury was not observed. All subjects were male; 6 were white and 1 was African American. They ranged in age from 22 to 35 years (mean age, 25.8 years), with a mental age of 7 years or greater. Consent for the studies was obtained from parents or guardians, and assent was obtained from each of the patients in accordance with a Johns Hopkins institutional review board–approved protocol. The control population consisted of 7 healthy individuals matched for sex and age.

MRI STUDIES

Standard MRI studies on each of the 7 patients with LNS and 7 age-matched controls were completed on a 1.5-T MRI scanner (GE Signa, Milwaukee, Wis) using the following protocol: 5-mm sagittal and 4-mm axial T1-weighted images; 5-mm axial proton-density and conventional (not fast spin-echo) T2-weighted images. The axial images were obtained parallel to the anterior commissure/posterior commissure (AC-PC) line. Axial contiguous 1.5-mm SPoiled GRASS images (described below) were then obtained.

Analysis of the MRI scans consisted of 3 phases. In phase 1, all patients had standard cranial MRI, and interpretations were supplied by an experienced neuroradiologist. In phase 2, scans from patients and controls were blindly reviewed by a neuroradiologist (R.R.L.), without knowledge of how many of the patients were thought to have cortical atrophy, and there were 12 patients with LNS. Mild to moderate diffuse cerebral atrophy was apparent in some, but not all, of these cases. The first study to use standard magnetic resonance imaging (MRI) in LNS reported on 4 patients. Two had normal studies, one had moderate cerebral atrophy, and one had decreased T2 signal in the basal ganglia. In a subsequent study, routine MRI results were reported to be normal in 12 patients who participated in a positron emission tomography procedure.

In the present study, we sought to identify subtle morphologic abnormalities in LNS. We evaluated standard brain MRI scans that were read routinely and, subsequently, by a neuroradiologist blinded to subject diagnosis in 7 classic LNS cases. We assessed changes in brain volumes using volumetric MRI in each of these patients. To our knowledge, there have been no published series that specifically focus on neuroradiologic findings. This is the first series of patients with LNS that provides a systematic description of cranial MRI measurements and that uses volumetric MRI procedures to measure basal ganglia volumes.

RESULTS

PHASE 1: STANDARD MRI FINDINGS

Routine reading of the 7 LNS cases as part of the normal clinical workflow identified few abnormalities. Only 2 patients were thought to have cortical atrophy, and there...
were specific comments about the basal ganglia in only a single patient.

**PHASE 2: BLINDED REVIEW WITH SPECIFIC FOCUS ON BASAL GANGLIA**

When the 14 cases (patients and controls) were retrospectively blindly reviewed in randomized order, with explicit attention to the basal ganglia, several additional features were identified in the patients with LNS only. The MRI scans were blindly read as normal for 6 of 7 control subjects; the scan of the seventh subject showed mild prominence of the sulci of the cerebellar vermis but was read as otherwise normal.

Blindly reviewed neuroradiologic findings on the 7 LNS cases are summarized in Table 1. Three of the 7 patients had small caudates and 2 others had caudates that were believed to be probably small. This assessment was based on the shape of the caudate nucleus and the shape and size of the adjacent frontal horns (Figure 1); small caudates create less of a bulge into the ventricles, resulting in more prominent frontal horns, out of proportion to the rest of the ventricular system. The putamina were believed to be possibly small in only 2 patients. The bicaudate index (bicaudate diameter divided by the outer tables of the skull at the level of measurement) was determined and is described in Table 2. A significant difference ($t_{13}=2.28; P=.04$) was documented between the LNS and control groups.

Parenchymal volume loss, manifested by prominent cerebral sulci, was assessed in 4 patients. In 1 patient, there was focal bifrontal atrophy (Figure 1, B). Two of 7 patients had slightly prominent ventricles. In 4 or 5 patients, there was brainstem atrophy, manifested by prominence of the preoptine cistern and other basal cisterns (Figure 2). One patient had a very large cerebellomedullary cistern, and 2 others were slightly large (Figure 2, A).

