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Levodopa is Not a Useful Treatment for Lesch-Nyhan Disease

Jasper E. Visser, MD, PhD^{1,2,*}, David J. Schretlen, PhD³, Bastiaan R. Bloem, MD, PhD¹, and Hyder A. Jinnah, MD, PhD⁴

¹Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands ²Department of Neurology, Amphia Hospital, Breda, The Netherlands ³Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA ⁴Departments of Neurology and Human Genetics, Emory University School of Medicine, Atlanta, Georgia, USA

Abstract

Lesch-Nyhan disease (LND) is characterized by dystonia, cognitive abnormalities, and self-injurious behavior. No effective therapies are available. LND is associated with a presynaptic dopaminergic deficit, but the reported effects of dopamine replacement therapy are conflicting. The current prospective open-label study assesses the effects of levodopa on both neurological and behavioral features of LND. All 6 study participants discontinued levodopa early, due to lack of effect and sometimes worsening of motor function. The results provide important clues for pathophysiological mechanisms and suggestions for future treatment options.

Keywords

Lesch-Nyhan disease; treatment; levodopa; dystonia; dyskinesias; self-injurious behavior

Introduction

Lesch-Nyhan disease (LND) is caused by a mutation in the gene encoding the purine salvage enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT).^{1,2} Near-complete HPRT deficiency causes hyperuricemia and a characteristic neurobehavioral phenotype. Patients exhibit a movement disorder dominated by dystonia, chorea, and hypotonia³; cognitive dysfunction characterized by attentional and executive deficits; and behavioral abnormalities including self-injurious behavior.^{4,5} Effective therapies for the neurobehavioral features of LND are currently lacking.²

Available evidence indicates that LND is associated with a presynaptic dopaminergic deficit. Postmortem human brain tissue shows a 60 to 90% decrease in basal ganglia dopamine levels, whereas other neurotransmitter systems are preserved.^{6,7} In vivo PET imaging studies demonstrate a low dopamine transporter (DAT) density⁸ and a decreased dopamine uptake in presynaptic terminals.⁹ The relation between HPRT deficiency and dopamine dysfunction is further supported by a 50% decrease in basal ganglia dopamine

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*Correspondence to: Dr. Jasper E. Visser, Department of Neurology (HP 935), Radboud University Nijmegen Medical Centre, PO Box 9101, Nijmegen 6500 HB, The Netherlands; j.visser@neuro.umcn.nl.

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content in HPRT-deficient knockout mice¹⁰⁻¹² and in HPRT-deficient dopaminergic cell lines.¹³ Despite the loss of dopamine-related markers, there is no loss of nigral dopamine neurons in autopsy studies.⁷

These findings suggest that treatment with the dopamine precursor levodopa (L-dopa) may be helpful, but the few reported effects so far are conflicting. Motor function improved in 3 patients,¹⁴⁻¹⁶ worsened in 4,^{17,18} and remained unchanged in another 2.^{14,19} Similar contradictory effects have been reported for the effects of L-dopa on self-injury, including improvement,¹⁷ deterioration,¹⁸ or no change.¹⁷ The interpretation of these reports is hampered by lack of detailed information about treatment duration and clinical assessment. Subtle changes in specific domains of motor, cognitive, or behavioral function may have been missed. To examine more carefully the effects of L-dopa on both neurological and behavioral features of LND, we conducted a prospective, open label, dose-escalation study.

Patients and Methods

Patients

We intended to include 10 LND patients, ranging from 2 to 40 years of age. Patients had been diagnosed with LND based on DNA mutation analysis or residual HPRT enzyme activity, and all demonstrated a clinical picture typical of LND (Table 1). Exclusion criteria included a known intolerance to L-dopa/carbidopa. Written consent was obtained from patients or their parents before inclusion. The study was approved by the local ethical committee.

