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Gait, balance and coordination impairments in Niemann Pick Disease, Type C1

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Abstract

This is the first study to objectively measure gait, balance, and UL coordination in a group of patients with NPC1 and compare the results to age and gender matched controls. This is also the first study to report effect sizes in these measures. Spatiotemporal gait analysis, static and dynamic posturography, and UL reaching motion analysis were performed. Our findings showed that the NPC1 subjects had statistically significant deficits on twelve out of the sixteen parameters investigated compared to controls, and large effect sizes for all but one parameter. When ranking the variables in terms of the effect sizes, the top five included at least one parameter from each of

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Conflicts of Interest

None

the three motor domains investigated. These results can provide insight to clinical researchers on the selection of outcome measures for longitudinal and interventional studies.

Keywords

Children; ataxia; developmental disability; lysosomal disease; rehabilitation

1. Introduction:

Niemann-Pick disease type C (NPC) is an autosomal recessive disorder due to mutations in the *NPC1* or *NPC2* gene. It has an estimated incidence of 1/92,000 with mutations in *NPC1* accounting for most of the cases (approximately 95%).¹ The pathophysiology of NPC involves impaired lipid transport leading to intracellular accumulation of unesterified cholesterol and glycosphingolipid.² The excess lipid storage in various tissues, including the brain, liver, spleen, leads to a broad spectrum of systemic, neurological and psychiatric signs and symptoms. NPC due to mutations in *NPC1* gene (NPC1), can be present as early as the prenatal period to late adolescence/adulthood. Observational studies associate early onset of symptoms, especially neurological, with a rapid rate of disease progression and early death.^{3,4}

The most common neurological symptoms in NPC1 include vertical supranuclear gaze palsy, cerebellar ataxia, dystonia, dysarthria and dysphagia, while ancillary symptoms like seizures, delayed developmental milestones and sensorineural hearing loss are less common.^{5,6} Progressive functional limitations are common in patients with NPC1 and may include difficulties with gait, balance and coordination. The clinical presentation typically includes slow and guarded movements, clumsiness, impaired fine motor skills affecting activities of daily living and other tasks, unsteady gait and frequent falls with many individuals eventually requiring wheeled mobility.⁶

While objective assessments of gait, balance, and coordination using valid and reliable methods are well documented in the pediatric literature in patients with various neurological disorders, there is a paucity of similar research in patients with NPC1. The only study reporting gait measures was a single case study reporting quantitative gait analysis post miglustat therapy⁷ and a couple of larger clinical trials using ambulation indexes or disability scales as outcome measures.^{8–10} In the field of coordination, we have found an analysis of upper limb (UL) motor physiology in NPC patients using accelerometers and EMG to measure dystonic, myoclonic, and choreiform patterns of movement.¹¹ However, none of these studies are case-control investigations objectively quantifying gait, balance, and coordination in the NPC1 patients.

The aim of this study was to objectively assess gait, balance, and UL coordination in a group of patients with NPC1 and compare the results to unimpaired age and gender matched controls. An additional aim of this study was to rank these measures in order of effect sizes to identify the ones with the greatest potential to be included in future, larger investigations.

2. Methods:

2.1 Subjects

Subject characteristics are displayed on Table 1. Our case-control study compared 10 subjects diagnosed with NPC1 (mean age: 15.63 ± 5.90 , range: 4.2–23.4 years) versus 15 corresponding gender- and age-matched healthy controls (mean age: 16.52 ± 5.29 , range: 4.5–23.7 years). The reason for the larger control group size was a pre-existing healthy volunteer gait dataset from which we were able to identify matched controls for some of our NPC1 subjects. The remaining unimpaired controls for gait, balance, and coordination came from individuals newly enrolled in the study. The impaired subjects in this study came from a larger cohort of patients enrolled in a phase 1/2a clinical trial (NCT01747135) and a natural history protocol (NCT00344331) on intrathecal 2-hydroxypropyl- β -cyclodextrin (VTS-270) for patients with NPC1.¹² All the patients enrolled in our study have a diagnosis of NPC1 confirmed by genetic testing and underwent clinical evaluation for confirmation of the disease in the Section on Molecular Dysmorphology at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). All but one of the NPC1 subject scores ranged from mild-moderately impaired (range 5–22 points at time of enrollment) based on the Severity Scale by Yanjanin et al.¹³ Subject 7 was severely impaired with a score of 32 at date of enrollment. The trial protocol was approved by the NICHD Institutional Review Board and informed consent was obtained from all the participants or their guardians when participants were under 18 years of age. Control subjects were excluded from the study if they presented any health conditions that could potentially interfere with their performance on gait, balance, and/or coordination tests.