No foci of abnormal T2 hyperintensity were observed in the brains of any patients or controls. However, 2 patients with LNS had suggestion of slightly decreased T2 signal within the globus pallidi and substantia nigra on the T2-weighted sequences, whereas all the controls had normal signal.

Rather striking abnormalities of the skull and sinus pneumatization were observed in 5 of 7 patients with LNS, whereas all controls had normal findings. Four patients had prominent thickening of the skull marrow, and 5 had abnormal T1 signal within the marrow that was isointense to brain, rather than exhibiting normal bright fatty signal (Figure 3). The marrow of the clivus and visualized cervical vertebrae also demonstrated this signal abnormality. On T1-weighted images, the marrow signal was not appreciably different from normal fatty mar-

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**Table 1. Qualitative MRI Findings in Lesch-Nyhan Syndrome**

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<th>Patient No.</th>
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<th>4</th>
<th>5</th>
<th>6</th>
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<td>0/−</td>
<td>−</td>
<td>0</td>
<td>0</td>
<td>−</td>
</tr>
<tr>
<td>Putamen size</td>
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<td>0</td>
<td>0</td>
<td>0/−</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrum</td>
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<td>0/−</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
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<td>0</td>
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<td>−</td>
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<td>0</td>
<td>0</td>
<td>−</td>
<td>−</td>
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<tr>
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<td>0</td>
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<td>0</td>
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<td>+</td>
<td>0/−</td>
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<td>+</td>
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<td>+</td>
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</tbody>
</table>

* MRI indicates magnetic resonance imaging; 0, normal; plus sign, increased; minus sign, decreased; 0/−, possibly decreased; and 0/1, possibly increased.

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**Figure 1.** A, Axial T1-weighted SPGR (SPoiled GRASS-Gradient Refocused Acquisition in the Steady-State) image of a patient with Lesch-Nyhan syndrome (LNS) (patient 2; aged 22 years) shows prominent frontal horns, caused by lack of the normal prominent bulging of the caudate heads into the ventricles. The caudate nuclei are small, and the bicaudate distance is large, measuring 1.12 cm at the level of the foramina of Monro. B, Axial T1-weighted SPGR image of a patient with LNS (patient 1; aged 19 years) also shows prominent frontal horns, caused by lack of the normal prominent bulging of the caudate heads into the ventricles. The caudate nuclei are small, and the bicaudate distance is large (1.03 cm). Also present is prominence of the frontal sulci and subarachnoid spaces. C, Axial T-weighted SPGR image of a healthy volunteer (aged 25 years) shows the normal thin configuration of the frontal horns, resulting from lateral impression of the caudate heads into the ventricles. These normal caudates (arrow) are larger and more full and rounded than in the 2 patients with LNS. Bicaudate distance is 0.8 cm.
row. Five patients with LNS also exhibited prominent pneumatization of the paranasal sinuses, especially the frontal sinuses, and the mastoid air cells.

PHASE 3: VOLUMETRIC MRI RESULTS

The MRI volumetric findings are shown in Table 3 and Table 4 and Figure 4. The blinded retrospective review, suggestive of low basal ganglia volume in the majority of cases, was confirmed by volumetric studies. As shown in Table 4, when compared with the 7 age-matched controls studied using the same MRI volumetric sequences, the 7 patients with LNS demonstrated a significant 34% decrease in volume in the caudate nucleus ($P<.001$) and a 12% reduction ($P=.19$) in the putamen that was not significantly different from the controls. The total caudate volume (mean±SD) was 7.9±0.04 cm$^3$ for control subjects and 5.2±0.097 cm$^3$ for patients with LNS ($P<.001$). The total brain volume for the control subjects was 1163.4±79.2 cm$^3$ and for the patients with LNS 963.1±213.96 cm$^3$, a 17% reduction in total brain volume ($P<.01$). Although there was little variability in cerebral size in the control subjects, considerable variability was found in the patients with LNS (range, 799.9–1409.3 cm$^3$). The greatest cortical volume was that of a patient with LNS whose total brain volume was 1409.3 cm$^3$, a value that is 237 cm$^3$ greater than the average of the control group. This patient had classic LNS with an HPRT level of 0.9% and reduction in caudate volume. His cognitive function was in the low normal range.

