*Brief Report*

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# Functional impairments in NBIA patients: Preliminary results

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**SUMMARY** Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group (genetically and phenotypically) of genetically determined disorders. Up to date there is no cure for this disease, so the applied treatments focus on symptoms control and palliative care. The main problems are delayed motor development, gait deterioration, postural instability, cognitive dysfunctions, abnormal muscle tone and many others. As gait and balance deficits are predominant features of NBIA patients this study aimed at the use of the objective, instrumented functional tests as well as functional assessment scales to assess their functional impairments. Twenty three NBIA patients recruited for the study underwent objective, instrumented gait analysis, balance assessment, pedobarography and functional evaluation with Gross Motor Function Measure (GMFM-88). The results showed high variability and heterogeneity of NBIA functional status (GMFM from 27.5 to 100.0), but also showed some differences in gait pattern between their types ($p < 0.05$ at the pelvis, hip and knee). We think that these results could help design objective assessment protocols in future clinical studies.

***Keywords*** NBIA, gait, balance, functional assessment

## 1. Introduction

Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group (genetically and phenotypically) of ultra-rare genetically determined disorders, in which the main feature is accumulation of iron in the brain. Its heterogeneity of symptoms and rarity makes diagnosis very difficult and challenging (*1*). The diagnosis is usually first suspected when MRI features (hypointensity of the basal ganglia) are connected with progressive movement disorders (*2*). The main feature of NBIA is iron deposition in the brain, but some studies show, that this deposition may be secondary to a metabolic impairment of the neural cells, concerning such pathways as mitochondrial functions, lipid metabolism autophagy and iron homeostasis (*3*). Its assumed prevalence is from 0.1 to 0.3 per 100,000. Analysis of publicly available Genome Aggregation Database revealed, that prevalence is most probably much higher, reaching 0.92 per 100,000 (*4*).

Panthotenate kinase-associated neurodegeneration (PKAN, formerly Hallevorden-Spatz syndome) accounts for 50 % of all diagnosed NBIA patients. The carrier frequency is estimated as 1 per 275 to 500 people. In classic PKAN (75 % of cases) the disease onset appears in early childhood and the progression is fast. The first symptoms comprise clumsiness, motor development delay, dyspraxia, followed by gait pattern deterioration (in some cases in the form of toe walking), postural instability and visual impairment. Often abnormal muscle tone is present in the form of spasticity or rigidity. In severe cases of increased muscle tone bone fractures could appear, as well as osteoporosis due to reduced mobility. In atypical PKAN the onset appears later, patients have speech difficulties, milder gait pattern abnormalities, mild dystonia, and sometimes neuropsychiatric features are present. In time patients develop cognitive dysfunction (very variable in severity), which is negatively correlated with the onset age. Lost with age skills are not regained, and the decline shows a step-like pattern, with periods of relative stability (*5*). Some patients suffer additionally from "eye of a tiger" sign, dysarthia and behavioral disturbances (*6*).

The second most common type is PLA2G6-associated neurodegeneration (PLAN), approximately 20 % of NBIA cases, and the third MPAN (10%) (*7*). In PLAN development delay with visual impairment and facial dysmorphism are present. In some patients

epileptic seizures and neuroaxonal dystrophy occur (*7*). Other manifestations could also be present, such as dystonia, visual problems, and in some patients there is rapid progression of the disease, ending with death at an early age (*6*).

Mitochondrial membrane protein-associated neurodegeneration (MPAN) patients present juvenile-onset gait deterioration, rapid cognitive decline and suffer from neuropsychiatric problems (*6*). In some MPAN pediatric patients early signs of cardiac autonomic dysfunction symptoms were found, so monitoring of heart function in patients with this type of NBIA is recommended (*8*).

There are also other, less common, types of NBIA. In the fatty acid hydroxylase-associated neurodegeneration (FAHN) type the gait abnormality is the most characteristic feature, while in less than half of patients abnormal cognition is present. In some patients there is late onset associated with rapid progression. The majority of patients have dystonia and ataxia (*6*). The beta-propeller protein-associated neurodegeneration (BPAN) type starts with early occurring psychomotor retardation, which remains stable until adulthood. In their twenties / thirties dystonia rapidly occurs with parkinsonism and dementia, accompanied with rapid eye movements, dysautonomia and sleep disorders (*9*). In Parkinson disease type 9 (PARK9) type the levodopa-resistant parkinsonism is present accompanied by visual abnormalities, autonomic and psychiatric dysfunctions and dementia (*9*).