2.2 Outcome Measures

All tests were conducted in the Computerized Motion Analysis Laboratory of a large tertiary research hospital. Data was collected by a team of two physical therapists and two engineers. Prior to testing all patients were assessed by the primary team (MDs, NP), the Medical Director of the Motion Analysis Laboratory or both. The outcome measures included three functional motor domains: gait, balance, and coordination. The NIH NPC Neurologic Severity Scale was applied to subjects in the NPC1 cohort in order to characterize neurological symptom burden.¹³ The Likert-like scale is comprised of 9 major domains and 8 minor domains, with a possible total score ranging from 0 (asymptomatic) to 61 (severely impaired). We adjusted the NPC Neurologic Severity Scale by age, to give a better idea of disease severity versus disease burden, and allow for better comparisons across patients without age as a confounding factor. The age adjusted severity score was calculated by dividing the NPC Neurologic Severity Scale by the age in year.

2.2.1 Gait—Temporospatial gait parameters for the NPC1 group were collected using a 6-meter long electronic walkway (GAITRite®; CIR Systems Inc., Sparta, NJ). For the age-matched controls, reflective markers were placed on the feet (heel, 2nd-3rd metatarsal head, and lateral foot) and marker trajectories were measured with ten infrared cameras (Vicon Motion Systems, Denver, CO) to calculate temporospatial gait parameters in Visual3D (C-Motion, Germantown, MD). The disparity between the methods of collecting the subject and control gait data was due to use of age and gender matched controls from a pre-existing

database that utilized the Vicon motion capture system. The GAITRite system has been previously validated against the Vicon motion capture system for the measurement of temporospatial parameters, and hence, findings from these two systems are comparable.¹⁴ The length of the walking path was the same for controls and patients; 6 meters. All subjects wore comfortable clothes and footwear. A PT guarded patients for safety during testing. All subjects were given instructions to walk at a self-selected comfortable pace. Three trials were collected, and the data was averaged for the following parameters: velocity (meters/second), cadence (steps/minute), step time (seconds), step length (meters), coefficients of variation of step length and step time, double support (DS) (percentage of the total gait cycle), and step width (meters). The coefficients of variation (CoV) were calculated as $\text{CoV} = (\text{standard deviation}/\text{mean}) \times 100$, expressed as percentage of step time or step length.¹⁵ All gait parameters were normalized to the height of the subject, except for step time and CoV, whereas DS was normalized to gait cycle time.

2.2.2 Balance: All balance testing was completed barefoot on a NeuroCom Balance SMART Equitest® System (Natus Medical Inc.). The following tests were performed:

- a. **Modified Clinical Test of Sensory Interaction on Balance (mCTSIB):** this test assesses static postural control under four conditions: standing with eyes open on a firm surface, eyes closed-firm surface, eyes open-foam, and eyes closed-foam. This test can indicate how the patient uses sensory information to control balance. Participants were asked to stand quietly and completely still for 10 seconds at a time, 3 times per condition. Average sway velocity (degrees/second) of the center of gravity (COG) was calculated for three trials on each condition. A higher sway velocity score indicates poorer postural control.
- b. **Limits of Stability (LOS):** this test assesses dynamic postural control. The participant is asked to lean towards a target in eight cardinal directions, intentionally displacing their COG without losing balance, stepping or reaching for assistance, while a computer screen displays their real time COG. The participant was allowed one unscored practice trial before the actual test. A few measures can be obtained with this test, but, the only variable of interest in this study was the Maximum Excursion (MXE, maximum distance travelled by the COG during the trial, expressed as a percentage of the subject's maximum theoretical LOS). A lower MXE score indicates poorer postural control.

