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Spiral Analysis in Niemann-Pick Disease Type C

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Abstract: Spiral analysis is a computerized method of analyzing upper limb motor physiology through the quantification of spiral drawing. The objective of this study was to determine whether spirals drawn by patients with Niemann-Pick disease type C (NPC) could be distinguished from those of controls, and to physiologically characterize movement abnormalities in NPC. Spiral data consisting of position, pressure, and time were collected from 14 NPC patients and 14 age-matched controls, and were analyzed by the Mann-Whitney *U* test. NPC spirals were characterized by: lower speed (2.67 vs. 9.56 cm/s, $P < 0.001$) and acceleration (0.10 vs. 2.04 cm/s^2, $P < 0.001$), higher loop width variability (0.88 vs. 0.28, $P < 0.001$), tremor (5/10 vs. 0/10 trials in the dominant hand, $P < 0.001$), and poor overall spiral rating (2.53 vs. 0.70, $P < 0.005$). NPC spirals also exhibited sustained drawing pressure profiles that were abnormally invariant with time. Other features, such as the tightness of loop widths, were normal. Our findings reveal that differing aspects of tremor, Parkinsonism, ataxia, and dystonia are quantifiable in NPC patients. © 2009 Movement Disorder Society

Key words: Niemann-Pick; spiral analysis; motor physiology

Niemann-Pick disease type C (NPC) is an autosomal recessive lipid storage disorder that is characterized by impaired intracellular cholesterol homeostasis and defective cholesterol trafficking through the late endosomal/lysosomal system.[1,2] The resulting accumulation of unesterified cholesterol, predominantly in cells of the spleen, liver, and brain, leads to a range of clinical manifestations. These include hepatosplenomegaly, psychiatric disorders, and neurological problems such as supranuclear vertical gaze paresis, dystonia, myoclonus, chorea, spasticity, ataxic gait, and seizures.[3–5]

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Although NPC has a wide phenotypic spectrum, ranging from early-onset in infancy with rapid deterioration, to late-onset in adolescence or adulthood with slower symptom progression,[3] movement abnormalities are almost always a major component of the disease. Infantile NPC can present with intention tremor and delayed motor milestones, while juvenile onset NPC involves gait dysfunction and impairment of fine motor control. The range of movement disorders is even more pronounced in adult onset NPC.[6] To date, however, there have been few motor physiologic studies to offer objective analyses that characterize the nature and severity of such movement abnormalities.[7,8]

In a recent study using surface EMG (sEMG) and accelerometric recordings, we found that the major physiologic abnormalities in NPC were consistent with cerebellar outflow tremor.[7] In this report, we further describe the motor abnormalities in NPC through the use of spiral analysis, a computerized method of objectively assessing upper limb kinematics by digitizing

and analyzing Archimedean spirals drawn on a graphics table.[9,10] To our knowledge, this is the first spiral analysis assessment of NPC patients.

PATIENTS AND METHODS

This study was conducted as part of a multicenter investigation of the efficacy of oral miglustat (Zavesca, Actelion Pharmaceuticals, Ltd., Switzerland), a reversible inhibitor of glucosylceramide, an enzyme involved in glycolipid synthesis.[11] It was approved by the Columbia University Medical Center Institutional Review Board; informed consent was obtained in writing from all subjects.

Fourteen patients enrolled in the study. All patients were over age 12 and had a diagnosis of NPC confirmed by abnormalities in cholesterol esterification and filipin staining. Patients were excluded from the study if they were enrolled in other clinical trials, took drugs or dietary supplements which could interfere with the absorption of study medication, had a history of gastrointestinal disorders, HIV, or hepatitis, or if they were unable to perform the spiral drawing task. Patients were assessed clinically in the Pediatric Neurology division before being referred for neurophysiologic testing. Clinical features are presented in Table 1. Fourteen age-matched normal controls were used for comparison. Control subjects had to be without neurologic or psychiatric disease, had to score 28/30 or higher on the mini-mental status examination (MMSE),[12] and were excluded if they had a history of drug or alcohol abuse, arthritis, head trauma, or if they had a family background of Parkinson's disease, essential tremor, or dystonia.

