Kinematic Analysis of Niemann-Pick Type C using Accelerometry and a Novel Spiral Analysis Technique

Columbia University Medical Center

Alicia G. Floyd,[1] Qiping Yu,[1] Panida Piboolnurak,[1] E. Wraith,[2] Marc C. Patterson,[1] and Seth L. Pullman[1]

[1]*Department of Neurology, Columbia University Medical Center, New York, NY*

[2]*Royal Manchester Children's Hospital, Manchester, UK*

Background & Objectives

Niemann-Pick Type C (NPC) is a lipid storage disease associated with motor symptoms including ataxia, dysmetria, dystonia, choreoathetosis, and action tremor. Onset periods are generally classified as infant, childhood, and adolescent through adult, with improved prognosis associated with later age of onset. The aim of this study was to provide the first upper limb kinematic description of a series of NPC patients, and to compare features with those of age-matched healthy individuals and patients with essential tremor (ET).

Methods

15 NPC patients were evaluated using accelerometry and a novel technique involving computerized analysis of freely drawn spirals. Measurements were taken bilaterally at the proximal joint of the third finger using piezoresistive uniaxial accelerometers. Multiple trials were completed at rest, while holding an arms extended posture, and during two kinetic conditions (moving finger-to-nose and transferring water between cups). Double integration of accelerometric data produced tremor amplitudes, and a Fast Fourier Transform decomposed the accelerometric oscillations into a component frequency spectrum. Rectified, integrated surface EMG data were collected from bilateral ECR and FCR muscles. EMG burst - accelerometry coherence was used to confirm the presence of tremor or other irregular movements in questionable cases. The sampling rate for all channels was set to 300 Hz, and trials were generally recorded in 4 sec sweeps for rest and postural conditions, and 10 sec sweeps for kinetic conditions. Activation condition, loading effects, frequency, amplitude, consistency, and bilateral symmetry were investigated. Trials and sides with more severe (larger amplitude) tremor were considered representative in group averages.

A second test, digital spiral analysis, expands the subjective neurological assessment of drawn spirals to a quantitative assessment of speed, tremor frequency and axis, and other three-dimensional patterns via mathematical unraveling the spiral using the relationship between Cartesian and polar coordinates. Data were acquired at approximately 70 Hz per channel, accurately recording tremor data to over 20 Hz.

Two comparison groups were used to highlight motor patterns in NPC. Features of spiral analysis were compared to age matched healthy controls and to patients with ET, and neurologic condition characterized by kinematically and physiologically well-described action and postural tremors.

Subjects

15 subjects (7 male, 8 female) with NPC were assessed as part of an ongoing clinical study to assess safety and efficacy of oral miglustat (Zavesca) (Actelion Pharmaceuticals, Ltd, Switzerland). Baseline measurements were used to provide this kinematic description. Subjects were diagnosed with NPC via tests for abnormal cellular cholesterol esterification levels. The mean age was at assessment was 25 ± 10 years, ranging from 12 to 42 years. The mean age at onset of clinical neurologic symptoms was 14 ± 10 years, ranging from 8 to 33 years (2 cases unknown). Three individuals had adult onset NPC. Comparison groups of ET patients and healthy controls were age matched to NPC patients within 5 years. Healthy controls were neurologically and cognitively screened, and ET patients were diagnosed at the Clinical Motor Physiology Laboratory of Columbia University based on clinical histories and quantitative assessments.

Results & Discussion

Accelerometry showed moderate to large amplitude, low frequency, erratic movements, generally absent at rest, present during postural measurements, and most severe with action. Only one NPC patient had rest tremor. 47% patients had postural tremor in the upper limbs (1.4±1.0 mm, 1.8±0.9 Hz). 87% had action tremor induced by finger-to-nose movements (6.3±4.3 mm, 2.7±0.6 Hz). Action tremor showed significantly larger amplitudes than postural tremor in the non-dominant hand only (p=0.02).

Frequency peaks in postural and both kinetic conditions were significantly lower in NPC than ET, however, amplitudes in both groups ranged from moderate to large and were not significantly different. Base ranges of significant frequency, activity in NPC patients tended to be somewhat more broadly peaked than ET patients. In addition, the variability of amplitudes was significantly larger for NPC patients in the finger-to-nose (kinetic) condition, but not in the postural condition.

Overall accelerometry data suggested that motor pathology in NPC is characterized by variable, low frequency irregular motion that increases with the complexity of the task (kinetic>postural>rest). More complicated tasks required greater fine motor adjustments in response to visual and somatosensory processing; thus, activation patterns as well as frequency range were consistent with cerebellar dysfunction. There was no correlation between age of onset of symptoms or years elapsed since onset and any of the outcome measures, which is likely a reflection of variability in disease progression.

Digital analysis of freely drawn spirals showed that NPC patient spirals exhibited significantly greater spatial deviations, greater rate of change in deviation patterns, higher pressure, lower speeds, and greater variability in speed when compared to controls ($p<0.05$). It is worth noting that the effect size for spatial deviation change ($t = 3.9$) was smaller than the effect size for the rate of these changes ($t = 5.3$). While it is expected that NPC spirals would be more irregular than normal spirals, there is an even more marked difference in the rate of change in irregularity patterns. It is possible that the severity and nature of action based motor symptoms were constantly fluctuating in NPC patients, perhaps based on abnormal sensory feedback. Future investigation involving spiral analysis might include a condition in which vision is occluded while drawing to evaluate the visuomotor abnormalities in NPC.