Table 2. Bicaudate Index in Lesch-Nyhan Syndrome (LNS)

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Bicaudate Diameter, mm</th>
<th>$OT_c^*$</th>
<th>Bicaudate Index</th>
</tr>
</thead>
<tbody>
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<td>Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11.3</td>
<td>130.7</td>
<td>0.087</td>
</tr>
<tr>
<td>2</td>
<td>11.2</td>
<td>127.0</td>
<td>0.088</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
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<tr>
<td>4</td>
<td>9.9</td>
<td>134.0</td>
<td>0.074</td>
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<tr>
<td>5</td>
<td>8.0</td>
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<td>10.3</td>
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<td>0.077</td>
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<tr>
<td>8</td>
<td>9.6</td>
<td>119.8</td>
<td>0.072</td>
</tr>
<tr>
<td>Mean=9.46</td>
<td>Mean=0.075</td>
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<td></td>
</tr>
<tr>
<td>Patients With LNS</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>1</td>
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<td>112.0</td>
<td>0.092</td>
</tr>
<tr>
<td>2</td>
<td>11.2</td>
<td>126.1</td>
<td>0.089</td>
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<td>3</td>
<td>8.4</td>
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<td>Mean=10.71</td>
<td>Mean=0.087†</td>
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</table>

* Distance between the outer tables of the skull at the level of the bicaudate diameter.
† $t_{13}=-2.28; P=.04$.

Table 3 and Table 4 and Figure 4. The blinded retrospective review, suggestive of low basal ganglia volume in the majority of cases, was confirmed by volumetric studies. As shown in Table 4, when compared with the 7 age-matched controls studied using the same MRI volumetric sequences, the 7 patients with LNS demonstrated a significant 34% decrease in volume in the caudate nucleus ($P<.001$) and a 12% reduction ($P=.19$) in the putamen that was not significantly different from the controls. The total caudate volume (mean±SD) was 7.9±0.04 cm$^3$ for control subjects and 5.2±0.097 cm$^3$ for patients with LNS ($P<.001$). The total brain volume for the control subjects was 1163.4±79.2 cm$^3$ and for the patients with LNS 963.1±213.96 cm$^3$, a 17% reduction in total brain volume ($P<.01$). Although there was little variability in cerebral size in the control subjects, considerable variability was found in the patients with LNS (range, 799.9–1409.3 cm$^3$). The greatest cortical volume was that of a patient with LNS whose total brain volume was 1409.3 cm$^3$, a value that is 237 cm$^3$ greater than the average of the control group. This patient had classic LNS with an HPRT level of 0.9% and reduction in caudate volume. His cognitive function was in the low normal range.

COMMENT

The standard MRI studies were read as unremarkable or as showing mild cortical atrophy, and the basal ganglia sizes were not specifically commented on by the neuroradiologists in the original readings. These results are consistent with findings in various case reports that imaging studies are unremarkable in LNS. Yet when these studies of 7 patients with LNS and 7 controls were read blindly by a neuroradiologist with specific attention given to the basal ganglia (without knowledge of how many of the 14 cases were affected with LNS, or which cases were affected), reduced brain volume, particularly in the caudate, was suggested, as well as increases in ventricular size and mild cortical atrophy and/or brainstem atrophy in several patients. (Scans for controls were all read as normal in the blinded readings, except for mild ver-
mian atrophy in 1 control subject.) One case (patient 1) demonstrated specific frontal lobe atrophy, manifested by more prominent frontal sulci than in the rest of the brain, and in this patient, the caudate nuclei were the smallest. Another case (patient 4) showed the greatest brain volume but also demonstrated small caudate nuclei. The main brain findings from the blinded directed readings of patients with LNS were reduction in total cerebral volume and reduced volumes in the caudate and putamen in some cases, when compared with control subjects.