Twenty handwritten spirals, 10 from each hand, were obtained from normal controls and NPC patients. Spirals were drawn inside a 10 × 10 cm square box on 8.5 × 11 inch paper, using a wireless, inked writing pen, and a graphics tablet (Intuos 2, Wacom Technology Corp, Vancouver, WA). Subjects were allowed to draw freely, to the extent that there were no constraints, attachments, or traceable templates, and they were asked to neither anchor nor rotate their drawing hand so that collection was standardized across all subjects. They also were instructed to sit with shoulders parallel to the front edge of the tablet, and not let their arms rest on the tablet. Before recording, a sample spiral was drawn by the examiner so that each subject understood what to draw; subjects were also given time to practice drawing spirals. The tablet had a resolution of 2,540 points/inch, an accuracy of

TABLE 1. *Clinical findings and spiral analysis data*

Patient	Age	Gender	First symptom or sign	Duration of disease (years)	*Degree of severity*	Ataxia	*Loop width variation*	Dystonia	*Drawing pressure*	Action tremor	*% Trials with tremor*	*Tremor power*	*Speed*
1	39	M	Change in balance	6	*2.01*	++	*0.94*	0	*160.29*	++	*90%*	*0.046*	*1.08*
2	18	M	Cognitive impairment	2	*1.72*	+	*0.35*	+	*107.37*	+	*70%*	*0.018*	*2.52*
3	17	F	Gait ataxia	7	*2.42*	++	*0.52*	+	*123.52*	+	*60%*	*0.052*	*1.90*
4	17	M	Cognitive impairment	1	*1.45*	+	*0.35*	0	*136.05*	0	*15%*	*0.001*	*2.73*
5	21	F	Difficulty walking	9	*2.50*	+	*0.51*	+++	*244.33*	++	*30%*	*0.009*	*2.42*
6	42	M	Incoordination	unclear	*2.61*	++	*1.25*	0	*227.88*	0	*55%*	*0.053*	*2.95*
7	42	M	Balance, coordination and speech problems	14	*2.46*	++	*1.49*	0	*219.57*	++	*75%*	*0.094*	*4.98*
8	17	F	Gait difficulty	3	*2.58*	0	*0.92*	0	*155.85*	+++	*80%*	*0.038*	*2.61*
9	12	F	Balance problems, incoordination	4	*2.77*	++	*0.84*	+	*235.02*	++	*65%*	*0.055*	*4.49*
10	34	M	Dysarthria	28	*3.04*	+++	*4.81*	+	*159.47*	++	*90%*	*0.183*	*9.94*
11	25	F	Gait disturbance	6	*2.57*	++	*1.54*	++	*238.38*	+	*65%*	*0.042*	*5.46*
12	18	F	Gait ataxia, tremor	3	*2.12*	++	*0.50*	+	*179.74*	++	*40%*	*0.015*	*4.41*
13	17	F	Incoordination	2	*2.76*	+	*0.66*	+	*225.12*	++	*95%*	*0.038*	*1.81*
14	32	F	Balance problems and arm tremors	6	*3.11*	++	*0.98*	+	*167.06*	+++	*100%*	*0.305*	*1.61*

Clinical information is paired with spiral analysis results (*in italics*). The clinical rating scales are scored as follows: dystonia: 0, not present; +, apparent only with action; ++, affecting one limb with action and at rest; +++, affecting two or more limbs including generalized dystonia. Ataxia: +, apparent only on tandem walking; ++, ataxic gait but able to walk without assistance; +++, unable to walk without assistance. Action tremor: 0, absent; + mild; ++ moderate; +++ severe. Spiral pressure data range = 0–255, % trials with tremor = from 20 trials, speed units = cm/s.

0.005 inches, and 256 levels of measurable pressure. Data were acquired at 100 Hz.

