

PRESYNAPTIC DOPAMINERGIC DEFICITS IN LESCH-NYHAN DISEASE

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Abstract Background. Lesch–Nyhan disease is a rare, devastating, X-linked recessive disorder of purine synthesis. Patients present with hyperuricemia, choreoathetosis, dystonia, and aggressive and self-injurious behavior. Although the genetic and biochemical abnormalities have been identified, the causes of the neuropsychiatric syndrome remain unclear.

Methods. We used positron-emission tomography to measure presynaptic accumulation of fluorodopa F 18 tracer in the dopaminergic regions of the brains of 12 patients with Lesch–Nyhan disease (age, 10 to 20 years) and 15 healthy controls (age, 12 to 23). The results were expressed as ratios of specific to nonspecific radioactive counts. A low ratio indicates decreased dopa decarboxylase activity and dopamine storage.

Results. The fluorodopa F 18 ratio was significantly lower in the putamen (31 percent of control values), cau-

date nucleus (39 percent), frontal cortex (44 percent), and ventral tegmental complex (substantia nigra and ventral tegmentum; 57 percent) in the patients with Lesch–Nyhan disease than in the controls. Uptake of the tracer was abnormally low even in the youngest patients tested, and there was no overlap in the values between patients and controls.

Conclusions. Patients with Lesch–Nyhan disease have abnormally few dopaminergic nerve terminals and cell bodies. The abnormality involves all dopaminergic pathways and is not restricted to the basal ganglia. These dopaminergic deficits are pervasive and appear to be developmental in origin, which suggests that they contribute to the characteristic neuropsychiatric manifestations of the disease. (N Engl J Med 1996;334:1568-72.)

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LESCH–NYHAN disease, a rare X-linked recessive disorder of purine synthesis, is characterized by the virtual absence of hypoxanthine–guanine phosphoribosyltransferase (HPRT), one of the major enzymes of the salvage pathway of purine synthesis. The clinical presentation includes hyperuricemia and a neuropsychiatric syndrome of choreoathetosis, dystonia, aggression, and self-injurious behavior.¹ The genetic defect and biochemical abnormality have been fully identified; however, the mechanism by which the lack of HPRT produces the typical neuropsychiatric manifestations of Lesch–Nyhan disease remains unclear.

Evidence from histopathological studies²; measurements of neurotransmitters and metabolites in brain tissue, blood, and cerebrospinal fluid³⁻⁵; and studies of behavioral and genetic animal models⁶⁻¹¹ point to dopaminergic dysfunction. To date, the strongest support for the dopaminergic hypothesis derives from postmortem findings of a deficit in dopamine, homovanillic acid, and dopa decarboxylase in the basal ganglia of three patients with Lesch–Nyhan disease.² However, the interpretation of postmortem studies is complicated by the effects of both the illness and the events surrounding the death of patients, the effects of drug treatment, and methodologic limitations (varying times between death, collection and freezing of samples, and analysis of samples as well as a shortage of samples). Functional brain imaging is an alternative to postmortem studies, and preliminary studies have sug-

gested a deficit in dopaminergic activity in patients with Lesch–Nyhan disease.¹²⁻¹⁵

We used positron-emission tomography with the tracer fluorodopa F 18 to test the hypothesis that dopaminergic activity is reduced in patients with Lesch–Nyhan disease. This tracer, an analogue of dopa, is a large, neutral amino acid that is transported into presynaptic neurons, where it is converted by the enzyme dopa decarboxylase into [¹⁸F]fluorodopamine, which subsequently enters catecholamine-storage vesicles. Hence, data obtained with the use of fluorodopa F 18 and positron-emission tomography reflect dopa decarboxylase activity and dopamine-storage processes.