2.2.3 Coordination—Coordination of UL was measured with kinematic assessment of the finger-to-nose test. This test is routinely used by clinicians as part of a full neurological examination. Each participant sat in a chair with a backrest with their hips, knees and ankles at approximately 90 degrees. Straps were placed over the participant's shoulders and attached to the chair with Velcro to prevent trunk movement during the task. A reflective marker, serving as the target, was placed on a cylinder on a table at approximately the height of the participant's sternal notch. The target was placed at a distance close to, but less than maximum reach, avoiding complete extension of the elbow, and this distance was measured by the physical therapist (sternum-target distance). The participants were asked to perform the finger-nose test by using their index finger to alternately touch the target and their nose

at a self-selected pace. A 3D motion-capture system (Vicon Motion Systems, Denver, CO) with 10 cameras and a recording rate of 100Hz was used to record the path of four reflective markers placed on each hand (a marker on the nail of digit 2/index finger, a marker each on the distal 2nd and 4th metacarpal and a marker in the center hand over the carpal area of digit 3/middle finger). Three trials with three repetitions of nose-target were conducted with each arm. The subjects were asked to choose their preferred side to start testing. All subjects were right handed, except for one control (9 year old male). Although right and left sides are reported in the present study, it was not our intention to compare sides, and the disorder is not known to affect one side more than the other. Outcome measures included path length (meters) that the subject traced with their hand and the task time (seconds) required to complete the activity. Path length was normalized by the sternum-target distance for each subject.

2.4 Data Analysis

The sample size for some outcome measures was small because not all individuals, due to their functional impairments, were able to perform all tests. Statistical analysis was performed only on data that had a minimum of five subjects per group. Data analysis was performed using IBM SPSS version 19 (IBM, Somers, NY). Skewness, kurtosis, and normality of the data were verified before group comparisons. Unpaired t-tests were conducted to compare groups on all gait, balance, and UL coordination variables, except for DS time, Firm EO, left UL path length, and left UL task time because these were not normally distributed. For these non-parametric variables Mann-Whitney U tests were conducted. Cohen's d values were calculated to determine the effect size of each measure using the following formula, which assumes unequal variances between the two groups:¹⁶

$$Cohen's\ d = \frac{(M_1 - M_2)}{\sqrt{\frac{(SD_1^2 + SD_2^2)}{2}}}$$

Where M_1 and M_2 are means of the two groups and SD_1 and SD_2 are the standard deviations of the two groups.

The criteria by J. Cohen was followed to classify the scores as mild, moderate, or large effect size.¹⁷ Finally, Pearson Product-Moment correlations were performed to analyze possible associations between the Age Adjusted Severity Scores and all gait, balance and coordination variables. The critical alpha level was established at 0.05.

3. Results:

Table 2 lists patients in ascending order of age and indicates the tests for which the tasks could be performed. The task with the best completion rate was gait, with 9 out of 10 patients being able to complete testing although the data could be analyzed only for 8 patients due to a technical difficulty with GAITRite® during data collection. The single subject who was unable to complete gait testing was unable to do so because of difficulty comprehending or following instructions due to cognitive impairment. The UL coordination