Quantification of handwritten spirals was based on "unraveling" the spiral drawing from the acquisition data series consisting of time, *x*, *y*, and pressure axis values. This captured kinematic, dynamic, and spatial attributes of spiral execution, and provided data points for computation of spiral indices, as previously described.[9] The indices used as primary outcome measures in this study were drawing speed and acceleration, loop-to-loop width tightness and variation, spiral pressure and hemi-pressure, tremor (frequency, power, and number of trials with tremor), and overall degree of severity (DOS). These outcome measures were chosen because they were major descriptors of spiral execution and motor control that were likely to distinguish NPC patients from controls. Furthermore, because tremor and drawing pressure are abnormal in kinetic tremor disorders and dystonia[13,14]; speed, acceleration, tightness, and spiral hemi-pressure are affected in Parkinson's disease[10,15]; and width variation highlights the fluctuations in fine motor control seen in ataxia,[16] these indices were relevant in determining whether spiral drawing features were suggestive of subtypes of movement disorders. Each index was calculated from 8 of the 10 trials for each hand, with the highest and lowest values removed.

Drawing speed was calculated as the distance between consecutive *x*, *y* points, averaged over the length of the spiral, divided by the sampling time (10 ms) between points. Drawing acceleration was calculated as the first derivative of speed. Loop tightness, a measure of clinical micrographia, was a determination of the average distance between consecutive spiral loops over all angles (in radians) divided by the maximum spiral radius (in cm). Tightness was normalized to one loop/cm, which approximates the clinically normal value of five loops within a 10×10 cm square. Loop width variability, a mathematical correlate of limb ataxia, was calculated as the coefficient of variation of loop width. Spiral pressure was calculated as the average of all pressure data points for a given spiral; spiral hemi-pressure was a measure of pressure symmetry in a given spiral, comparing pen pressures on the right and left hemi-spirals, and calculated as the ratio of right-to-left mean pressure values.

Three indices were chosen to characterize and quantify tremor: (1) total number of trials for the dominant and nondominant hands that showed tremor oscillations in the *x*-*y* plane, (2) tremor frequency, and (3) power of tremor frequency, a measure of tremor amplitude. Tremor presence was determined for each spiral using the discrete Fourier transform to detect frequencies with peak power greater than two standard deviations over established baseline levels after lowpass filtering at 20 Hz, incrementally rotating the spiral drawing at 5-degree intervals in the *x*-*y* plane.

A global degree of severity score (DOS) was generated as a measure of overall spiral execution and spatial irregularity.[9] DOS was designed as a computerized equivalent to the standard five-point clinical rating scale (0 to 4) of handwritten spirals where 0 to 1 = normal, 1 to 2 = mild, 2 to 3 = moderate, and 3 to 4 = severely abnormal. The DOS index is correlated with the clinical neurologic exam, and has been validated with total motor UPDRS scores.[10]

Differences in spiral indices between the control and patient groups were analyzed by the Mann-Whitney *U* test for nonparametric data, with a level of significance of $P < 0.005$ after applying the Bonferroni adjustment for multiple comparisons of medians (*SPPS, version 16.0*, Chicago, IL). For spiral indices that were considered a priori to be related to specific clinical features, pair-wise correlations were performed between these measures and clinical scores: DOS, loop width variation, drawing pressure and trials with tremor.

RESULTS

Fourteen NPC patients (six men and eight women, mean age ± SD = 25.07 ± 10.54 years) and 14 age-matched normal controls (seven men and seven women, mean age ± SD = 26.21 ± 5.19 years) were evaluated. In both groups, 13 of 14 subjects were right handed.

NPC patient spirals were grossly abnormal, characterized by wavy, crossed lines, and irregular spacing (Fig. 1) with an array of quantifiable abnormalities

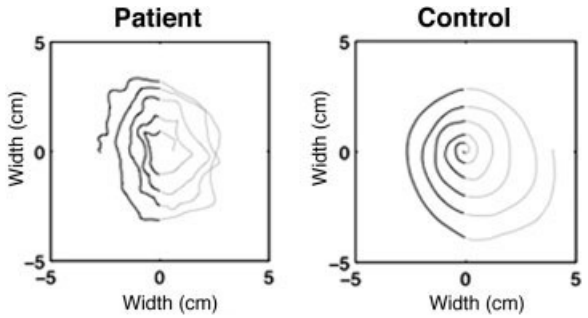

FIG. 1. Representative spirals from a patient and a control, matched for handedness, gender, and age. Dark and light grey lines denote the left and right halves of the spirals, respectively. Gross spatial irregularities—wavy, crossed lines with more variable loop spacing—can be seen in the NPC spiral.

