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Parkinsonism Syndrome in Heterozygotes for Niemann Pick C1

Hans H. Klunemann¹, John G. Nutt², Marie Y. Davis³, and Thomas D. Bird^{3,4}

¹Department of Psychiatry, University of Regensburg, Germany

²Department of Neurology, Oregon Health and Sciences University, Portland, Oregon

³Department of Neurology, University of Washington, Seattle, WA

⁴GRECC, VA Puget Sound Health Care System, Seattle, WA

Abstract

Niemann Pick C (NPC) disease is a rare autosomal recessive lipid storage disorder. We report here the unique occurrence of three adult heterozygous carriers of mutations in the *NPC1* gene who also have a parkinsonism syndrome. This suggests the possibility that mutations in *NPC1* could be a risk factor for Parkinson disease similar to the phenomenon that is now recognized with Gaucher disease and the glucocerebrosidase (*GBA*) gene. This report should be a stimulus for larger more detailed epidemiological studies.

Keywords

Parkinson disease; Niemann Pick C disease; Parkinsonism; Genetics; Lysosomal storage

Introduction

More than ten genes or genetic loci have been associated with Parkinson disease (PD)¹. Of special interest are the associations of PD with mutations in the lysosomal enzyme glucocerebrosidase (*GBA*)² and a recent report of the p.L302P mutation in the lysosomal enzyme gene *SMPD1* as a risk factor for PD³. Also, *ATP13A2* is another lysosomal related gene associated with a rare autosomal recessive form of parkinsonism⁴. We report here three individuals with PD or a parkinsonism syndrome who are heterozygous carriers for a mutation in the Niemann Pick C (*NPC1*) gene, suggesting a potential association of PD with another lipid storage disease.

Case 1

This 74 year old man noted difficulties with concentration and dragging of his left foot at age 65. He was a non-smoker. He was given the diagnosis of Parkinson's disease and treated

Correspondence: Thomas D. Bird, MD, 1660 S Columbian Way; S-182-GRECC, Seattle, WA 98108, tomnroz@uw.edu, Phone: 206-277-1453.

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with L-dopa/carbidopa and Requip. Examination at age 68 showed a normal mental status with bradykinesia, masked facies, positive glabellar reflex, soft voice, increased muscle tone in both arms, stooped posture and a gait with small steps. The bradykinesia was more prominent in his left arm and he had a decreased left arm swing. There was no resting tremor on medication. He developed mild dementia at age 71. His twelve year old grandson had a diagnosis of Niemann-Pick C disease. That boy had an enlarged spleen incidentally noted at age one. At age seven he had gait ataxia, clumsy hand movements, restricted vertical eye movements and hypoactive tendon reflexes. Skin biopsy revealed reduced esterification of cholesterol and positive filipin stain. Analysis of the *NPC1* gene revealed compound heterozygosity for the I1061T and R1186G mutations. His maternal grandfather (Case 1) with PD was found to also carry the I1061T mutation.

Case 2

At age 67 this man developed bradykinesia and dragging of his right leg. His right hand was clumsy with resting tremor and he had autonomic dysfunction including orthostatic hypotension, constipation, urinary urgency and impotence. He had episodes of thrashing and calling out at night. He was given the diagnosis of PD and treated with up to 375mg L-dopa TID without improvement. At age 69 he had increased tone, more right than left, with occasional right hand resting tremor. Fine motor movements were slow, there was mild dysmetria on finger to nose testing, deep-tendon reflexes were brisk without clonus, and plantar reflex was equivocal. He walked with a flexed posture, wide-base, short steps and decreased arm swing on the right. The clinical impression was a parkinsonism syndrome, probable multiple system atrophy. He was the maternal grandfather of two children with NPC with R978C and c.3246-2 A>G mutations in *NPC1*. The grandfather (Case 2) was found to be a carrier of the R978C mutation.

Case 3

This woman was diagnosed with PD at age 72. Her initial symptoms were impaired olfaction, increased tone of the left side, resting tremor, hypomimia, and impaired fine motor skills on the left. MRI was normal. The resting tremor responded to L-dopa. This woman had a daughter with NPC that presented in adulthood. The daughter had hearing loss at age 32 followed by dystonia, ataxia, cataplexy and cognitive slowing. She was a compound heterozygote for the I1061T and T825C mutations in *NPC1*. Her mother with PD carried the T825C mutation.

Conclusions

The exact frequency of NPC disease in the general population is unknown but estimated to be about 1 per 100,000–120,000 births⁵. Thus the heterozygote carrier frequency would be about 1–2 per 200. The three NPC carriers described here with a parkinsonism syndrome raise the possibility that NPC could be another storage disease in which mutations are a risk factor for PD. Potential mechanisms similar to the *GBA* association would include partial loss of enzyme function altering cytoplasmic lipid homeostasis or overwhelming the ubiquitin-proteasome pathway. Chiba and colleagues have reported neuropathology in a case of *NPC1* that included Lewy body α -synuclein aggregation suggesting a possible connection

between these two conditions⁶. The only previous example of this association was a brief report of a 75 year old woman with rhythmic, oscillating tremor and heterozygous for a Gly992Arg mutation in *NPC1*⁷. However, because PD is a relatively common neurologic disease it is possible that such associations are simply a rare coincidence. In fact we have seen a 32 year old man with NPC who is a compound heterozygote for two mutations in *NPC1* and whose maternal great-aunt had PD but did not carry either of the *NPC1* mutations. Since most *NPC1* heterozygotes do not have PD, further extensive population genetic studies are required to resolve this question of coincidence versus a genuine genetic risk factor.

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Table 1

NPC Heterozygotes with Parkinsonism Syndrome

Subject	Sex	Age	Onset of PD	Bradykinesia	Tremor	Increased Tone	Masked Facies	Misc	L-Dopa Response	NPC/ Mutation	NPC Relative (Mutations)
1	M	75	65	+	-	+	+	Stooped, festinating gait	+	I1061T	Grandson I1061T R1186G
2	M	73	67*	+	+	+	+	autonomic deficiency ; nocturnal behavior disorder	-	R978C	Grandson Granddaughter R978C c.3246-2 A>G
3	F	74	72	+	+	+	+	↓ olfaction	+	T825C	Daughter T825C I1061T

* Parkinsonism syndrome; likely MSA