Intervention

L-Dopa/carbidopa (4:1) was initiated at a low dose, typically starting at 50/12.5 mg once per day, and titrated to a maximum of 20 mg/kg L-dopa (divided 3 times per day) over 2 to 6 weeks. The study had a prospective open-label design.

Outcome Measures

The primary outcome measure was dystonia severity, as assessed in an unblinded fashion, using the Burke-Fahn-Marsden dystonia rating scale.²⁰ Clinical assessments were scheduled at baseline, before starting medication, and at least 1 month after reaching the target or maximally tolerated dose. Secondary outcome variables included the severity of self-injurious behaviors, determined via a weekly telephone questionnaire developed for this purpose (Supporting Information Table 1).

Results

None of the subjects completed the planned titration phase, and enrollment was terminated before the target number of 10 participants was reached. The average duration of therapy was ~2 weeks (range 1 day to 4 weeks). The average daily dose of L-dopa/carbidopa reached was 200/50 mg (range 50/12.5 to 600/150 mg) per day.

The reasons for early discontinuation are shown in Table 2. Four participants showed increased motor dysfunction, in the form of rigidity and tongue stiffness, limb flailing, and wild, agitated movements. One participant discontinued the medication after his brother developed side effects, even though he had not. There were no significant effects of L-dopa on self-injury in any participant.

Discussion

Available biochemical, functional imaging, and experimental data indicate that LND is associated with an early, relatively selective presynaptic dopaminergic deficit, and that the subsequent basal ganglia dysfunction is an important contributor to the motor, cognitive, and behavioral abnormalities.²¹ The current prospective open-label study investigated the effect of L-dopa therapy on motor and behavioral abnormalities in LND. L-Dopa treatment did not prove to be beneficial in either domain and was associated with a worsening of motor function in several patients, resulting in an early termination of the study. This early L-dopa-induced exacerbation of the movement disorder provides some clues to LND pathogenesis.

As opposed to adults, where it usually results in parkinsonism, decreased dopamine in children usually causes dystonia, for which L-dopa may be beneficial. Examples include inherited deficiency of tyrosine hydroxylase (TH), or GTP cyclohydrolase (GTP-CH).²² Experimental studies support the concept that the age at which striatal dopamine depletion occurs has a profound influence on both motor outcome and response to L-dopa. For example, in adult rats, destruction of nigrostriatal dopamine neurons results in a motor syndrome resembling parkinsonism, but the same lesion in neonatal rats causes hyperactivity and aggressiveness.²³ And, unlike the amelioration of motor impairments observed in adult-lesioned rats, treatment of neonatally lesioned animals with L-dopa exacerbates their hyperactivity.²⁴ It has been proposed that differences in adaptive neuroplasticity—referring to receptor function, postreceptor signaling pathways, electrophysiological function, and synaptic changes—may account for these phenotypic differences caused by dopaminergic lesions at young compared to adult age.

Analogous adaptive processes have been suggested for the etiology of L-dopa-induced dyskinesias in advanced Parkinson's disease (PD).²⁵ It is tempting to speculate that similar neuroplastic changes may be responsible for the dystonia and the L-dopa-induced exacerbation in LND. Indeed, descriptions of the motor complications, by patients and their caretakers, closely resemble L-dopa-induced dyskinesias.²⁶ Similarly, impulse control disorders in PD, which have been regarded as the behavioral counterpart of L-dopa-induced dyskinesias,²⁵ might share intrinsic properties with the impulsive behaviors in LND, and it has been hypothesized that also the pathogenesis of self-injurious behavior in LND is similar to drug-induced dyskinesias.²⁷ The absence of major effects of L-dopa on self-injurious behavior in the current study might be explained by insufficient treatment duration, or different pathological mechanisms (and sensitivity) causing motor and behavioral symptoms in LND.