Up to date there is no cure for NBIA, so the applied treatments focus on symptom control, and palliative care. In cases of severe increased muscle tone botulinum toxin or baclofen are used. In some cases also benzodiazepines, deep brain stimulation and transcranial magnetic stimulation of the premotor cortex are considered. In cases of parkinsonism features (tremor, rigidity, severe bradykinesia) levodopa treatment is implemented. An intensive rehabilitation approach is also part of treatment, with occupational therapy, speech and swallow therapy. Assistive devices and environment adaptation to the patients' needs are recommended (*5,10-13*).

In case of PKAN two experimental therapies are now considered: iron chelation and high-dose pantothenate therapy (*5,14*), although the efficacy of them is, so far, doubtful (*9*).

The European Treat Iron-Related Childhood-Onset Neurodegeneration (TIRCON) project carried under EU FP7 connected dispersed NBIA scientific, clinical and patient-oriented communities from different European and non-European countries, enabling the creation of the NBIA registry and biobank and scientific international collaboration. This project identified also several problems and shortcomings, among others: problems with defining the reasonable endpoints in the future clinical studies, lack of disease-specific clinical scales assessing current status of patients, and lack of defined markers of disease progression (*15*). All these conditions are indispensable for assessment of efficacy of applied treatments. Therefore this study aimed at the use of the objective, instrumented functional tests as well as functional assessment scales in NBIA patients.

## 2. Patients and Methods

### 2.1. Patients

Twenty three NBIA patients, aged from 4 to 21 year (14 patients with MPAN, 5 with PKAN, 4 with BPAN), participated in the study. This was an opportunistic study, but all parents/guardians were informed about the possible use of the data for research and the purpose of the study, the methods used, and gave their consent. Those patients who were able to understand the study, regardless of their age, were also informed and gave their consent. The study conformed to the provisions of the latest version of the Declaration of Helsinki. All patients underwent functional assessment performed by an experienced physiotherapist, and instrumented gait analysis. Due to balance and communication problems pedobarography and balance assessment were performed in less than half of the patients. Ten patients underwent the second evaluation with instrumented, objective tests approximately one year after the initial assessment. This was because of two reasons: first, decline in functional status and loss of walking ability in the case of 11 patients, and second, various times of patients' recruitment to the study. The study was performed from February 2021 until March 2023.

### 2.2. Gait analysis

The instrumented gait analysis was performed with VICON system with 12 MX cameras. The lower body Plug-In-Gait marker set and model were used. The patients were walking several times along the 10 m walkway with self-selected gait speed, and six technically correct trials were later averaged in Polygon, averaged data extracted and analyzed. Spatio-temporal data were expressed as per cent of the age and sex matched reference data, except for step width, which was normalized by ASIS-ASIS distance (distance between anterior superior iliac spines). The following kinematic data were extracted: pelvic tilt, pelvic range in transversal plane, hip range in sagittal plane, knee flexion at initial contact, midstance, and swing, foot range at push-off, and foot progression.

Additionally several gait indices, reflecting the patient's gait pathology, were calculated. In Nexus software the Gait Deviation Index (GDI) was calculated for each trial of each patient, separately for left and right leg, and later averaged for the patient's session.

GDI (*16*) is a single number, resulting from kinematic plots and principal component analysis. The methodology

uses three dimensional angles of the pelvis and hip, at the knee and ankle joints only angles in sagittal plane are used, and foot progression angle. This index is transformed and scaled in such a way, that its average for healthy subjects is 100, with a standard deviation of 10.

Another index is Gait Profile Score (GPS), which describes the overall gait pathology (*17*). It is composed of Gait Variable Scores (GVSs) calculated from 9 main kinematic gait variables, which can be presented as a Movement Analysis Profile (MAP). GVS is calculated as root mean square (RMS) difference between kinematic variable across gait cycle of the patient and reference variable representing healthy subjects. They are calculated for: pelvic tilt, hip flexion, knee flexion, ankle dorsiflexion, pelvic obliquity, hip abduction, pelvic rotation, and foot progression. From GVSs an overall index, GPS is calculated.

2.3. Pedobarography

Plantar loads during gait were registered on the Emed system (Novel Company) in 10 patients. Children were asked to walk barefoot several times on a pathway with a built-in pedobarography platform with their normal, self-selected speed. Data from three plantar loads of left and three plantar loads of right foot were averaged and taken for further analysis. Total load and loads on foot segments (feet were divided into segments automatically by the Novel software) were normalized to the patient's body weight.

2.4. Balance

The patients underwent balance test on Kistler force plates in two conditions: with eyes open (9 patients) and eyes closed (8 patients). Patients were asked to stand as quietly as possibly on the platform for 40 to 50 seconds with feet parallel, the distance between them equal to pelvis width, arms hanging freely along the torso. The data from the middle 30 seconds were used for the analysis. Matlab's own procedure was used to extract medio-lateral (separately for left and right) and antero-posterior (separately for anterior and posterior) displacements, the mean radius of sway and total sway path.