TABLE 2. *Spiral indices for NPC patients and controls*

Index	*P* value	Patient			Control		
		25%	Median	75%	25%	Median	75%
Significant	$P < 0.005$						
Degree of severity (DOS)	0.000	2.09	2.53	2.76	0.44	0.70	0.93
Speed	0.000	1.88	2.67	4.62	7.50	9.56	12.61
Acceleration	0.000	0.04	0.10	0.27	1.32	2.04	3.55
Width variation, Ataxia	0.000	0.50	0.88	1.31	0.25	0.28	0.29
Trials with tremor, dominant hand	0.000	3.00	5.00	9.25	0.00	0.00	1.00
Trials with tremor, nondominant hand	0.000	5.75	8.00	9.00	0.00	1.00	2.00
Tremor power	0.000	0.02	0.04	0.07	0.00	0.00	0.01
Non-significant	$P > 0.005$						
Tightness	0.019	1.10	1.52	2.50	0.83	1.03	1.21
Tremor frequency	0.198	4.19	4.58	4.66	4.19	4.86	5.40
Hemi-pressure ratio	0.765	0.97	1.00	1.02	0.98	1.00	1.00
Drawing pressure	0.890	150.90	173.40	229.67	167.27	185.31	220.08

(Table 2). Patients executed spirals at lower speeds (M_d = 2.67 cm/s compared with 9.56 cm/s, $P < 0.001$) and drew with less acceleration (M_d = 0.10 cm/s^2 compared with 2.04 cm/s^2, $P < 0.001$) (Fig. 2A,B). Their spirals were characterized by high loop width variability (M_d = 0.88 compared with 0.28, $P < 0.001$), indicating that they tended to draw with irregular spacing between loops (Fig. 2C). Patient degree of severity (DOS) was notably worse than controls (M_d = 2.53 vs. 0.70, $P < 0.005$).

Spiral analysis also detected significantly more tremors in patients (Fig. 2D,E). NPC patients had a median of 5 of 10 trials with tremor in the dominant hand (0 of 10 in controls, $P < 0.001$) and 8 of 10 trials in the nondominant hand (1 of 10 in controls, $P < 0.001$). Most patients (79%) had greater than 8 of 10 trials with tremor in at least one hand. In contrast, most controls (93%) had tremors in less than 2 of 10 trials in either hand. NPC patients showed no difference in median tremor frequency (4.58 Hz compared with 4.86 Hz in controls, $P > 0.005$), but had greater tremor amplitudes as revealed by the higher tremor frequency power (0.044 vs. 0.001 in controls, $P < 0.005$).

However, patient spirals showed no differences in loop tightness (M_d = 1.52 compared with 1.03, $P > 0.005$), pressure (patients: M_d = 173; controls: M_d = 185; $P > 0.005$), or hemi-pressure (patients: M_d = 0.997; controls: M_d = 1.001, $P > 0.005$) (Fig. 3A).