It has been hypothesized that the improvement reported in a single LND patient treated with L-dopa aged from 10 months is attributable to the (at least partial) prevention of the compensatory neuroplastic changes by restoring L-dopa levels at an early stage in neurodevelopment.¹⁵ Unfortunately, this observation was not substantiated by objective measures. Such a preventive effect of very early L-dopa treatment cannot be ruled out but could not be confirmed in our 2 youngest subjects of 3 years of age. Another LND patient, treated after the study ended, started at 12 months of age and showed no obvious improvement of the motor disorder after a year. It should be noted that starting treatment before age 2 is not practical in LND patients, as diagnoses typically often are delayed for years.²

The observation that some patients with TH deficiency are acutely sensitive to L-dopa-induced hyperkinesias,²⁸ prompted us to start with very low doses. It could, however, be argued that the dyskinesias observed reflected an extreme sensitivity that could have been avoided by using even lower doses or slower titrations—similar to some experiences with

dopa-responsive dystonia. Such an extreme sensitivity seems unlikely, for several reasons. First, again after the formal study ended, we treated an adult with dystonia due to partial HPRT deficiency with escalating doses of L-dopa for 6 months. He never benefited, but developed worsening of his motor disorder after 4 to 5 months, ultimately leading to discontinuation of the drug. Additionally, 4 classic LND patients included in the current study were given trials of dopamine agonists, starting with 0.5 mg ropinirole or 0.125 mg pramipexole daily and titrating upward. None experienced dyskinesias, but none benefited either and all discontinued. Finally, mechanistically, TH and GTP-CH deficiency are associated with a selective loss of catecholamines whereas LND causes loss of TH, aromatic L-amino acid decarboxylase, vesicular monoamine transporter, and DAT.² Therefore, the mechanism in LND is clearly more complex than DOPA-responsive dystonia, and responses to medications can, therefore, be expected to be different.

Based on the assumption that the neurobehavioral features in LND share pathophysiological mechanisms with dyskinesias in PD, treatments that have proven beneficial for dyskinesias could be considered for LND in the near future. Examples include the glutamate antagonist amantadine,²⁶ or deep brain surgery (DBS). In fact, 4 LND patients who underwent DBS have been reported in the literature to date,^{27,29,30} and some showed improvements in motor dysfunction and behavior. However, long-term effects are unclear, and more studies are needed before DBS can be considered effective and safe in LND.

In summary, the current study demonstrates that L-dopa is not useful for the treatment of LND and might worsen the movement disorder, but it also provides important clues for pathophysiological mechanisms and hints to future treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Lesch M, Nyhan WL. A familial disorder of uric acid metabolism and central nervous system function. *Am J Med.* 1964; 36:561–570. [PubMed: 14142409]
2. Jinnah, HA.; Friedmann, T. Lesch-Nyhan disease and its variants. In: Scriver, CR.; Beaudet, AL.; Sly, WS.; Valle, D., editors. *The metabolic and molecular bases of inherited disease*. New York: McGraw-Hill; 2001. p. 2537-2570.
3. Jinnah HA, Visser JE, Harris JC, et al. Delineation of the motor disorder of Lesch-Nyhan disease. *Brain.* 2006; 129:1201–1217. [PubMed: 16549399]
4. Schretlen DJ, Harris JC, Park KS, Jinnah HA, del Pozo NO. Neurocognitive functioning in Lesch-Nyhan disease and partial hypoxanthine-guanine phosphoribosyltransferase deficiency. *J Int Neuropsychol Soc.* 2001; 7:805–812. [PubMed: 11771623]
5. Matthews WS, Solan A, Barabas G. Cognitive functioning in Lesch-Nyhan syndrome. *Dev Med Child Neurol.* 1995; 37:715–722. [PubMed: 7672468]
6. Lloyd KG, Hornykiewicz O, Davidson L, et al. Biochemical evidence of dysfunction of brain neurotransmitters in the Lesch-Nyhan syndrome. *N Engl J Med.* 1981; 305:1106–1111. [PubMed: 6117011]
7. Saito Y, Ito M, Hanaoka S, Ohama E, Akaboshi S, Takashima S. Dopamine receptor upregulation in Lesch-Nyhan syndrome: a postmortem study. *Neuropediatrics.* 1999; 30:66–71. [PubMed: 10401687]