test was second in order of compliance with 8 participants completing the test on the L side and 7 on the R side. Two patients could not complete this task because of cognitive impairments affecting their ability to comprehend or follow directions, and one patient had an intravenous catheter on the R arm so data could only be collected on the L side. Balance testing had the lowest compliance, with 7 patients being able to successfully complete the mCTSIB, and only 5 completing the LOS. The LOS forward (MXE1) and right directions (MXE3) were the only measures with at least 5 NPC1 subjects completing the test, and therefore the only directions of the LOS that are reported here. The reasons that the subjects could not complete balance testing were that they either could not stand barefoot unassisted for at least 10 seconds at a time, or they were unable to follow directions on the LOS test. The verbal directions for this task are complex and it was challenging for some patients to comprehend the instructions to lean toward a target by bending at their ankles while maintaining an upright trunk position. In addition to the above issues; three patients (2, 5 and 6) became visibly tired during testing, to the point that one of them (patient 6) had to stop and return the next day for completing the remaining balance assessment.

3.1 Between-group Analysis

Table 3 compares groups on each gait, balance, and coordination measure, and shows their respective statistical significance and effect sizes. All gait variables were significantly different between groups, except for cadence, step length, and step width. Patients walked significantly slower, spending more time on double support and showing more variability in terms of step time and step length when compared to the control group. Results for all balance variables tested with sufficient patient numbers are listed in Table 2, which shows that all were significantly different between groups, except for LOS in the right direction (MXE3). The findings revealed that during quiet stance on a firm surface with eyes open and closed, the NPC1 subjects swayed significantly faster than controls. Also, the NPC1 subjects displayed significantly reduced forward excursion on the LOS test compared to controls. Finally, results on the UL coordination test showed that NPC1 subjects took a significantly longer path length and longer time on average to complete the finger-to-nose task compared to controls. Cohen's *d* values were all above 0.8, indicating a large effect size across all gait, balance, and UL coordination, except for step length which was 0.60 (classified as medium effect size). Overall, the top 5 largest effect sizes observed were the following: R path length (2.75), L path length (1.73), MXE forward (2.58), CoV step time (2.05), and CoV step length (1.71).

3.2 Individual Descriptive Analysis

In order to better understand the variability in our dataset and the deficits each subject shows in comparison to controls, we present here a descriptive analysis of individual scores, where each patient was paired with their respective age and gender matched healthy control (Figures 1–3).

Figure 1 shows individual scores on gait. The most prominent and consistent differences between patients and controls were found on the gait variability measures, CoV step time and step length. With the exception of patient 5 who scored close to normal on variability of step time, all other patients showed greater, and in some cases more than double the

variability of their controls. It is not surprising, therefore, that gait variability reached significance in the statistical analysis, and scored among the top five largest effect sizes among all variables investigated. Also, in Figure 1, other gait variables that are more traditionally studied in the field of human movement science, such as velocity, step time, and double support time showed less prominent and less consistent differences. In contrast to the variables described above, cadence and step length were similar to controls with the following exceptions (patients 7, 8 – step length, patient 9 – cadence). Not surprisingly, these variables failed to reach significance on the statistical tests. Finally, step width was the least consistent variable in terms of differences between patients and controls; while a few patients showed wider than normal step width (patients 5, 6 and 7), one patient (patient 3) contrary to expectations, showed an abnormally narrow base of support; and the remaining patients did not differ much from controls. These details on individual scores help understand why step width did not reach significance on the statistical tests.

Figure 2 shows individual scores on balance. Figure 2A displays all four conditions of the quiet stance test (mCTSIB). A higher number of patients were able to perform the two first conditions, which involved standing on a firm surface, than the last two conditions which involved standing on a foam surface. Comparing the first two conditions, standing on a firm surface with eyes closed yielded more pronounced and consistent differences than standing on a firm surface with eyes open for all patient-control pairs, except for patient 4. These results explain the reason for both variables reaching statistical significance but the second condition of mCTSIB (standing with eyes closed) yielding a larger effect size. On the conditions involving the foam, which are gradually more challenging, patients 3, 5 and 10 were unable to continue, and patients 6 and 8 experienced falls (indicated by the maximum score of 6 degrees/second). Because test compliance was an issue under these conditions ($n < 5$), no statistical analysis was performed. Figure 2B refers to the LOS test. Only patients 2,4,5,6 and 8 were able to complete this. When comparing the two variables in the LOS test, MXE in the forward direction yielded more consistent and marked differences between patients and their controls than MXE in the right direction.