2.5. Functional evaluation

This evaluation was performed by one, experienced physiotherapist with Gross Motor Function Measure (GMFM-88), an assessment tool designed to measure the changes of gross motor functions in children with cerebral palsy, but can be used also for children with developmental problems. GMFM-88 assesses 88 activities in 5 dimensions: A. Lying and rolling, B. Sitting, C. Crawling and kneeling, D. Standing, E. Walking, Running and Jumping. These activities are ordered based on the levels of difficulty, and the scale has ratings from 0 to 100. This measure is validated on children from 5 months old to 16 years of age (*18-20*).

2.6. Statistics

Depending on the type of the distribution the data were summarized by means and standard deviation or median, minimum and maximum. The comparisons of the results between the three types of NBIA (MPAN, PKAN and BPAN) were done with ANOVA test or its non-parametric equivalent test. The comparisons between first and second evaluation was done using sign test for dependent samples. The dependence between the GMFM and gait indices was explored with a Spearman rank correlation test. The statistical significance was assumed at the level 0.05, and the STATISTICA 10.0 (TIBCO Software Inc.) was used.

## 3. Results and Discussion

3.1. Summary of the results

To our knowledge this is the first study which assessed in an objective way the functional status of children with NBIA by instrumented methods and functional tests, and therefore the comparisons of our results with the results concerning NBIA of others is impossible (confirmed by literature search in databases such as PubMed, World of Science, and ScienceDirect using combinations of the key words: NBIA, function, functional evaluation *etc.*).

The results of the objective and functional tests are summarized in Tables 1-5.

From the literature (Introduction) it is known that most patients with various types of NBIA suffer from gait and balance disorders. They are variable and their progression is not uniform. Our results confirm these statements. Despite the high variability it can be seen that the gait speed is reduced in comparison to healthy peers due to reduced cadence and step length. In the case of the balance study only 2 patients had all measured parameters within normal range during standing with eyes open, and one of these patients had also all parameters within normal range while standing with eyes closed, but in the case of a majority of evaluated patients at least one parameter exceeded the normal range, and in some patients nearly all of them.

The maximum number of parameters exceeding

**Table 1. The spatio-temporal parameters of NBIA patients gait**

| Parameter | Mean | SD | Min | Max |
|---|---|---|---|---|
| Gait speed [%] | 54.1 | 24.4 | 11.0 | 100.0 |
| Cadence [%] | 72.3 | 20.6 | 35.0 | 100.0 |
| Step width / ASIS-ASIS | 0.72 | 0.21 | 0.18 | 1.05 |
| Step length [%] | 73.2 | 21.4 | 21.0 | 100.0 |

**Table 2. The kinematic data**

| Parameter | Median | Min | Max | Normal value (*21*) |
|---|---|---|---|---|
| Tilt [°] | 14.0 | -3.0 | 24.0 | 12 - 15 |
| Pelvis range transverse [°] | 14.0 | 4.0 | 35.0 | 8 - 10 |
| Hip range sagittal [°] | 33.5 | 14.0 | 50.0 | 43 |
| Knee initial contact [°] | 10.0 | -22.0 | 36.0 | 0 - 4 |
| Knee flexion in stance [°] | 4.0 | -22.0 | 35.0 | 0 - 4 |
| Knee max in swing [°] | 54.5 | 23.0 | 65.0 | 60 - 65 |
| Push-off range [°] | 24.5 | 0.0 | 53.0 | 25 - 30 |
| Foot progression [°] | -5.0 | -50.0 | 8.0 | -12 - -15 |

**Table 3. The Gait Variability Scores (GVS), Gait Profile Score (GPS) and Gait Deviation Index (GDI)**

| Parameter | Median | Min | Max |
|---|---|---|---|
| GVS pelvis sagittal | 5.77 | 1.38 | 15.30 |
| GVS hip sagittal | 8.62 | 4.01 | 26.26 |
| GVS knee sagittal | 11.99 | 5.54 | 31.64 |
| GVS ankle sagittal | 6.96 | 2.96 | 28.45 |
| GVS pelvis frontal | 3.03 | 0.81 | 5.60 |
| GVS hip frontal | 5.17 | 1.43 | 14.62 |
| GVS pelvis transverse | 5.13 | 1.55 | 14.97 |
| GVS hip transverse | 11.12 | 4.71 | 45.42 |
| GVS foot progression | 10.66 | 2.35 | 35.94 |
| GPS | 8.63 | 5.40 | 17.69 |
| GDI | 73.70 | 48.70 | 97.20 |

