Saccades in adult Niemann-Pick disease type C reflect frontal, brainstem, and biochemical deficits

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ABSTRACT

Background: The autosomal recessive disorder Niemannn-Pick type C (NPC) presents in adulthood with psychosis or cognitive deficits associated with supranuclear gaze palsies. While saccadic innervation to the extraocular muscles is generated in the brainstem, the frontal lobes play an integral role in the initiation of volitional saccades and the suppression of unwanted reflexive saccades. No study has examined the frontally driven volitional control of saccadic eye movements in NPC.

Objective: To examine self-paced and antisaccades as well as reflexive saccades in adult patients with NPC, a disorder known to affect brainstem and frontal cortical function.

Methods: Three biochemically confirmed adult patients with NPC were compared with 10 matched controls on horizontal saccadic and antisaccadic measures using an infrared limbus eye tracker. Patients' cholesterol esterification and filipin staining, Mini-Mental State performance, and NPC symptom level were rated.

Results: Reflexive saccade latency ranged from shorter to longer than normal, reflexive saccade gain was reduced, asymptotic peak velocity was reduced, fewer self-paced saccades were generated, and increased errors on antisaccades were made by patients compared to controls. Patients with more severe biochemical, cognitive, and symptom deficits performed most poorly on brainstem and frontal ocular motor measures. Paradoxically, less severe illness was associated with an abnormally reduced saccadic latency.

Conclusions: Ocular motor measures provide an index of disease severity in Niemannn-Pick type C (NPC) and may be a useful adjunct for monitoring the illness progress and medication response. Reduced saccadic latency may result from inadequate fixation input from abnormally functioning frontal eye fields in NPC. ***Neurology***® **2009;72:1083–1086**

GLOSSARY

MMSE = Mini-Mental State Examination; **N/A** = not applicable; **NPC** = Niemannn-Pick type C; **PPRF** = paramedian pontine reticular formation; **RIMLF** = rostral interstitial nucleus of the medial longitudinal fasciculus; **VOR** = vestibulo-ocular reflex.

Niemann-Pick type C (NPC) disease is an autosomal recessive disorder of lipid metabolism which results in intracellular accumulation of cholesterol and gangliosides. In adult patients, psychiatric and cognitive abnormalities co-occur with supranuclear gaze palsy, ataxia, and dysarthria.[1] Vertical eye movements are lost much earlier in the course of the illness than horizontal ones , due to greater cell loss in the rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF), compared to the paramedian pontine reticular formation (PPRF),[2,3] where horizontal saccades are generated. Peak saccadic velocity is related to the integrity of excitatory burst neurons, and thus provides an index of dysfunction in the RIMLF or PPRF. Other measures of saccadic function include latency and gain (the ratio of saccade amplitude to target displacement). Because horizontal saccades decline later in the course of the disease, they

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Table 1 Eye movement parameters for the three patients, along with averaged data from our control group

	Brainstem measures				Frontal measures				
						Antisaccade responses (%)			
Patient	Reflexive latency (ms)	Reflexive gain	Vmax (deg/s)	α (ms/deg)	Self-paced saccades (30 s)	Correct responses	Corrected errors	Uncorrected errors	Antisaccade latency (ms)
P1	140*	0.80*	411	1.38	65	16.7*	66.7*	0	576*
P2	169	0.71*	301*	2.52*	51	Could not do task	N/A	N/A	N/A
P3	185	0.52*	125*	8.82*	36*	0*	56*	25*	N/A
Controls	175 ± 11.13	0.98 ± 0.07	502 ± 100	1.66 ± 0.36	84.7 ± 20.4	87.75 ± 9.5	12.25 ± 9.46	0	281 ± 41.2

Control subject means ± SDs for saccade data are from 10 young normal subjects tested on same apparatus using identical procedures.
*Outside ±2 SD for control data.
N/A = not applicable.

were recently used as an outcome indicator in a clinical trial of Miglustat as a treatment for NPC.[4]

Pathologic changes in NPC are not confined to the brainstem and frontal lobe atrophy may be prominent, and is associated with psychosis.[5,6] Frontal cortex plays an important role in addition to the brainstem saccadic control through the frontal eye fields, supplementary eye fields, and dorsolateral prefrontal cortex, which are involved in the initiation of volitional saccades and the suppression of unwanted reflexive saccades.[7] The antisaccade and self-paced saccade tasks are utilized in disorders where volitional behavior is impaired because they are under volitional rather than reflexive control, although they have not been studied in NPC. The current study examined self-paced and antisaccades in three adult patients with NPC who presented with a psychotic illness.