Figure 3 shows individual scores on upper limb coordination. Overall both variables show the majority of the patients scoring substantially worse than controls, however, there seems to be more consistent and prominent differences in path length when compared to task time. Another notable observation was the large gap in scores between patient 10 and their respective control, especially on the left side. Although all variables reached statistical significance, left task time had the smallest effect size. This was not surprising given the large difference between patient 10 and their control, which may have skewed the data.

3.3 Correlations

Significant positive associations were found between age adjusted severity scores and the mCTSIB (Figure 4.A.). As severity scores worsened, so did postural instability under both eyes open and eyes closed conditions during testing on a firm surface. In addition, significant positive associations were found between age adjusted severity scores and UL coordination (Figure 4.B.). As severity scores worsened, path length and task time increased on both right and left sides.

4. Discussion:

This is the first study to objectively measure gait, balance, and UL coordination in a group of patients with NPC1 and compare the results to age and gender matched controls. This is also the first study to report effect sizes of these types of measures. Our findings showed that the NPC1 subjects had significant deficits on twelve out of the sixteen parameters investigated compared to controls and large effect sizes for all but one parameter. When ranking our variables, the top five largest effect sizes included at least one parameter from each of the three motor domains investigated (UL coordination, balance, and gait). These results can be very informative to other researchers and provide insight to clinicians by guiding their selection of outcome measures for future research.

On the finger-to-nose coordination test, right UL path length had the largest effect size of all measures (Table 3), with the patient group showing a significantly longer path length (more than double) than that of controls with the majority of patient's results being consistent when individual scores were examined (Figure 3). The effect size for left UL path length, although slightly lower as compared to right, was also large and has the fourth largest effect size of the variables measured in this study. Although we measured coordination on both sides, it wasn't our intention to statistically compare them, since marked asymmetries are not characteristics of NPC1. These results are consistent with reports from similar studies investigating patients with ataxia^{18–21} and hemiplegic cerebral palsy,²² which also measured UL trajectories, although with more sophisticated motion analysis methodology, and different types of reaching tasks. Their findings include: longer path trajectories,²² decreased movement precision,^{18,19} slower movements and longer duration of the task.^{18,20–22} The other coordination variables investigated in this study, R and L task times, also showed significant results, which is consistent with the literature, however in this study, the effect size and individual results were not found to be as notable as path length. The results from this study confirm the coordination problems in the NPC1 population which are recognized by the clinicians and researchers. As seen in other patients with ataxia or cerebral palsy, the NPC1 patients performed more path adjustments during the task in order to reach the same level of accuracy and hence increasing the path length and the time required to complete the trajectory. This test is easily carried out requiring relatively simple motion analysis methodology, and was shown to have one of the highest completion rates among our patients. In addition, our UL coordination measures correlated significantly with the severity level of our patients (Figure 4). For practical reasons and based on the results of this study, the authors recommend the above measures, especially path length, for future studies investigating coordination in NPC1.

With regards to the two balance tests investigated here, statistical results on the LOS were more robust than the mCTSIB, with LOS MXE forward ranking as the second largest effect size among all variables (Table 3). Despite a very small sample size (n=5) for this variable, individual patients' scores were markedly and consistently reduced compared to controls (Figure 2B), yielding significant results on the group analysis (Table 3). Comparing the results of this study to the literature, there were no studies found that evaluated the LOS to investigate balance in children, but several studies in adult patients with neurological disorders including stroke,²³ Parkinson's disease²⁴ and in older adults with history of falls²⁵

which reported similar findings. These studies have demonstrated reduced values for LOS which is indicative of impaired balance during dynamic activities such as reaching and bending, which is also the case for our patients, as we could confirm it clinically. Based on the above findings, the authors recommend the LOS test as a potential objective balance measure in future studies, however, researchers should keep in mind they may encounter compliance issues as the LOS was a difficult test for many if not most of the impaired subjects in this study. Despite a majority of the group attempting to complete the task, only half of our NPC1 cohort executed the test correctly. Although the mCTSIB is a measure of static, not dynamic postural control, this test may be an alternative objective balance measure for future studies that might include patients who are unable to perform the LOS.