8. Wong DF, Harris JC, Naidu S, et al. Dopamine transporters are markedly reduced in Lesch-Nyhan disease in vivo. *Proc Natl Acad Sci USA*. 1996; 93:5539–5543. [PubMed: 8643611]
9. Ernst M, Zametkin AJ, Matochik JA, et al. Presynaptic dopaminergic deficits in Lesch-Nyhan disease. *N Engl J Med*. 1996; 334:1568–1572. [PubMed: 8628337]
10. Dunnett SB, Sirinathsinghji DJ, Heavens R, Rogers DC, Kuehn MR. Monoamine deficiency in a transgenic (Hprt-) mouse model of Lesch-Nyhan syndrome. *Brain Res*. 1989; 501:401–406. [PubMed: 2573408]
11. Finger S, Heavens RP, Sirinathsinghji DJ, Kuehn MR, Dunnett SB. Behavioral and neurochemical evaluation of a transgenic mouse model of Lesch-Nyhan syndrome. *J Neurol Sci*. 1988; 86:203–213. [PubMed: 3221240]
12. Jinnah HA, Wojcik BE, Hunt M, et al. Dopamine deficiency in a genetic mouse model of Lesch-Nyhan disease. *J Neurosci*. 1994; 14:1164–1175. [PubMed: 7509865]
13. Egami K, Yitta S, Kasim S, et al. Basal ganglia dopamine loss due to defect in purine recycling. *Neurobiol Dis*. 2007; 26:396–407. [PubMed: 17374562]
14. Manzke H, Gustmann H, Koke HG, Nyhan WL. Hypoxanthine and tetrahydrobiopterin treatment of a patient with features of the Lesch-Nyhan syndrome. *Adv Exp Med Biol*. 1986; 195(Pt A): 197–203. [PubMed: 3728152]
15. Serrano M, Perez-Duenas B, Ormazabal A, et al. Levodopa therapy in a Lesch-Nyhan disease patient: pathological, biochemical, neuroimaging, and therapeutic remarks. *Mov Disord*. 2008; 23:1297–1300. [PubMed: 18528895]
16. Mizuno TI, Yugari Y. Letter: self mutilation in Lesch-Nyhan syndrome. *Lancet*. 1974; 1:761. [PubMed: 4132504]
17. Jankovic J, Caskey TC, Stout JT, Butler IJ. Lesch-Nyhan syndrome: a study of motor behavior and cerebrospinal fluid neuro-transmitters. *Ann Neurol*. 1988; 23:466–469. [PubMed: 2455472]
18. Watts RW, Spellacy E, Gibbs DA, Allsop J, McKeran RO, Slavin GE. Clinical, post-mortem, biochemical and therapeutic observations on the Lesch-Nyhan syndrome with particular reference to the Neurological manifestations. *Q J Med*. 1982; 51:43–78. [PubMed: 7111674]
19. Hunter TC, Melancon SB, Dallaire L, et al. Germinal HPRT splice donor site mutation results in multiple RNA splicing products in T-lymphocyte cultures. *Somat Cell Mol Genet*. 1996; 22:145–150. [PubMed: 8782493]
20. Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. *Neurology*. 1985; 35:73–77. [PubMed: 3966004]
21. Visser JE, Bar PR, Jinnah HA. Lesch-Nyhan disease and the basal ganglia. *Brain Res Brain Res Rev*. 2000; 32:449–475. [PubMed: 10760551]
22. Muller U. The monogenic primary dystonias. *Brain*. 2009; 132:2005–2025. [PubMed: 19578124]
23. Moy SS, Criswell HE, Breese GR. Differential effects of bilateral dopamine depletion in neonatal and adult rats. *Neurosci Biobehav Rev*. 1997; 21:425–435. [PubMed: 9195600]
24. Breese GR, Baumeister AA, McCown TJ, et al. Behavioral differences between neonatal and adult 6-hydroxydopamine-treated rats to dopamine agonists: relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. *J Pharmacol Exp Ther*. 1984; 231:343–354. [PubMed: 6149306]
25. Voon V, Fernagut PO, Wickens J, et al. Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *Lancet Neurol*. 2009; 8:1140–1149. [PubMed: 19909912]
26. Fabbrini G, Brotchie JM, Grandas F, Nomoto M, Goetz CG. Levodopa-induced dyskinesias. *Mov Disord*. 2007; 22:1379–1389. quiz 1523. [PubMed: 17427940]
27. Taira T, Kobayashi T, Hori T. Disappearance of self-mutilating behavior in a patient with lesch-nyhan syndrome after bilateral chronic stimulation of the globus pallidus internus. Case report. *J Neurosurg*. 2003; 98:414–416. [PubMed: 12593632]
28. Grattan-Smith PJ, Wevers RA, Steenbergen-Spanjers GC, Fung VS, Earl J, Wilcken B. Tyrosine hydroxylase deficiency: clinical manifestations of catecholamine insufficiency in infancy. *Mov Disord*. 2002; 17:354–359. [PubMed: 11921123]