METHODS

Study Population

The study was approved by the Human Subjects Protection Committee of the National Institute of Mental Health, and informed consent was obtained from all subjects or their parents. The study population consisted of 15 healthy control subjects (9 male and 6 female; age, 12 to 23 years) and 12 male patients with Lesch–Nyhan disease (age, 10 to 20). Because of the difficulty of recruiting healthy control subjects, particularly adolescents, female subjects were included in the control sample. Control subjects were evaluated by physical examination, routine laboratory tests, and a structured psychiatric interview — the revised diagnostic interview for adolescents and parents for diagnoses listed in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R).^{16,17} Exclusion criteria included acute or chronic medical illnesses, DSM-III-R axis I psychiatric disorders,¹⁷ medical problems including a chronic seizure disorder (one patient who had had a single seizure several years before the scan was included in the study), and a history of head trauma with loss of consciousness.

The patients with Lesch–Nyhan disease were referred to our study from around the United States. In all patients tested, HPRT levels were measured in erythrocytes or fibroblasts at the University of California, San Diego, or Baylor Medical School, Houston, and each had HPRT levels that were less than 1 percent of control values. Treatment with allopurinol, which controls uric acid production, was con-

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tinued throughout the study in all patients, as was treatment with benzodiazepines (2 to 6 mg per day) in six patients.

All the patients had a neuropsychiatric syndrome typical of Lesch-Nyhan disease^{18,19} and were wheelchair-bound with the use of either full or partial restraint 100 percent of the time. A valid index of the severity of self-injurious behavior could not be established, since such behavior was prevented by the restraints, and the extent of restraint depended more on the availability of caretakers for close supervision than on the patient's state. Severity of aggression against others, which included such acts as spitting, cursing, and head butting, was rated by the parents on a 5-point Likert rating scale (on which a score of 1 indicated no aggression and a score of 5 severely aggressive behavior). Testing with the Stanford-Binet Intelligence Scale²⁰ provided an estimate of IQ in the patients with Lesch-Nyhan disease. This measure largely underrated the IQ of the patients, given their severely dysarthric speech, lack of motor coordination, and restricted learning experience.¹⁸ All patients and controls had a magnetic resonance imaging scan that was read as clinically normal by a neuroradiologist.

Positron-Emission Tomography

The tracer fluorodopa F 18 was administered in a one-minute intravenous infusion at a dose of 1.0 mCi in minors (nine patients and nine controls) and 5.0 mCi in adults (those 18 years of age or older; three patients and six controls). To increase the availability of fluorodopa F 18 in plasma to the brain, the peripheral decarboxylation of fluorodopa was blocked by the administration of 100 to 150 mg of carbidopa (aromatic L-amino acid decarboxylase inhibitor) one hour before the injection of the tracer.²¹⁻²³ To minimize the accumulation of nonspecific cerebral radioactivity, which originates mostly from the peripheral metabolite 3-O-methyl-6-[¹⁸F]fluorodopa, the transport system in the blood-brain barrier for large neutral amino acids was saturated by the intravenous infusion of a solution of large, neutral, unlabeled amino acids (5 percent Travasol) starting 60 minutes after the injection of the tracer and maintained at a rate of 40 mg per kilogram of body weight per hour throughout the scanning period.²² The ratio of specific to nonspecific radioactivity was chosen as the measure for analysis because it provides accurate and reliable data and is sensitive to changes in dopaminergic function.²⁴ During the first 80 minutes of tracer uptake, the subjects were watching a videotape. A custom-fitted plastic head holder was used to immobilize the subject's head during the subsequent 40 minutes of scanning time (90 to 120 minutes after the injection of the tracer).