Our findings on the mCTSIB showed statistically significant group differences, large effect sizes, and relatively good compliance for the two initial conditions of this test, which involve standing on a firm surface (Tables 2 & 3). In addition, performance on these two conditions were significantly associated with a clinical severity scale, with postural sway velocity increasing as disease severity increased (Figure 4), adding to the evidence that supports the mCTSIB test as an important tool in clinical research. In contrast, the conditions that required standing on a foam surface, were too challenging for the subjects in this study and statistical analysis could not be performed on this variable secondary to poor compliance (Figure 2A). Comparing the two firm surface conditions (eyes open, eyes closed), the eyes closed condition yielded more notable results in terms of effect size (Table 3) as well as in individual scores (Figure 2A) and correlations with a clinical tool (Figure 4). These findings of abnormally increased sway velocity on firm surface with eyes closed indicate that individuals with NPC1 have impaired use of proprioceptive inputs for postural stability. A clinical correlate of this particular mCTSIB condition is the Romberg test, which is routinely used to screen for proprioception problems. However, had the Romberg test alone been used in our study, it would not have been as informative as the mCTSIB, as the Romberg's test only provides a "positive sign" if the patient falls it is not as quantifiable as the mCTSIB. None of the NPC1 subjects in this study fell (Figure 2 A) or exhibited such high sway velocity that it could be visually observable to the naked eye. However, the NPC1 group did have significantly faster sway than controls with an average sway velocity of 0.97 degrees/second which was three times that of the controls. These results are consistent with previous studies that have also reported higher sway velocity, with very similar numbers (close to 1 degree/second), on this mCTSIB condition in children with cerebral palsy and posterior fossa tumors.^{26–28} These findings support the use of mCTSIB in future studies that investigate sensory control of balance in NPC1.

In terms of gait, coefficients of variability for step time and step length demonstrated statistical significance and greatest effect sizes when compared to the other gait variables investigated (Table 3). On examining the individual plots, these variables were the ones with the most consistent and marked differences between patient-control pairs among all gait variables (Figure 1). In the field of human movement science, variability in gait has been seen a measure of automaticity, as it depicts how regular, rhythmic, and safe ambulatory function is in an individual. While variable stride length has been found to be a clinically relevant measure in adults with neurodegenerative diseases like Alzheimer and Parkinson disease,²⁹ concurrent variability in stride length and time have been suggested to be more

indicative of cerebellar ataxia.³⁰ In the pediatric literature, there is supporting evidence for this concept in newly diagnosed patients with autism having cerebellar and basal ganglia involvement (4–6 years old) who showed abnormally increased variability of stride length and time on objective gait analysis, and demonstrated clinical features of cerebellar ataxia on qualitative observational gait analysis.³¹ Since the NPC1 population investigated in the present study is likely to have cerebellar and basal ganglia involvement,^{6,32} similar findings of gait irregularities in our study with respect to CoV step time and step length are not surprising. Based on our findings, CoV measures seem to be the best among all gait variables to differentiate between patients with NPC1 and controls, and should be among the first gait outcome measures to be considered in future investigations of gait in this disease.

Three other gait variables also showed significant results and large effect sizes; these were double support, velocity and step time, in order of effect size (Table 3). These results were expected as there is a considerable amount of research showing that patients with balance problems, as it is the case in our cohort, walk significantly slower and spend more time in double support than single support in order to compensate for their postural instability.^{33,34} Results were more revealing when the individual plots were closely examined (Figure 1). The assessment clearly showed that the NPC1 population fell into two subgroups: those with considerable deficits on both velocity and double support time compared to their controls (patients 5, 7, 8 and 9) and who also scored poorly on the balance tests, with a second subgroup at the other end of the spectrum who had nearly normal velocity and double support (patients 2, 4, 6) and who also performed better on the balance tests. In addition to supporting the literature, these findings also inform future studies where researchers may consider gait variables (especially double support time) as an alternative indicator of dynamic balance in populations who are unable to perform mCTSIB and LOS balance tests, which may exceed their balance capabilities or ability to follow directions due to cognitive difficulties.

