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Normal Dopaminergic Nigrostriatal Innervation in SPG3A Hereditary Spastic Paraplegia

Roger L. Albin^{1,2}, Robert A. Koeppe³, Shirley Rainier², and John K. Fink^{1,2}

¹Geriatrics Research, Education, and Clinical Center, Ann Arbor VAHS, Ann Arbor, Michigan, USA

²Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA

³Department, of Radiology (Nuclear Medicine), University of Michigan, Ann Arbor, Michigan, USA

Abstract

SPG3A/atlastin-1 gene mutations cause an autosomal dominant form of hereditary spastic paraplegia (SPG3A-HSP). We used positron emission tomography with [¹¹C]DTBZ to assess nigrostriatal dopaminergic integrity in two unrelated adults with SPG3A-HSP due to the common *SPG3A/atlastin-1* mutation, R239C. Nigrostriatal dopaminergic terminal density was normal. A difference from the human pattern of neurodegeneration is a critical limitation of this *Drosophila* model of SPG3A-HSP. This major difference between human *SPG3A/atlastin-1* mutations and the *Drosophila atl^l* phenotype has several possible explanations.

Keywords

atlastin; dopamine; striatum; dihydrotetrabenazine; positron emission tomography

INTRODUCTION

The hereditary spastic paraplegias (HSPs) are a genetically heterogeneous group of disorders characterized by lower extremity spasticity and weakness (Fink, 2007). Postmortem studies of uncomplicated HSP reveal axonal degeneration in distal ends of corticospinal tracts and *fasciculus gracilis* fibers.

SPG3A/atlastin-1 gene mutations cause an autosomal dominant form of hereditary spastic paraplegia (SPG3A-HSP) that usually manifests with early-childhood-onset spastic gait (Zhao et al., 2001). *SPG3A/atlastin-1* encodes a 63.5-kD protein (atlastin-1) that contains conserved GTPase motifs and bears a sequence similarity to guanylate-binding protein 1, a member of the dynamin family of large GTPases (Zhao et al., 2001). Through database analysis, Zhu et al. (2003) identified two highly similar proteins, designated atlastin-2 and -3.

Lee et al. (2008) reported that *Drosophila* bearing a null mutation (designated *atl^l*) in an *SPG3A/atlastin-1* homolog exhibited paralysis following mechanical shock, premature mortality, and age-related degeneration of dopaminergic neurons. The motor impairment could be rescued by feeding *atl^l* mutant *Drosophila* the dopamine precursor L-dopa or the dopaminergic D1 receptor agonist, SK&F 38393. The entire phenotype could be rescued by transgenic expression of wild-type *atl*. Observations of dopaminergic neuron vulnerability in

atl-mutant *Drosophila* raise the possibility that degeneration of central dopaminergic neurons could contribute to the phenotype of SPG3A-HSP. Lee et al. point out correctly that this would have treatment implications for individuals with SPG3A-HSP. We evaluated this possibility by assessing nigrostriatal terminal integrity in two unrelated subjects with HSP due to a *SPG3A/atlastin-1* mutation.

METHODS

This investigation was approved by our Institutional Review Board.

Clinical

We studied two unrelated female subjects, ages 38 and 37, with autosomal-dominant SP3A-HSP due to *SPG3A/atlastin-1* mutation R239C, one of the common *SP3A/atlastin-1* mutations. Each subject had a childhood onset of spastic gait that did not significantly worsen in subsequent decades. There was no evidence of cogwheel rigidity, tremor, bradykinesia, hypomimia, hypokinetic dysarthria, slow tongue movements, slowed finger tapping, or other clinical signs of nigrostriatal dopamine deficiency.

Neuroimaging

To quantify nigrostriatal terminal integrity, both subjects underwent [^{11}C] dihydrotetrabenazine positron emission tomography (DTBZ-PET), as described previously (Bohnen et al., 2005). Nigrostriatal terminal density was quantified in dorsal caudate, ventral striatum, anterior putamen, and posterior putamen. DTBZ binding was measured as peak distribution volume (DV) in each subregion. DTBZ binds to the type 2 vesicular monoamine transporter (VMAT2), the protein responsible for pumping monoamines from the cytosol into synaptic vesicles. VMAT2 is expressed at uniquely high levels by nigrostriatal terminals. DV is a measure of binding-site density. Results were compared with a dataset of 22 age-matched controls.

RESULTS

Both HSP subjects had normal striatal DTBZ binding in all striatal subregions (Table 1 and Figure 1).

DISCUSSION

DTBZ-PET demonstration of normal nigrostriatal innervation correlates with the absence of Parkinsonism in our patients and previously described SPG3A subjects. Although *Drosophila* appears to be a useful species in which to study the molecular pathogenesis of other forms of HSP, *Drosophila* bearing the null *atl*^l mutation do not reproduce faithfully the distribution of neurodegeneration seen in SPG3A-HSP (Orso et al., 2005). DTBZ-PET and other PET methods assessing dopaminergic nigrostriatal terminal density are specific and sensitive measures of nigrostriatal projection integrity. DTBZ-PET was used to detect modest reductions of nigrostriatal terminal density in rapid eye movement sleep behavior disorder, which is often a precursor of Parkinsonism (Albin et al., 2000). Similar PET methods have been used to detect the loss of nigrostriatal terminals in presymptomatic carriers of mutant alleles, causing Mendelian forms of Parkinson's disease (Adams et al., 2005). The natural history of SPG3A-HSP is discrepant with the course of the *atl*^l mutation phenotype. Lee et al. described age-dependent motor impairment, premature mortality, and age-dependent neurodegeneration. The SPG3A-HSP phenotype, in contrast, develops in childhood and then remains static.