METHODS

Subjects. P1 was a 31-year-old woman who presented with 3 months of agitation and delusions of persecution and reference, after 5 years of gait deterioration and dysarthria. She demonstrated mild gait ataxia, dysmetria, and limited upward/absent downward saccades, with a preserved vestibulo-ocular reflex (VOR). She scored 30 on the Mini-Mental State Examination (MMSE) and rated 7/18 on the Iturriaga NPC rating scale.[8] Cholesterol esterification rate of cultured fibroblasts was 5.3 pmol/hour/mg, with filipin staining in 50–60% of cells, and a G992R/R1186H mutation in NPC1, consistent with the variant biochemical NPC phenotype.

P2 was a 30-year-old man and the younger sibling of P1. He had presented with schizophrenia at age 16, marked by persecutory and grandiose delusions. At age 25, P2 presented with worsening dysarthria and gait ataxia. Neurologically he displayed severe gait ataxia, marked dysmetria, and limited upward/absent downward saccades, with a preserved VOR. P2 scored 25 on the MMSE, with impaired attention and memory, and a symptom score of 11. Cholesterol esterification rate of fibroblasts was 2.9 pmol/hour/mg, filipin staining was 60–70%, and the same mutations as in P1 were present.

P3 was a 30-year-old man who was diagnosed with juvenile NPC and presented at age 25 with disturbed sleep, elevated mood, and psychosis. He demonstrated splenomegaly, ataxic gait, and limited upward/absent downward and sluggish horizontal saccades, with a preserved VOR. He scored 15 on the MMSE and had a symptom score of 13. Cholesterol esterification rate of 0.3 pmol/hour/mg and 95–100% filipin staining with the homozygous I1061T mutation confirmed the classic biochemical phenotype.

Ten normal subjects (2 men, mean age 28.9 ± 4.43), matched for age with the patients and free of any neurologic or psychiatric condition or medication known to affect eye movements, completed the same ocular motor tests as the patients.

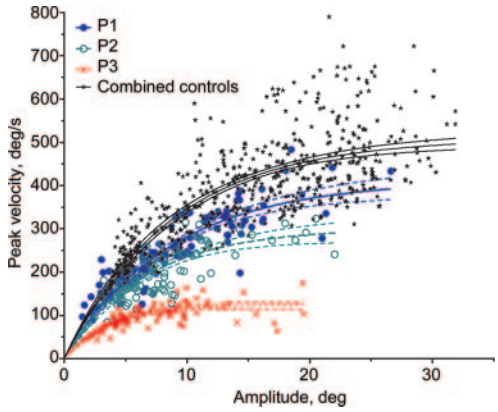
Procedure. The study was approved by the local research and ethics committee and patients provided written informed consent. Testing was done in a dimly lit room; a chinrest was used to support the head. Horizontal eye and target position was recorded with a Microguide 1000 infrared limbus eye tracker. Stimuli were green 5 mm LEDs on an arc 1.6 m in front of the participant, which subtended ±20 degrees. Only data from the better-recorded eye were analyzed, given conjugate gaze in NPC. For calibration, the target stepped from 0 to 20 degrees left and right every 5 seconds. For reflexive saccades, 60 target steps between 5 and 30 degrees were randomly presented. For antisaccades, 20 targets at ±5 and 10 degrees were presented randomly, with participants instructed to look away from the stimulus. For self-paced saccades, targets at ±10 degrees were illuminated and

Table 2 Biochemical and cognitive parameters for the three patients, along with averaged data from our control group

	Biochemical measures			
Patient	Filipin staining (%)	Esterification rate (pmol/h/mg)	Cognitive, MMSE	Illness, Iturriaga scale
P1	50-60	5.3	30	7
P2	60-70	2.9	20	11
P3	95-100	0.3	15	13
Controls	(<5)	(>3)	(>24)	—

Measures for filipin staining, cholesterol esterification, and Mini-Mental State Examination (MMSE) are established limits of healthy controls.