29. Cif L, Biolsi B, Gavarini S, et al. Antero-ventral internal pallidum stimulation improves behavioral disorders in Lesch-Nyhan disease. *Mov Disord.* 2007; 22:2126–2129. [PubMed: 17853483]
30. Pralong E, Pollo C, Coubes P, et al. Electrophysiological characteristics of limbic and motor globus pallidus internus (GPI) neurons in two cases of Lesch-Nyhan syndrome. *Neurophysiol Clin.* 2005; 35:168–173. [PubMed: 16530134]

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Table 1

Demographics and clinical characteristics of enrolled subjects

Case	Age (yr)	Mutation	HPRT activity	Medication	Motor disorder		
					Clinical signs	BFM	Self-injurious behavior
1	27	428–432del TGCAG, insAGCAAA	<1%	Allopurinol, chlorothiazide	Dystonia, chorea, ballism, hypotonia, ophistotonus, hyperreflexia	97.5	Biting fingers, lips
2	12	IVS7+5G>A	<1%	Allopurinol, diazepam, omeprazole, fluticasone, mometasone, cetirizine, levalbuterol	Dystonia, rigidity, spasticity, hyperreflexia	69.5	Biting various body parts; head banging
3	10	IVS7+5G>A	<1%	Allopurinol, diazepam,	Dystonia, hypotonia	33.5	Biting fingers, arms
4	3	508C>T	<1%	Allopurinol, gabapentin, benzodiazepine, ranitidine	Dystonia, hypotonia, ophistotonus	57.5	Biting fingers; head banging; hitting himself
5	3	10delC	N/A	Allopurinol, gabapentin, lorazepam	Dystonia, hypotonia	61.0	Biting buccal mucosa; hitting

Abbreviations used: HPRT, hypoxanthine-guanine phosphoribosyl transferase; BFM, Burke-Fahn-Marsden dystonia rating scale; N/A, not available.

Table 2

Effect of L-dopa on motor function and self-injury

Case	Treatment duration	Maximum dose L-dopa/carbidopa (mg daily)	Effect on motor disorder	Effect on self-injury
1	4 weeks	600/150	Stiff arms, pronounced and less controllable movements	No obvious change
2	1 day	50/12.5	No apparent change ^a	No obvious change
3	1 day	50/12.5	Hyperactive	No obvious change
4	2 weeks	150/37.5	Twisted and stiff tongue, facial twitching, limb flailing	No obvious change
5	4 weeks	150/37.5	Stiff and agitated movements	Better mood, accompanied by less need for restraints

^aThe mother of subject #2 discontinued L-dopa because of side effects experienced by his brother, subject #3.