There at least three explanations for the observed species-specific differences in the patterns and time course of neurodegeneration due to *SPG3A/atlastin-1* mutation and its *Drosophila* orthologue. First, these differences could reflect the nature of the discrete mutations in *SPG3A/atlastin-1* and *atl* mutations investigated. The dominant character of the SPG3A-HSP raises the possibility that the human disease results from a gain of function effect. Some data, however, suggest that SPG3A-HSP results from haploinsufficiency. Muglia et al. (2002) described a pedigree with an Arg217Gln missense mutation in a highly conserved part of the GTPase domain of *atlastin*, probably altering the GTPase active site. Tessa et al. (2002) describe another pedigree with a frameshift mutation leading to a premature translation termination. Second, it is possible that the discrepancy between human *SPG3A/atlastin-1* mutations and the *atl*^l phenotype is related to species-specific differences in selective neuronal vulnerability. Third, it is possible that there are significant differences in the molecular functions of *SPG3A/atlastin-1* mutation and its *Drosophila* ortholog.

CONCLUSIONS

It is notable that while there is one *Drosophila atlastin*-like locus, human and murine *atlastins* are a small family of related proteins (*atlastin-1*, -2, and -3). The possibility exists that dopaminergic degeneration in the *Drosophila atl*^l null mutation is analogous to the loss of function of either *atlastin-2* or -3. It might be worthwhile to evaluate these loci (*atlastin-2* or -3) as potential causes of Mendelian forms of Parkinson's disease.

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REFERENCES

- Adams JR, van Netten H, Schulzer M, Mak E, Mckenzie J, Strongosky A, Sossi V, Ruth TJ, Lee CS, Farrer M, Gasser T, Uitti RJ, Calne DB, Wszolek ZK, Stoessl AJ. PET in LRRK2 mutations: comparison to sporadic Parkinson's disease and evidence for presymptomatic compensation. *Brain* 2005;128:2777–2785. [PubMed: 16081470]
- Albin RL, Koeppe RA, Chervin RD, Consens FB, Wernette K, Frey KA, Aldrich MS. Decreased striatal dopaminergic innervation in REM sleep behavior disorder. *Neurology* 2000;55:1410–1412. [PubMed: 11087796]
- Bohnen NI, Albin RL, Koeppe RA, Wernette K, Kilbourn MR, Minoshima S, Frey KA. Positron emission tomography of monoaminergic vesicular binding in aging and Parkinson's disease. *JCBFM* 2006;26:1198–1212.
- Fink, JK. The hereditary spastic paraplegias. In: Rosenberg, R., editor. *Molecular and Genetic Basis of Neurologic and Psychiatric Disease*. Vol. 4th Ed.. Philadelphia: Lippincott Williams & Wilkins; 2007.
- Lee Y, Paik D, Bang S, Kang J, Chun B, Lee S, Bae E, Chung J, Kim J. Loss of spastic paraplegia gene *atlastin* induces age-dependent death of dopaminergic neurons in *Drosophila*. *Neurobiol. Aging* 2008;29:84–94. [PubMed: 17030474]
- Muglia M, Magariello A, Nicoletti G, Patitucci A, Gabriele AL, Conforti FL, Mazzei R, Caracciolo M, Ardito B, Lastilla M, Tedeschi G, Quattrone A. Further evidence that SPG3A gene mutations cause autosomal dominant hereditary spastic paraplegia. *Ann. Neurol* 2002;51:669–672. [PubMed: 12112070]
- Orso G, Martinuzzi A, Rossetto MG, Sartori E, Feany M, Daga A. Disease-related phenotypes in a *Drosophila* model of hereditary spastic paraplegia are ameliorated by treatment with vinblastine. *J. Clin. Invest* 2004;115:2968–2971.
- Tessa A, Casali C, Damiano M, Bruno C, Fortini D, Patrono C, Cricchi F, Valoppi M, Nappi G, Amabile GA, Bertini E, Santorelli FM. SPG3A: an additional family carrying a new *atlastin* mutation. *Neurology* 2002;59:2002–2005. [PubMed: 12499504]

- Zhao X, Alvarado D, Rainier S, Lemons R, Hedera P, Weber CH, Tükel T, Apak M, Heiman-Patterson T, Ming L, Bui M, Fink JK. Mutations in a novel newly identified GTPase gene cause autosomal dominant hereditary spastic paraplegia. *Nat. Genet* 2001;29:326–331. [PubMed: 11685207]
- Zhu PP, Patterson A, Lavoie B, Stadler J, Shoeb M, Pate R, Blackstone C. Cellular localization, oligomerization, and membrane association of the hereditary spastic paraplegia 3A (SPG3A) protein atlastin. *J. Biol. Chem* 2003;278:49063–49071. [PubMed: 14506257]

Figure 1. Transaxial parametric DTBZ-PET images of nigrostriatal terminals in SPG3A-HSP subjects and representative control. SPG3A-HSP and control are identical.

Table 1

Striatal Control and Individual HSP Subject Data

Region	Dorsal caudate	Ventral striatum	Anterior putamen	Posterior putamen
Controls: mean BP	2.422	1.668	2.516	2.398
(COV%)	(17.9%)	(19.7%)	(15.7%)	(17.4%)
HSP subject 1	2.484	1.505	2.613	2.596
% of control mean BP	102.6%	90.3%	103.9%	108.3%
HSP subject 2	2.104	1.742	2.337	2.368
% of control mean BP	86.9%	104.5%	92.9%	98.7%

Values are the binding potential (BP; DVR – 1).