Figure 1 Plot of peak velocity vs saccade amplitude for the three patients with Niemann-Pick type C, along with the saturating exponential curves from which Vmax was calculated



Also shown is the curve fitted to the pooled normal data; 95% confidence limits are shown for all curves.

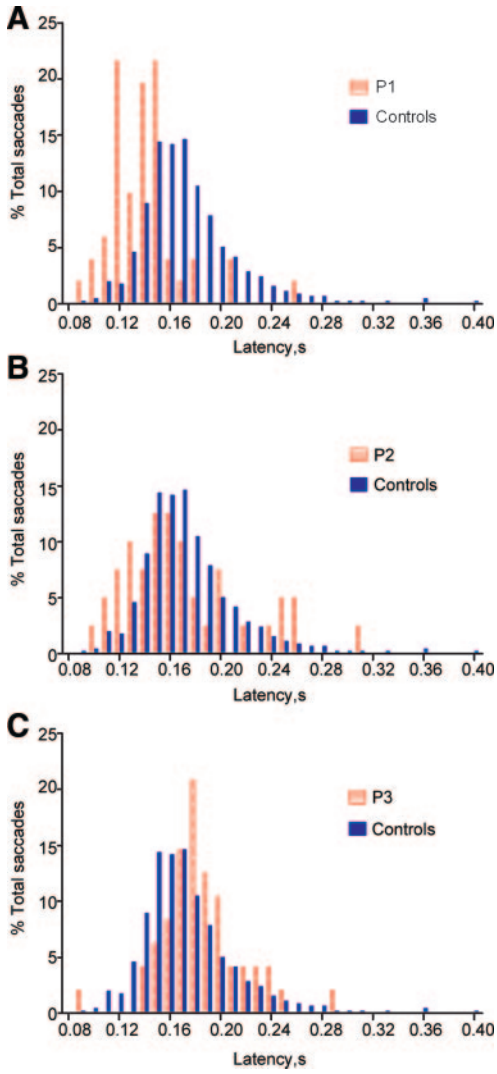
the participant asked to look between them as rapidly as possible for 30 seconds.

Data were analyzed interactively under Matlab with a program that identified saccade onset at 30 deg/sec and 8,000 deg/sec^2; reflexive saccade amplitude, latency, and peak velocity were analyzed, as were spontaneous saccade amplitude and peak velocity. We also calculated α, the slope of the peak duration vs amplitude plot. Antisaccade errors were tallied according to whether a subsequent correction was made. Finally, the number of self-paced saccades generated in 30 seconds was counted by direct inspection. The mean values obtained for each patient were compared to the mean ± 2 SD ranges for control data.

RESULTS Saccade measures and biochemical and clinical analyses are shown in tables 1 and 2. Figure 1 shows the saccade velocity–amplitude relationship for the three patients and the grouped data from control participants, fitted with the equation $V = Vmax(1 - e^{-amp/c})$, where Vmax is asymptotic peak velocity and c a constant. Vmax declines from P1 to P2, to P3, with P2 marginally and P3 clearly 2 SD below the control mean. All three had gain outside normal limits. P1 showed significantly shorter than normal saccadic latencies; her brother fell in the normal range, as did P3. Figure 2 shows that express and fast regular saccades were dominant in P1, prominent in P2, and absent in P3.

Volitional saccade performance was also significantly impaired in all three patients compared with controls. P1 performed some correct antisaccades (at markedly long latencies) but fell outside the normal range of errors, whereas P2 was unable to generate antisaccades and P3 generated antisaccades but never without first looking at the target. On the self-paced task, P1 and P2, but not P3, fell within the normal range, but performance again declined from P1 to P3.

Figure 2 Reflexive saccade latency histograms (shown as percentage of saccades made) for patients and compared to control group



Most of P1's (A) and a proportion of P2's (B) saccades were in the express or fast regular range, while P3's (C) latency distribution was skewed to the right of the controls'.