**Table 4. The loads normalized to the body weight, arch index and hallux angle**

| Parameter | Median | Minimum | Maximum | Normal value |
|---|---|---|---|---|
| Max force/BW [%] | 131.9 | 110.3 | 164.9 | 130.0 |
| MH1/BW [%] | 19.7 | 7.1 | 33.2 | 20.0 |
| MH2/BW [%] | 23.5 | 10.9 | 30.9 | 30.0 |
| MH3/BW [%] | 23.2 | 13.5 | 33.1 | 35.0 |
| MH4/BW [%] | 16.9 | 10.4 | 36.8 | 30.0 |
| MH5/BW [%] | 10.4 | 3.4 | 28.7 | 20.0 |
| Big toe/BW [%] | 13.1 | 1.0 | 39.7 | 20.0 |
| Second toe/BW [%] | 3.6 | 0.4 | 10.2 | 10.0 |
| Toes3-5/BW [%] | 4.3 | 0.8 | 15.1 | 15.0 |
| Hinfoot/BW [%] | 75.9 | 31.1 | 115.8 | 70.0 |
| Midfoot/BW [%] | 32.3 | 6.4 | 54.0 | 20.0 |
| Arch index | 0.25 | 0.11 | 0.36 | 0.21 – 0.26 |
| Hallux angle [°] | 1.0 | -5.0 | 15.0 | < 15.0 |

**Table 5. The results of Gross Motor Function Measure (GMFM)**

| | Median | Min | Max |
|---|---|---|---|
| GMFM_total | 77.4 | 27.4 | 100.0 |
| GMFM_A | 96.1 | 72.5 | 100.0 |
| GMFM_B | 98.3 | 35.0 | 100.0 |
| GMFM_C | 85.7 | 2.4 | 100.0 |
| GMFM_D | 74.4 | 0.0 | 100.0 |
| GMFM_E | 45.8 | 4.2 | 100.0 |

normal range was 4 in the case of eyes open condition (1 patient) and 6 (all of parameters) in the case of eyes closed condition (1 patient).

3.2. Comparison between NBIA types

The differences between MPAN, PKAN and BPAN are presented in Figure 1 (gait), and Table 6. There were only four gait parameters, which were statistically significantly different between the NBIA types. In the case of balance, pedobarography and GMFM (total and in 5 dimensions) no statistically significant differences were found.

The three types in our NBIA group (MPAN, PKAN and BPAN) present slightly different types of gait disorders. During level walking the MPAN patients have increased knee flexion at initial contact, while PKAN patients start contact with ground with either straight or hyperextended knee. The position of the knee of BPAN patients is similar to their healthy peers. GVS of pelvis in transverse plane is the smallest in BPAN patients, which means the movement closest to healthy persons. All NBIA patients have high values of GVS hip in transverse plane: which means a lot of abnormal movement, but in the case of MPAN patients most of them have lower than the other two groups values, meaning more normal movement. Also there are some differences between the three types in the placement of the feet in relation to the line of progression, with high out toeing in the case of MPAN group. Surprisingly we

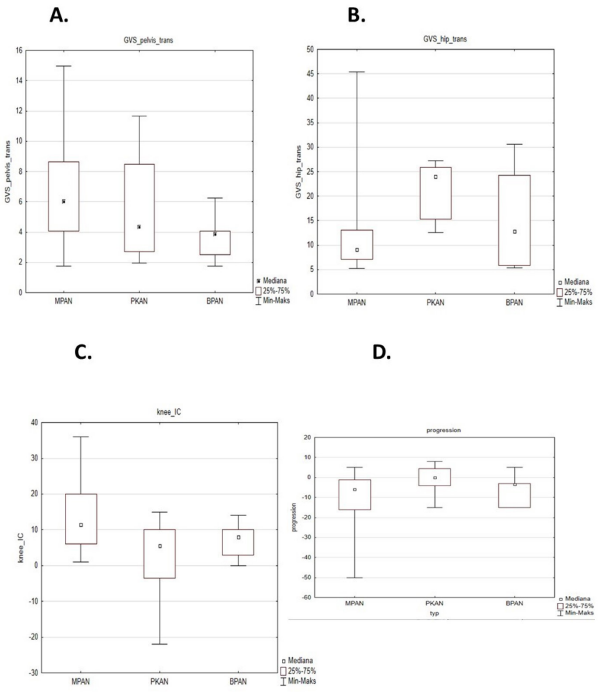


**Figure 1. Differences between NBIA types during gait.**

did not find any differences between the three groups in GMFM-88 assessment, neither in total nor in any of the 5 dimensions. Probably despite the fact that this evaluation is detailed and takes into consideration many aspects of activity in all of the functional dimensions its