A seven-slice positron-emission tomogram (Scanditronix, Uppsala, Sweden) of the brain was used. The in-plane and axial resolutions were 5.2 mm and 11.8 mm, respectively. Four transverse levels of 7 slices each were collected, for a total of 28 slices, at 3.5-mm intervals. Transmission scans were used to correct for attenuation at all four transverse levels. Thirty-two circular regions of interest of 37 pixels (pixel size, 4 mm²) each were placed on positron-emission tomographic images in order to match a standard template based on the atlas of Matsui and Hirano.²⁵ Each region of interest was identified by a single rater who was unaware of the identity or health status of the subjects. A high level of interrater reliability is achieved with this type of procedure.²⁶

Sedation of the patients with Lesch-Nyhan disease was necessary during the scanning procedure to decrease the risk of patients' injuring themselves and to avoid movement artifacts. Sedation was initiated by an anesthesiologist with a bolus of 1.2 to 2.0 mg of propofol per kilogram given intravenously 85 minutes after the injection of the tracer (i.e., after the tracer had been taken up by the dopaminergic cells and reached a relative steady state). Maintenance levels of propofol were achieved with an infusion rate of 60 to 160 μ g per kilogram per minute. In a parallel study using identical procedures in which some subjects were studied with sedation and some without sedation, preliminary data confirmed that anesthesia had little if any effect on the activity of fluorodopa F 18 in the brain.

Statistical Analysis

Regions of interest were combined into the four dopamine-rich regions of caudate nucleus, putamen, ventral tegmental complex, and

Table 1. Characteristics of the Patients with Lesch-Nyhan Disease and the Controls.*

CHARACTERISTIC	PATIENTS WITH LESCH-NYHAN DISEASE (N = 12)	CONTROLS (N = 15)
Age (yr)	14.7 \pm 3.9	17.0 \pm 3.2
Socioeconomic status [†]	63.6 \pm 21.5	62.0 \pm 35.6
IQ [‡]	66.9 \pm 17.2§	113.5 \pm 13.6
Tanner stage of minors¶	1.8 \pm 1.0§	4.3 \pm 0.7
Severity of aggression against others	3.1 \pm 1.5	—

*Plus-minus values are means \pm SD.

[†]Socioeconomic status was measured with the Hollingshead rating scale²⁷ in which a score of 20 indicates the highest status and a score of 134 the lowest status.

[‡]IQ was assessed with the Wechsler Adult Intelligence Scale²⁸ and the revised Wechsler Intelligence Scale for Children²⁹ in control subjects and with the Stanford-Binet Intelligence Scale²⁰ in all patients with Lesch-Nyhan disease.

[§]P<0.001 by Student's t-test for the comparison between groups.

[¶]Nine minors in each group were clinically assessed. Tanner stage 1 indicates immature secondary sexual characteristics, and Tanner stage 5 mature characteristics.³⁰

^{||}Aggressiveness was assessed with a Likert rating scale by the patients' parents; a score of 1 indicated that the subject was not at all aggressive, a score of 3 moderately aggressive, and a score of 5 extremely aggressive.

frontal cortex and the dopamine-poor region of occipital cortex. The ventral tegmental complex included the mesencephalic dopamine-rich cell bodies of the substantia nigra and the ventral tegmentum. The fluorodopa F 18 activity in the occipital cortex (the mean fluorodopa F 18 activity in the four occipital regions of interest) served as the measure of nonspecific activity, since this region is devoid of dopaminergic nerve terminals. This value was used to normalize the values for fluorodopa F 18 activity in the dopamine-rich areas in order to minimize the effects of differences in tracer and measurement errors on the data used for statistical analyses. These normalized values, or ratios, obtained with the formula (fluorodopa F 18 activity in the region of interest - occipital fluorodopa F 18 activity) \div occipital fluorodopa F 18 activity, were the variables used for analysis.

Comparisons between the patients with Lesch-Nyhan disease and the control group were made with one-way analysis of variance and were not corrected for sex or benzodiazepine treatment because these factors were found, by Student's t-test, not to affect regional fluorodopa F 18 activity.

The association of clinical measures with regional fluorodopa F 18 activity was assessed with Pearson product-moment correlation coefficients.

RESULTS

Study Population

The characteristics of the patients and controls are listed in Table 1. As compared with the controls, the patients had a significantly lower mean IQ (P<0.001) and Tanner stage of sexual development (P<0.001).