Although the relative decrease in caudate volume and cerebral volume in LNS are similar, the reduction in caudate volume is not merely a reflection of reduction in overall cerebral volume. If the small caudate volume merely reflected a globally small brain, the respective proportions of all structures would be preserved; there would be no relative prominence of the frontal horns, and the bicaudate index would be expected to be normal, not large as documented in Table 2. The overall loss of brain volume is thus composed of proportionately smaller caudates (and perhaps their cortical projections) superimposed on a small brain.

The reduction in brain size was accompanied by thickened calvaria and increased sinus pneumatization or sinus size. The increased thickness of the skull and in sinus size may reflect a failure of continued brain growth, probably beginning in infancy. When brain growth does not continue at the normal rate throughout the developmental years, a compensatory thickening in the skull and sinuses may occur.10

The abnormal thickening and abnormal signal intensity of the skull marrow, with isointense rather than normal fatty hyperintense T2 signal, suggest abnormal increase in marrow hematopoietic activity, consistent with known anemia in LNS.11

Table 3. MRI Volumetric Data*

<table>
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<th>Subject No.</th>
<th>Age, y</th>
<th>L Caudate</th>
<th>R Caudate</th>
<th>L Putamen</th>
<th>R Putamen</th>
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*All volumetric data are given as cubic centimeters. MRI indicates magnetic resonance imaging; LNS, Lesch-Nyhan syndrome.

Table 4. Mean Volumes of Brain and Basal Ganglia Structures for Patients With Lesch-Nyhan Syndrome (LNS) and Controls

<table>
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<tr>
<th>Structure</th>
<th>Mean±SD Volume, cm³</th>
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<th>Control Group</th>
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<td>Globus pallidus</td>
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<td>Total basal ganglia</td>
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<td>18.7±2.1</td>
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<td>Total cerebral</td>
<td>963.1±214.0</td>
<td>1163.4±79.2</td>
<td>.03</td>
<td></td>
</tr>
</tbody>
</table>

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gestion of possible mild T2-dark signal in the globus pallidus found in LNS. Lehericy et al reported that MRI

tent with the movement disorder and cognitive impair-
these patients when compared with control groups. Directed reading suggested the need for volumetric stud-
directly related to the basal ganglia and the skull. Based on our
findings, MRI readings of patients with LNS should in-
duced to be a neurodevelopmental disorder. Rather than
should focus on the caudate, putamen, and brainstem. The second
directed reading suggested the need for volumetric studies
to substantiate differences in the basal ganglia size of
these patients when compared with control groups.

Our subsequent volumetric MRI findings of re-
duced caudate as well as total cerebrum size are consist-
tent with the movement disorder and cognitive impair-
ment found in LNS. Lehericy et al reported that MRI
scans of patients with dystonic spasms had focal lesions
in the striatopallidal complex, involving the putamen pos-
terior to the anterior commissure and extending into the
dorsolateral part of the caudate nucleus, the posterior limb
of the internal capsule, or the lateral segment of the glo-
bus pallidus. Thalamic lesions associated with dystonia
were located in the ventral intermediate and ventral cau-
dal nuclei. Other authors have reported similar find-
ings. Our findings of significantly reduced caudate vol-
ume and a trend toward reduced putamen volume in
patients with LNS are consistent with the striatopallidal
form of dystonia rather than a thalamic form.