**Table 6. Summary statistics of statistically significant different parameters of gait for MPAN, PKAN and BPAN patients**

| Group | GVS pelvis transverse Median (Min – Max) | GVS hip transverse Median (Min – Max) | Knee initial contact [°] Median (Min – Max) | Foot progression [°] Median (Min – Max) |
|---|---|---|---|---|
| MPAN | 6.78 (2.61 – 11.96) | 8.42 (5.24 – 18.57) | 10.0 (4.0 – 36.0) | -9.5 (-20.0 – 0.0) |
| PKAN | 2.85 (1.55 – 11.66) | 17.05 (5.46 – 26.32) | 5.0 (-7.0 – 15.0) | 3.0 (0.0 – 5.0) |
| BPAN | 2.78 (1.74 – 4.07) | 14.0 (10.77 – 30.62) | 10.0 (0.0 – 15.0) | -4.0 (-15.0 – 0.0) |

**Table 7. Correlation coefficients (R) and determination coefficients ($R^2$) between GPS, GDI and GMFM**

| | GPS | | GDI | |
|---|---|---|---|---|
| | R | R^2 | R | R^2 |
| GMFM total | -0.65 | 42.3 | -0.65 | 42.3 |
| GMFM A | -0.46 | 21.2 | -0.46 | 21.2 |
| GMFM B | - | - | - | - |
| GMFM C | -0.62 | 38.4 | -0.62 | 38.4 |
| GMFM D | -0.68 | 46.3 | -0.68 | 46.3 |
| GMFM E | -0.69 | 47.6 | -0.69 | 47.6 |

sensitivity is much lower than parameters and indices from objective, instrumented gait analysis.

The dependence between overall gait indices GDI and GPS and GMFM and its dimensions is presented in Table 7. The only functional domain, which did not show any relation with gait indices is Sitting, which is not surprising. The correlations are medium, and calculated from the correlation coefficients the determination coefficients ($R^2$) are all below 50.0. The determination coefficient is a measure, which shows how well the change of one parameter can be explained by the change occurring in the second one. The obtained values were between 21.2 and 47.6, showing that there are other factors not accounted for. These values prove that functional assessment measures and gait are interrelated, but they are complementary: they assess different aspects of motor performance of NBIA patients.

### 3.3. First *vs.* second assessment

In the case of balance assessment and pedobarography there were no statistically significant differences between the first and second evaluation, in the case of gait analysis only two parameters differed statistically significant, both reflecting pelvic movement. GVS pelvis in sagittal plane changed from median value 6.73 to 5.29 ($p = 0.032$), and GVS pelvis in transverse plane from median value 4.96 to 6.41 ($p = 0.041$).

Eleven of our patients could not come to the second evaluation after one year from the first one, confirming the fact, that many NBIA patients suffer from rapid decline of their functional status and could within a very short time lose their ability to walk. But in those who participated in their second evaluation there was nearly no change in their gait patterns. The only two parameters were indices assessing the pelvic movements: GVS in sagittal plane decreased, and GVS in transverse plane increased. Both changes are positive. Decreased GVS pelvis in sagittal plane means change of pelvis movement toward the more normal pattern. In many patients with locomotor problems the compensatory movements are present in pelvis in transverse plane, so paradoxically the increase of GVS pelvis in transverse plane could indicate that they gained greater opportunity to use the pelvis to compensate for their deficits. The main conclusion from these findings is, that NBIA patients who do not rapidly lose their walking ability could maintain their gait pattern on a stable level for quite a long period of time.

There are many shortcomings connected with this study. Gait and balance objective assessments require the cooperation and understanding of the instructions by the patients. Due to communication problems, developmental delays, *etc*. some patients were unable to undergo pedobarography or balance evaluations. Some patients could not stand still for the required 40-50 sec, so balance evaluation was impossible. The number of evaluated patients is small, but such is the nature of NBIA as a rare disease. The majority of the group were MPAN patients, as this type dominates in Poland. This small number together with heterogeneity, and individual variability of NBIA makes statistical analysis and drawing meaningful conclusions difficult.

## 4. Conclusions

Despite the small number of patients and limitations of this study we think that these results could help design objective protocols in the future. Especially instrumented gait analysis turned out to be the easiest objective test to perform, even in those patients who had problems with understanding and obeying instructions, mainly because of the high engagement of the parents, and together with GMFM-88 it can constitute the basis for future clinical trials.

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