Fluorodopa F 18 Activity

The typical extent of the deficit in fluorodopa F 18 activity in the patients with Lesch-Nyhan disease is illustrated in Figure 1, which shows two transverse slices obtained by positron-emission tomography at the level of the basal ganglia in a 20-year-old man with Lesch-Nyhan disease and a 20-year-old healthy man. There is

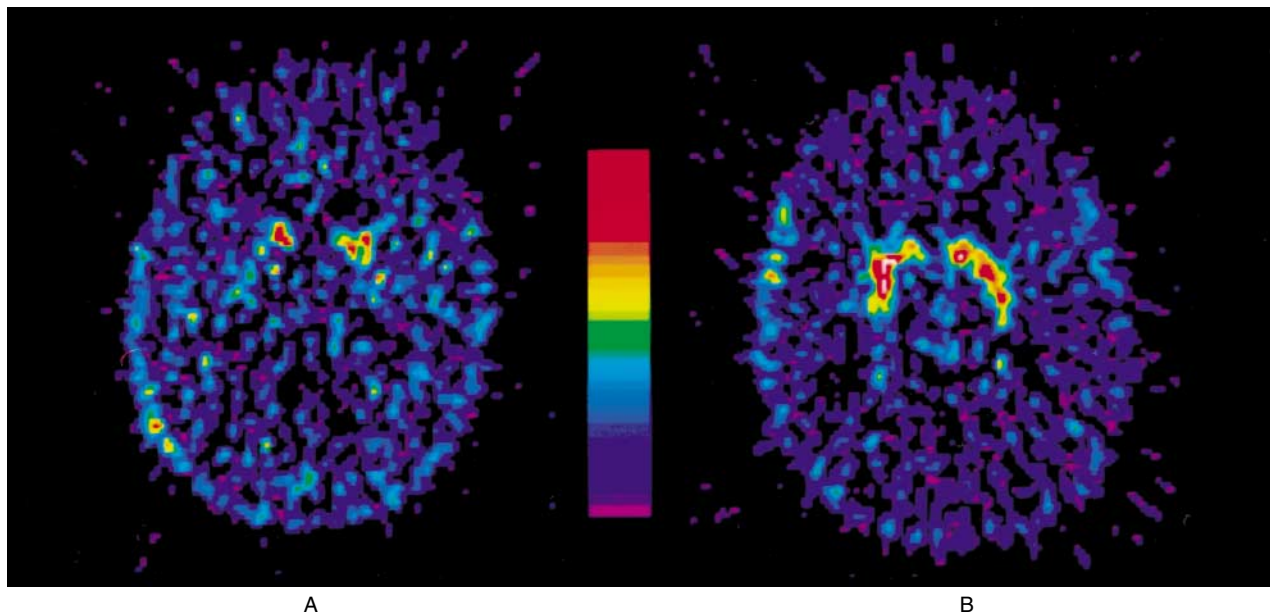


Figure 1. Transverse Positron-Emission Tomogram at the Level of the Basal Ganglia in a 20-Year-Old Man with Lesch–Nyhan Disease (Panel A) and a 20-Year-Old Healthy Man (Panel B).

The features of these images are typical of the findings in the two groups, with profound reductions in fluorodopa F 18 activity in the patients with Lesch–Nyhan disease. According to the color scale, areas with the greatest activity are white and those with the least activity are purple.

considerably less activity in both the right and left basal ganglia of the patient, with a remnant of activity in the caudate nuclei.

One-way analyses of variance confirmed that fluorodopa F 18 activity was significantly lower in the group with Lesch–Nyhan disease than in the control group in all dopaminergic regions measured (putamen, 31 percent of control values; caudate nucleus, 39 percent; frontal cortex, 44 percent; and ventral tegmental complex, 57 percent) (Table 2). These differences were present at all ages examined (Fig. 2).