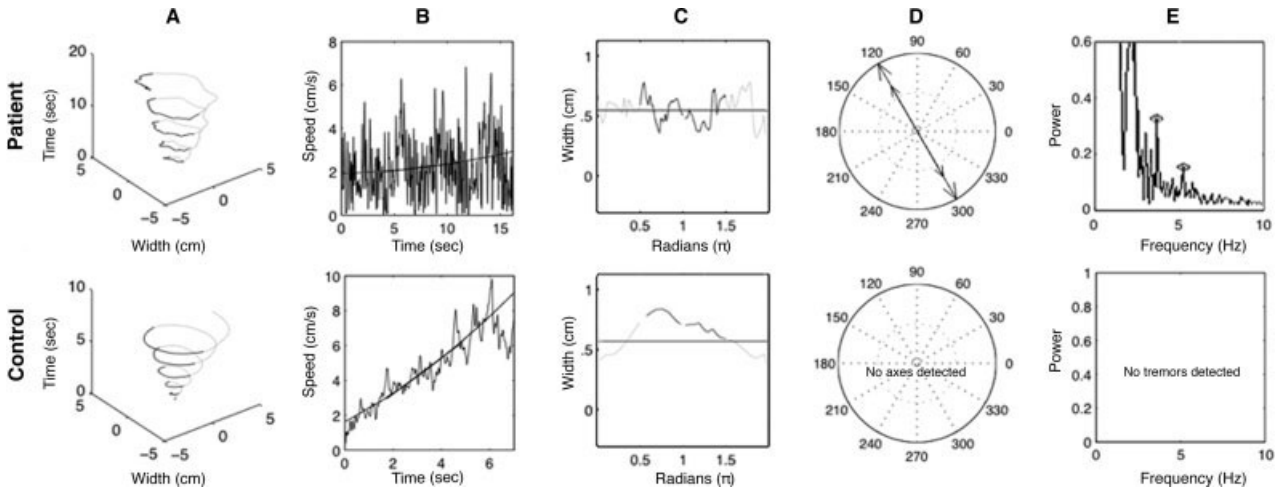

FIG. 2. Representative graphs of selected spiral indices, derived from the same two spirals depicted in Figure 1. **A**. Position vs. time graphs. The patient required more time to draw the same number of loops as the control. **B**. Speed vs. time graphs. The patient drew at slower speeds and with less acceleration (slope) than the control. **C**. Spiral loop width (*y*-axis) averaged over the full (360°) spiral drawing (2π radians). The patient spiral shows characteristically increased loop width variability. **D**. Tremor axes detection. Spiral analysis found two tremor axes in the patient spiral, both oriented at 120°, with the frequency peaks noted in (**F**); no tremors were detected in the control spiral. **E**. Frequency analyses. Peaks were detected at 3.81 and 5.37 Hz in the patient spiral, while no tremors were detected in the control.

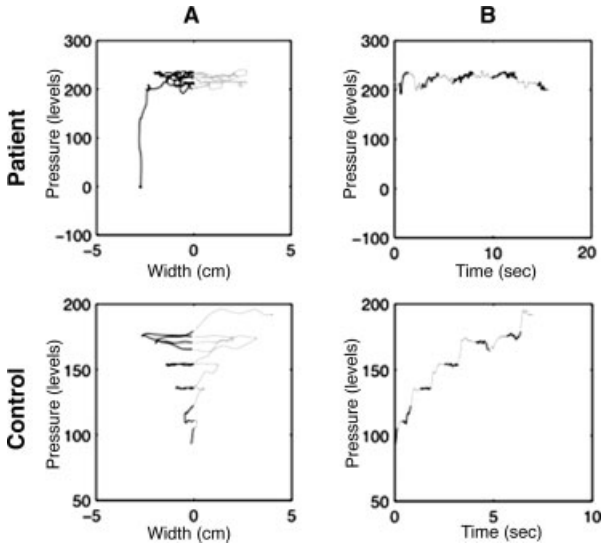

FIG. 3. Representative graphs of pressure indices, derived from the same two spirals depicted in Figure 1. **A**. Patients and controls drew with similar pressures (when individual pressure points are averaged), but differences exist temporally. Controls tend to draw with a constant increase in pressure, with increasing spiral radius, while patients drew with consistently elevated pressures. **B**. Pressure vs. time analyses show that there was little change in patient pressure over time, whereas control pressure tended to increase in a step-wise manner.

When analyzed against time, however, pressure differences were observed: controls drew with a gradual increase in pressure over time while NPC patients drew with a constant, elevated pressure (Fig. 3B).

Select spiral indices are shown in Table 1 along with patient clinical information. Two spiral indices correlated with clinical features: loop width variation with clinical ataxia ($r^2 = 0.611$, $P = 0.02$); loop width variation with duration of disease ($r^2 = 0.913$, $P = 0.0001$); and % trials with tremor with clinical action tremor ($r^2 = 0.601$, $P = 0.03$). Several other indices revealed suggestive trends including: DOS with disease duration ($r^2 = 0.363$, $P = 0.27$); pressure with dystonia ($r^2 = 0.126$, $P = 0.18$); tremor power with clinical tremor ($r^2 = 0.294$, $P = 0.06$).