In the NPC1 group, in addition to cognitive status, age was found to be a factor that influenced patient performance on all of these tests. This is not surprising given that the motor and cognitive impairments associated with NPC1 are known to be progressive. Therefore the finding that older patients (e.g. patients 7, 8, 9 and 10) seem to have more significant deficits and performed poorly on most tests is expected. Also of note is that when corrected for age, our movement analysis measures using mCTSIB and the UL coordination test correlate well with the disease specific clinical severity score.

The main limitations of this study were small sample size and selection by convenience of the NPC1 group out of a larger clinical study. Our original sample size was reduced further when patients were unable to complete some tests, mainly due to cognitive limitations. However, given the rarity of the disease, this sample size for this type of study is not uncommon. Selecting our patients out of a larger clinical study at times made it difficult to coordinate patient testing either due to scheduling conflicts with other tests or due to fatigue associated with other tests/procedures. It is possible, but uncertain, that fatigue may have negatively impacted the performance of three NPC1 subjects on the tests. Therefore, the authors recommend that for all future research, the NPC1 patients should be scheduled on

the day of admission itself and ensure that they are well rested, and to particularly avoid testing following sedation or other stressful medical procedures.

5. Conclusion:

Finding significant results and large effect sizes for most variables investigated in this study, in such a small and variable sample of NPC1 patients, is encouraging for the research and clinical fields. As there is still a need for larger studies in this disease, it was our hope that these findings along with the practical observations provided here, could contribute to guiding the design and methodology of future studies. Future research efforts that objectively measure gait, balance and coordination in patients with this disorder should focus on longitudinally tracking the variables highlighted in this study to investigate change over time. Eventually, if these measures turn out to be sensitive markers of disease progression, future investigations should consider including them as outcome measures in clinical trials.

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Figure 1.

Individual gait values for patients and their matched control. Depicted above are normalized values for velocity, cadence, step length, and double support time. Also the following variables, which were not normalized, are depicted: coefficients of variability of step time and step length, and step time. Abbreviations: m=meters, sec=seconds, ht=height in meters, min=minutes

Figure 2.

Individual balance values for patients and their matched controls. Part A depicts the sway velocity during the Modified Clinical Test of Sensory Interaction on Balance under the conditions eyes open (EO) and eyes closed (EC) on firm and foam surface. Part B depicts the Maximum Excursion, expressed as a percentage of the maximum theoretical Limits of Stability (LOS) in the forward and right direction. The remaining directions were attempted but, due to inability of the patients to complete them, they were not plotted. Abbreviations: sec=seconds, % LOS= percentage of theoretical limit of stability

Figure 3.

Individual coordination values for patients and their matched controls. On the top, the Y axis denotes normalized values for path length on right (R) and left (L). On the bottom, task times in seconds for right (R) and left (L) are depicted. Abbreviations: path=path length covered by the finger in meters (m) and target= sternum-target distance in meters (m), sec=seconds

Figure 4.

Correlations between Age Adjusted Severity Scores and balance (A), as well as upper limb coordination (B). Abbreviations: sec=seconds, path=path length covered by the finger in meters (m) and target= sternum-target distance in meters (m)

Table 1:

Patient characteristics.