Associations between Clinical Measures and Cerebral Fluorodopa F 18 Activity

Age, Tanner stage, and IQ did not correlate with fluorodopa F 18 activity in any of the regions examined in either group of subjects. In the 12 patients with Lesch–Nyhan disease, the severity of aggression against others was significantly associated with fluorodopa F 18 activity in the putamen ($r=0.70$, $P<0.01$) and the ventral tegmental complex ($r=0.58$, $P<0.05$), but not in the caudate nucleus ($r=0.17$, P not significant) or frontal cortex ($r=0.43$, P not significant).

DISCUSSION

Lower levels of fluorodopa F 18 activity in the dopaminergic brain regions of 12 patients with Lesch–Nyhan disease than in those of healthy controls reflect decreased dopa decarboxylase activity and reduced dopamine storage. We found no overlap in values between the two groups. With the use of a discriminant value,

determined post hoc, of 1.85 for fluorodopa F 18 activity in the basal ganglia, the measurement of fluorodopa activity was 100 percent sensitive and 100 percent specific for Lesch–Nyhan disease in this small group of subjects. In contrast, magnetic resonance imaging scans of the same subjects were all interpreted as normal.

The apparent involvement of the ventral tegmental complex (which contains dopaminergic cell bodies) along with the basal ganglia and the frontal cortex, which contain dopaminergic nerve terminals, suggests that the neuropathologic process associated with the lack of the enzyme HPRT affects both dopaminergic nerve terminals and cell bodies and probably involves the three dopaminergic pathways: mesocortical, mesolimbic, and nigrostriatal. Dysfunction of these pathways, thought to regulate cognitive, emotional, and motor function, respectively, could account for the complex neuropsychiatric manifestations of Lesch–Nyhan dis-

Table 2. Regional Fluorodopa F 18 Activity in the Patients with Lesch–Nyhan Disease and the Controls.*

REGION	PATIENTS WITH LESCH–NYHAN DISEASE (N = 12)	CONTROLS (N = 15)	PERCENT DIFFERENCE IN VALUES	P VALUE FOR THE DIFFERENCE
Caudate nucleus	1.42±0.31	3.62±1.10	39	<0.001
Putamen	1.07±0.32	3.38±1.08	31	<0.001
Ventral tegmentum	0.59±0.30	1.04±0.57	57	<0.02
Frontal cortex	0.36±0.21	0.80±0.46	44	<0.01

*Plus–minus values are means ±SD. Fluorodopa F 18 activity was determined with the following equation: (fluorodopa F 18 activity in basal ganglia – occipital fluorodopa F 18 activity) ÷ occipital fluorodopa F 18 activity.

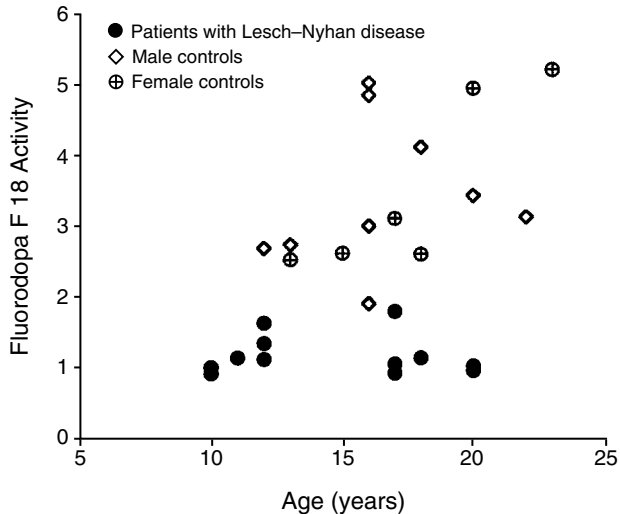


Figure 2. Scatterplot of Individual Fluorodopa F 18 Values in the Basal Ganglia (Caudate Nuclei and Putamen) of Patients with Lesch-Nyhan Disease and Control Subjects as a Function of Age.