DISCUSSION Our patients demonstrated impairments at both brainstem and prefrontal levels of saccade control, and performance ranked identically to biochemical, cognitive, and illness measures. Although NPC affects horizontal saccades less than vertical,[3,4] the patients described here show a range of horizontal saccade deficits. All showed reduced reflexive saccade gain, which has been associated with damage to the dorsal vermis of the cerebellum,[9] known to occur in NPC.[2,3,6]

The patients also demonstrated peak velocities that varied from normal (P1) to just below normal (P2) to severely reduced (P3), consistent with the cell

losses in the PPRF.[3] NPC affects vertical saccades earlier and more severely, consistent with greater cell loss in the RIMLF.[3] Reports of normal horizontal saccades in NPC[2] may reflect individual differences in disease progression; this may also underlie the range of peak velocities seen in our patients.

The abnormally short latency in NPC reflexive saccades has been reported without explanation previously.[2] It has been suggested that such "express" saccades, and antisaccade errors, could arise from inadequate fixation input from the frontal eye fields or posterior parietal cortex to the superior colliculus.[10] Given frontal atrophy in NPC,[5,6] a loss in fixation input could account for several of the behaviors seen in our patients.

In these three patients, the gradation of eye movement abnormalities from P1 to P3 mirrored the gradation seen in their biochemical, cognitive, and symptomatic measures of illness severity. P1's cholesterol esterification rate, and her MMSE score, were within the normal range, although she clearly showed abnormal filipin staining and compound heterozygote status on mutation analysis. Most of her eye movement measures fell within, or just below, the normal range. P2 showed a different course of illness, with earlier manifestation of more severe psychiatric and neurologic symptoms. His esterification rate was approximately 50% lower, albeit having an identical mutation. The more severe biochemical deficit in the classic phenotype of P3, with a greater than 10-fold reduction in esterification rate in P3 compared to P2, appears to be reflected in most clinical measures, including age at onset, ocular motor and cognitive deficits, and illness severity.

We have shown that both brainstem and frontal control of eye movements in adult NPC are impaired, and that the severity of these changes mirrors the severity of other illness variables. This suggests that these ocular motor measures may be an index of disease severity in a range of neurologic and neurocognitive domains, and may be a useful adjunct for monitoring the progress of the illness and response to medication.

AUTHOR CONTRIBUTIONS

M.W., D.V., and L.A. conceived the study. L.A. and E.B. were involved in the collection and interpretation of eye movement data. M.F. performed the biochemical and genetic analyses. L.A. conducted the statistical analyses. All authors contributed to drafting of the manuscript.

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REFERENCES

1. Sevin M, Lesca G, Baumann N, et al. The adult form of Niemann-Pick disease type C. Brain 2006;130:120–133.
2. Rottach KG, von Maydell RD, Das VE, et al. Evidence for independent feedback control of horizontal and vertical saccades from Niemann-Pick type C disease. Vision Res 1997;37:3627–3638.
3. Solomon D, Winkelman C, Zee DS, Gray L, Buettner-Ennever JA. Niemann-Pick Type C disease in two affected sisters: ocular motor recordings and brainstem neuropathology. Ann NY Acad Sci 2005;1039:436–445.
4. Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. Lancet Neurol 2007;6:765–772.
5. Klunemann HH, Elleder M, Kaminski WE, et al. Frontal lobe atrophy due to a mutation in the cholesterol binding protein HE1/NPC2. Ann Neurol 2002;52:743–749.
6. Walterfang M, Fietz M, Fahey M, et al. The neuropsychiatry of Niemann-Pick Type C disease in adulthood. J Neuropsychiatry Clin Neurosci 2006;18:158–170.
7. Pierrot-Deseilligny C, Muri RM, Nyffeler T, Milea D. The role of the human dorsolateral prefrontal cortex in ocular motor behavior. Ann NY Acad Sci 2005;1039:239–251.
8. Iturriaga C, Pineda M, Fernandez-Valero E, Vanier M, Coll M. Niemann-Pick C disease in Spain: clinical spectrum and development of a disability scale. J Neurol Sci 2006;249:1–6.
9. Takagi M, Zee DS, Tamargo RJ. Effects of lesions of the oculomotor vermis on eye movements in primate: saccades. J Neurophysiol 1998;80:1911–1931.
10. Biscaldi M, Fischer B, Stuhr V. Human express saccade makers are impaired at suppressing visually evoked saccades. J Neurophysiol 1996;76:199–214.