ID	Age (years)	Gender	Age at onset of neuro symptoms (years)	Severity score	Age adjusted severity score
1	4.7	F	1	5	1.1
2	8	M	6	9	1.1
3	10.7	F	6	22	2.1
4	13.9	F	8	15	1.1
5	16.5	F	8	17	1.0
6	18	M	9	19	1.1
7	18.4	F	6	32	1.7
8	20.1	F	1.2	18	0.9
9	22.6	F	11	16	0.7
10	23.4	M	10	30	1.3

Abbreviations: F=Female, M=Male

Table 2:

Test compliance for the NPC1 group. Checkmarks indicate the patient completed the test.

ID	Gait	mCTSIB	LOS	UL Coordination
1	✓			✓
2	✓	✓	✓	✓
3	✓	✓		
4	✓	✓	✓	✓
5	✓	✓	✓	✓
6	✓	✓	✓	✓
7	✓			
8	✓	✓	✓	✓
9	✓			✓
10		✓		✓

Abbreviations: mCTSIB=Modified Clinical Test of Sensory Interaction on Balance, LOS= Limits of Stability Test.

Table 3:

Between-group comparisons for gait, balance and UL coordination measures.

Variable		n	(mean±SD)		95% CI		p value	Cohen's d	
			NPC1	Control	NPC1	Control			
Gait	Velocity ((m/sec)/ht)	8	0.58±0.16	0.81± 0.15	0.45–0.72	0.69–0.93	0.011 *	1.48 [†]	
	Cadence ((steps/min)/ht)	8	62.89±12.73	74.07±12.09	52.25–73.53	63.96–84.18	0.093	0.9 [†]	
	Step Time (sec)	8	0.63±0.10	0.52±0.05	0.54–0.71	0.47–0.56	0.015 *	1.39 [†]	
	Step Length (m/ht)	8	0.36±0.09	0.40±0.03	0.37±0.43	0.61–0.66	0.275	0.6	
	CoV Step Time (%step time)	8	0.09±0.028	0.04±0.02	0.06–0.11	0.02–0.05	<0.001 *	2.05 [†]	
	Cov Step Length (%step length)	8	0.09±0.04	0.04±0.01	0.06–0.13	0.03–0.05	0.003 *	1.71 [†]	
	Double Support (%gait cycle)	8	32.37±7.15	23.68±3.47	26.39–38.34	20.78–26.58	0.003 *	1.55 [†]	
	Step Width (m/ht)	8	0.10±0.04	0.07±0.01	0.06–0.14	0.06–0.07	0.066	1.03 [†]	
Balance	mCTSI	Firm EO (degrees/sec)	7	0.73±0.78	0.23±0.20	0.01–1.45	0.05–0.41	0.038 *	0.88 [†]
		Firm EC (degrees/sec)	7	0.97±0.70	0.31±0.20	0.32–1.62	0.13–0.49	0.035 *	1.28 [†]
	LOS	MXE1 (%LOS)	5	58.80±15.66	94.40±11.65	39.36–78.24	79.93–108.87	0.004 *	2.58 [†]
		MXE3 (%LOS)	5	72.40±25.66	90.40±17.74	40.54–104.26	68.37–112.43	0.233	0.82 [†]
UL Coordination	R Path Length (m/target)	7	3.73±0.92	1.84±0.31	2.88–4.59	1.55–2.13	<0.001 *	2.75 [†]	
	L Path Length (m/target)	8	3.96±1.68	1.87±0.29	2.56–5.37	1.63–2.11	0.001 *	1.73 [†]	
	R Task Time (sec)	7	8.58±3.53	4.92±1.17	5.31–11.85	3.84–6.01	0.034 *	1.39 [†]	
	L Task Time (sec)	8	9.99±6.90	4.81±0.97	4.22–15.76	4.0–5.62	0.012 *	1.05 [†]	

Abbreviations:

* denotes p values < 0.05 on unpaired T tests for all parametric variables and on Mann Whitney U test for non-parametric variables,

[†] denotes effect sizes > 0.08, which can be categorized as large,

m=meters, sec=seconds, min=minutes, CoV=Coefficient of variation, MXE1=Maximum excursion forward direction, MXE3=Maximum excursion right direction, target=sternum-target distance in meters.