Fluorodopa F 18 activity was determined with the following equation: (fluorodopa F 18 activity in basal ganglia - occipital fluorodopa F 18 activity) ÷ occipital fluorodopa F 18 activity.

ease. However, the findings in the frontal cortex and ventral tegmental complex must be interpreted with caution. The low fluorodopa F 18 activity in the frontal cortex and the small size of the dopaminergic nuclei make these measurements less reliable than those in the basal ganglia and therefore require confirmation by other means. An additional problem in estimating the extent of the reduction in dopaminergic activity in the frontal cortex is that the fluorodopa F 18 may originate from the noradrenergic terminals, since dopa is the precursor of both dopamine and norepinephrine. However, there is little evidence to date that the noradrenergic system is seriously involved in the pathophysiologic processes of Lesch-Nyhan disease.^{2,4}

Given these caveats and those already mentioned concerning postmortem studies, the data are remarkably consistent with the results of Lloyd et al.,² who found lower-than-normal concentrations of dopamine in the caudate nucleus (33 percent of control values), putamen (11 percent), and substantia nigra (71 percent) of three patients with Lesch-Nyhan disease examined at autopsy. Furthermore, the magnitude of the dopaminergic deficit in Lesch-Nyhan disease is at least as great as that reported in Parkinson's disease. For example, studies of patients with Parkinson's disease show that rate constants of fluorodopa F 18 uptake, which are highly correlated with fluorodopa F 18 ratios, are 28 to 84 percent of normal values in the caudate nucleus and 39 to 61 percent of normal in the putamen.³¹⁻³³

Although both disorders affect primarily the motor system and share some symptoms, there are important differences. Whereas Parkinson's disease is characterized by a diminution in motor output (bradykinesia),

Lesch-Nyhan disease is a disorder of uncontrolled and exaggerated motor activity (choreoathetoid and ballistic movements), accompanied by compulsive self-injury. The clinical differences may reflect the critical role of ontogeny or the alteration of different neural pathways. For example, in rodents, the developmental stage at which dopaminergic deficit occurs has been shown to be pivotal in the manifestation of abnormal behavior.⁷ The early presence of dopamine in the embryonic brain of primates³⁴⁻³⁶ suggests a role for this neurotransmitter in the neurogenesis of the dopaminergic system and maturation of the striatum. The severity of symptoms in Lesch-Nyhan disease remains constant once the neurobehavioral syndrome is fully expressed.¹⁸ This is consistent with the absence of changes in dopaminergic abnormalities with age, at least within the age range of our sample of patients (10 to 20 years old). A stable dopaminergic deficit suggests a developmental rather than a continuing degenerative process.

The simplest explanation for the relation between aggression and the cerebral accumulation of fluorodopa F 18 in the presence of a profound decrease in dopamine in all the patients is that dysfunction of the dopaminergic system is both the cause and the mediator of the aggression against others. Supersensitivity of postsynaptic dopamine receptors has been suggested to result from this dopamine loss and to mediate the aggressive behavior.^{6,37} However, this cannot be the sole explanation. The facts that long-term treatment with dopamine antagonists has not been useful in Lesch-Nyhan disease¹⁸ and that the results of open-treatment trials with dopaminergic drugs are inconsistent^{4,38} suggest the need for an alternative hypothesis. One such hypothesis is that the aberrant behavior is the result of a reorganization of the neural circuitry involving the basal ganglia-thalamocortical pathways³⁹ during development. The fact that self-injury typically starts during the second year of life¹⁸ suggests that maturation of certain neural pathways is required before the cerebral neuropathological abnormalities translate into maladaptive behavior. Developmental neurobiology may succeed in identifying the neurochemical and structural events that contribute to the expression of the neuropsychiatric syndrome of Lesch-Nyhan disease. Such knowledge may then suggest therapeutic interventions.

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