These changes differ from those found in Hun-
tington disease or in Parkinson disease. In Huntington
disease, a neurodegenerative disorder, there is a progres-
sive reduction in basal ganglia volumes with age, whereas

in our LNS series there is no apparent decline when the
younger and older patients are compared. In fact, one of
the younger patients (age 22 years) has a caudate vol-
ue similar to that of the 35-year-old patient. In Hun-
tington disease, caudate atrophy has been documented
with CT (bicaudate ratio), and caudate, putamen, and
globus pallidus volume reductions have been reported
on MRI in 10 gene marker-positive asymptomatic persons.
Atrophy of basal ganglia structures has been asso-
ciated with disease duration, severity of dementia, se-
verity of movement disorder, and functional capacity. In
patients with Huntington disease who had mild-to-
moderate motor signs, Harris et al found that putamen
volume was reduced by 50.1% and caudate volume was
reduced by 27.7%. Aylward et al suggest that caudate
volume may show an initial decline and remain fairly
stable in the early stages of Huntington disease, while pu-
tamen volume continues to decline.

In Parkinson disease, CT and MRI scans are usu-
ally normal or show minor degrees of atrophy that are
consistent with involutinal changes in Parkinson dis-
 ease. In Rett syndrome, another neurodevelopmental
disorder, quantitative MRI scans show reduced cerebral
volume, greater loss of gray matter in comparison with
white matter, regional variation in cortical gray matter,
with frontal regions showing the largest decrease, and re-
duced volume of the caudate nucleus and midbrain (ap-
parently taking into account the general reduction in brain
size). Quantitative MRI studies of children and adults
with Tourette syndrome have shown left-sided reduc-
tions in the caudate, putamen, and pallidum.

There are few neuroanatomic studies in LNS. The
brains of 11 patients have been autopsied with variable
reports regarding small brain size. Focal softenings
were noted in 3 reports,areas of gliosis in 3 rep-
ports, and loss of cerebellar cells in 3 reports. The
brain size was considered small in 4 of these
cases. Less commonly noted findings include
demyelinating lesions, cerebellar edema, marked
hydrocephalus, and periodic acid–Schiff–positive in-
clusions in the olivary nuclei. These abnormalities may
be related to postmortem changes secondary to chronic
renal failure in untreated patients or ischemia in pa-
tients dying of pneumonia and aspiration. It is notewor-
thy that neuropathologic examination results were com-
pletely normal in 3 patients. Although the small
brains observed in several prior neuroimaging and neu-
ropathologic studies have been interpreted as showing
 diffuse atrophy, the term atrophy may be misleading since it
implies a pathophysiologic process that has not been
substantiated. In particular, the small brain may reflect
a developmental, rather than a degenerative, process. Our
findings suggest that future neuropathologic studies
should focus on the caudate, putamen, and brainstem.

In contrast to Huntington disease, LNS is consid-
ered to be a neurodevelopmental disorder. Rather than
degenerative atrophy, it is proposed that dopaminergic
innervation of the basal ganglia is curtailed. Reductions
in dopaminergic innervation of the striatum have received
confirmation with positron emission tomographic scan-
ing using a presynaptic dopamine marker (WIN 35,428) and
fluorodopa F. The cause of this
dopamine reduction is unknown. Wong et al. 31 applied partial-volume corrections for caudate and putamen in 6 of the 7 LNS cases reported herein to ascertain reductions in presynaptic dopamine density. Our findings suggest that anatomic abnormalities may extend beyond presynaptic loss of dopamine fibers to account for these changes in volume. The relationship of subcortical atrophy and cortical atrophy has also been considered in Huntington disease, 15 and cortical changes are thought to be secondary to subcortical ones. This is also a consideration in LNS.

In summary, we have documented that there are reductions in caudate volumes in the brain associated with LNS, using volumetric MRI. These findings must be considered when positron emission tomographic scan studies are conducted in patients with LNS since they may make partial-volume correction necessary for appropriate interpretation. Future analyses should focus onascertaining the relationship of these neuroanatomic changes to enzyme levels and the genetic defect. Moreover, it is likely that there are regional cortical changes in the patients, some of which might be predicted by the cortical projection areas of the caudate; these projection areas might be disproportionally smaller than other cortical areas. In the future, cortical brain analysis techniques 32 may be used to obtain these measurements.

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