DISCUSSION

Computerized spiral drawing tasks have been successfully used to assess upper limb motor function in a variety of movement disorders.[10,16–18] In this study, we demonstrate that the motor impairments in patients with Niemann-Pick disease type C (NPC) can be detected and objectively quantified through spiral analysis. We found that spiral abnormalities in NPC patients compared with age-matched controls can be broadly categorized along three domains: (1) spatial distribution (i.e., width variability, tightness), (2) tremor (i.e., number of trials with tremor, frequency, and power), and (3) spiral execution (i.e., speed, acceleration, pressure). We also found that some spiral indices correlated significantly with NPC clinical features, while other indices revealed subclinical movement abnormalities.

NPC patients drew with pronounced spatial irregularities, indicated by their high loop-to-loop width variation. Whereas control spirals had loops with relatively even spacing, NPC spirals tended to have uneven and crossed loops. We postulate that this width fluctuation is analogous to cerebellar ataxia, in which abnormalities in visuomotor and sensory modulation can manifest as over- or under-correction of spiral loop widths.[8,19–21] Loop width variation correlated significantly with disease duration and clinical measures of ataxia, revealing its potential utility as an objective marker. Patients with essential tremor, in which cerebellar degeneration may play a major role,[22,23] have also been found to draw spirals with high width variation.[24] This increase in spatial irregularity (ataxia), added to our finding of low frequency (4.6 Hz) tremors, is suggestive of cerebellar degeneration, in keeping with what is known from NPC neuropathology and mouse models.[25,26] Spiral analysis also confirmed our previous findings of cerebellar involvement using sEMG and accelerometry,[7] in a way that is easy to administer and captures functional disability.

NPC spirals were marked by abnormalities in execution. Although the median drawing pressure was normal in NPC patients, it was temporally abnormal, sustained at elevated pressures over time. This finding shares some features of the abnormal writing pressure profiles in patients with writer's cramp.[13] Patients also drew at significantly slower speeds than controls and failed to accelerate with increasing spiral radius. The latter finding is remarkable in that it deviates from the principles of isogony (quantified by the 2/3 power law[27]) and isochrony, two phenomena that have been robustly observed in the execution of continuous, planar drawing movements, independent of shape, size, and direction.[28–30] Isogony implies that drawing speed is inversely related to the curvature of the line drawn, and isochrony refers to the temporal invariance of drawing longer curved lines over the same angular displacement with increasing spiral radius. In keeping with these theories, we found that controls drew spirals with increasing speed, maintaining constant angular velocity over the same arc length. This feature was notably absent in NPC patients, even though the principles of isochrony and isogony have been qualitatively

found in children as early as 5 years of age, and are thought to evolve with age and motor skill.[31] It is possible, however, that the absence of isogony can be attributed to the slower speeds and increased joint combinations of NPC patients when drawing.[32]

The spiral findings in this study may help quantify NPC motor dysfunction in the context of more common and better understood movement disorders. The high loop width variability is consistent with cerebellar dysfunction. The abnormal pressure-time relationships are consistent with some of the abnormal dynamics seen in focal dystonia. The slow speed and decreased acceleration are suggestive of parkinsonism,[10] although the absence of micrographia and right-to-left hemi-pressure abnormality differs from parkinsonism.

Limitations of this study are that the small number of patients precludes greater significance between individual NPC patient phenotypes and spiral indices, although clear group differences, as well as significant correlations between spiral indices and clinical features, were found. Further, while the NPC case number is low, it is one of the largest cohorts of this rare disorder and provides added insight into neurological findings of NPC, which have previously been focused on nonmotor issues such as cognitive impairment, and on abnormalities of saccadic eye movements, speech, and balance.[11]

In their aggregate, our findings show that the upper limb motor dysfunction in NPC patients is distinguishable from controls through spiral analysis: patients had a spiral drawing profile comprising elements of action tremor, ataxia, Parkinsonism, and dystonia, as well as some normal features. Further studies employing spiral analysis may improve our understanding of this disorder by monitoring natural disease progression, serving as ancillary measures of NPC pathophysiology, and allowing for the objective evaluation of new therapies.

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Author Roles: A.W. Hsu—design and execution of statistical analysis, writing of manuscript. P.A. Piboolnurak—organization and execution of research project. A.G. Floyd—organization and execution of research project. Q.P. Yu—execution of research project. J.E. Wraith—review and critique of manuscript. M.C. Patterson—review and critique of manuscript. S.L. Pullman—conception of project, design of project execution, statistical analysis, writing, review, and critique of manuscript.

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