Accelerometry based analysis of tremor: Summary Data

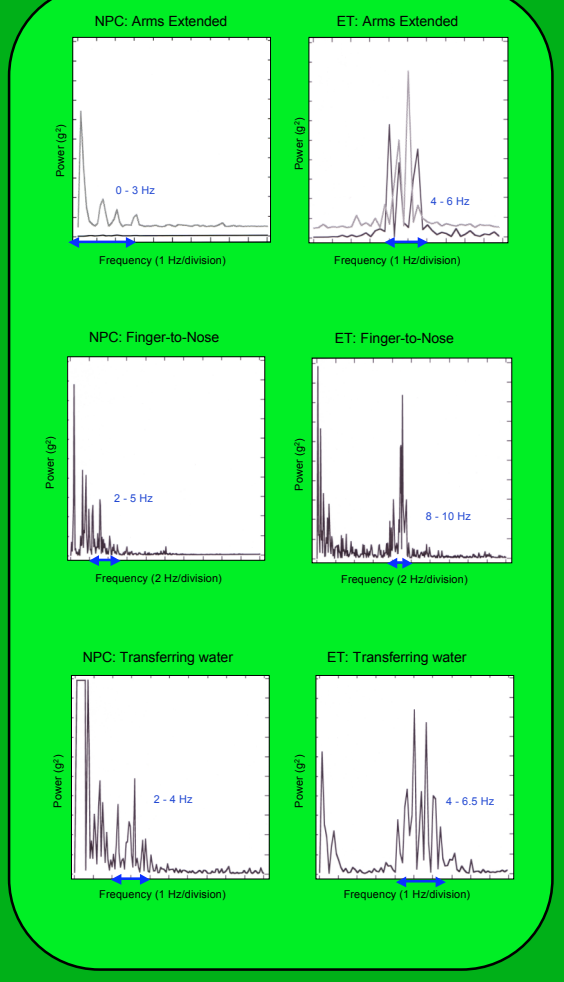
		Percent with tremor activation	Mean Frequency (Hz)	Mean Amplitude (mm)	Mean Amplitude COV
Rest	NPC	1/15 = 7%	-	-	-
	ET	2/12 = 17%	-	-	-
Postural	NPC	7/15 = 47%	1.8±0.9	1.4±1.0	0.59±0.20
	ET	10/12 = 83%	9.1 ± 2.2	3.6±3.1	0.46±0.14
Kinetic: Finger to nose	NPC	13/15 = 87%	2.7±0.6	6.3±4.3	0.60±0.20
	ET	12/12 = 100%	7.7±2.8	6.7±7.8	0.46±0.13
Kinetic: Pouring water	NPC	11/15 = 73%	3.2±1.7	1.9±1.1	0.61±0.19
	ET	6/7 = 86%*	6.5±3.0	3.6±5.5	0.67±0.30

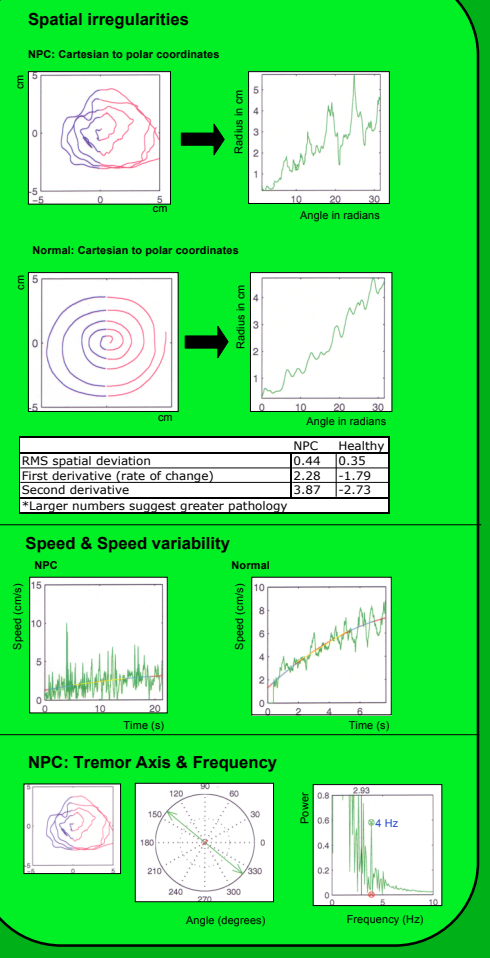
*: Indicates significant differences between NPC and ET at the two tailed p<0.05 level

Spiral Analysis: Summary Data

	NPC	Healthy
Pressure	210±50 units	137±86 units
Speed	4.2±3.0 cm/s	6.4±2.8 cm/s
RMS acceleration	0.034±0.02	0.024±0.01

*Indicates significant difference between NPC and healthy controls at the two-tailed p<0.05 level.





	NPC	Healthy
RMS spatial deviation	0.44	0.35
First derivative (rate of change)	2.28	-1.79
Second derivative	3.87	-2.73

*Larger numbers suggest greater pathology