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Extensive digital health technology assessment detects subtle motor impairment in mild and asymptomatic Pompe disease

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The aim of this case-control study was to evaluate the ability of digital health technology (DHT) to detect and quantify mobility alterations in late-onset Pompe Disease. The study enrolled eight subjects with Pompe Disease, including three young mildly affected/asymptomatic subjects, who underwent an extensive DHT mobility assessment and were contrasted to 52 matched controls. DHT enabled the detection of subtle mobility alterations, indicating a lower speed in walking, and worse performances in postural transition and turning in patients compared to controls. Interestingly, in the three mildly affected/asymptomatic cases, step time variability and step length showed detectable alterations compared to controls, despite scores within the normal range on clinical scales and timed tests.

Keywords Pompe disease, Digital technology, Digital health technology, Mobility, Progression

Pompe disease, also known as Glycogen storage disease type II (GSDII), is an autosomal recessive disorder caused by a deficiency of the acid alpha-glucosidase (GAA) enzyme, whose function is to hydrolyze glycogen to glucose in the lysosome[1,2].

GSDII has been classified according to age at onset into severe infantile form and late-onset form (LO-GSDII) which presents a more heterogeneous involvement of respiratory and skeletal muscles[2–4]. Since 2006, the use of the recombinant enzyme alglucosidase alfa (Myozyme®/Lumizyme®) has demonstrated its efficacy in stabilizing motor and pulmonary function, leading to a life-changing scenario for both infantile and adult patients[3,5]. However, among LO-GSDII patients, a high level of variability in their responses to the treatment was observed, and many subjects experienced some degree of secondary decline after 3–5 years[6]. During the last decade, this led to several studies aimed at expanding the therapeutic options to include novel rhGAAs (avalglucosidase alfa), chaperone- enhanced rhGAA (cipaglucosidase), and even gene therapy[7,8].

One of the main issues in managing LO-GSDII patients is the best way to assess the response to treatment because the sensitivity of the current clinical scales and timed tests does not seem optimal, especially in evaluating mild forms[2,9].

Recent studies have supported the use of digital health technologies (DHTs) to assess subtle mobility changes in response to interventions in different clinical conditions[10–12].

In this study we applied a comprehensive DHT assessment of gait, turning, and postural transition to detect subtle mobility impairment in LO-GSDII patients and investigate a subgroup of mildly affected or asymptomatic LO-GSDII subjects. The study demonstrated that step length and time variability are altered in all patients, including those who are asymptomatic or have only mild symptoms. Furthermore, subjects with mild to

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moderate symptoms also exhibited alterations in the maximal velocity during a task of postural transition and angular velocity during turning when compared to matched controls.

Patients and methods

Clinical assessment

This prospective study included patients with a genetic diagnosis of LO-GSDII followed at the ERN-Euro NMD Center for Neuromuscular Diseases in Brescia, Italy (Unit of Neurology and NeMO-Brescia Clinical Center for Neuromuscular Diseases, ASST Spedali Civili and University of Brescia) under enzyme-replacement treatment (ERT) with alglucosidase alpha.

Neurologically healthy controls were recruited from patients' families and from healthy volunteers and were matched for age with the patients. The following inclusion criteria were applied for both groups: (i) age over 18 years old, (ii) ability to walk without aids, (iii) lack of medical conditions or medication with potential impact on gait and mobility (including other neurological diseases, orthopaedic issues), other than LO-GSDII for the case group. No limitations were imposed regarding the utilization of non-invasive ventilatory devices.

The research protocol was approved by the Ethics Committee of the Brescia Hospital, Brescia, Italy (DMA study, NP 1471). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants.

Each LO-GSDII patient underwent an extensive clinical protocol including several clinical scales used in clinical trials and observational studies. Functional endurance was assessed by the 6-minute walking test (6MWT), which measures aerobic capacity by the distance (meters) walked in 6 min and is a well-known secondary outcome measure in clinical trials for GSDII[7]. The motor performances in daily life were evaluated by the Gardner-Medwin-Walton (WGM) scale, Timed Up and Go (TUG) test, and Gait, Stairs, Gower, Chair score (GCSG) scale[9]. WGM scale is a validated score ranging from 0 to 10, with 0 indicating the normal conditions and 10 the inability to conduct any activity. GSGC scale has recently been introduced and investigate the performances in four motor tasks (Gait by walking or 10 m, climbing 4 steps on a stair, Gower's manoeuvre, rising from a Chair), ranging from 4 (normal performance) to 27 (worst performance in non-ambulatory patients).

The daily life impact of the disease was assessed by Rasch-Built Pompe-specific Activity scale (R-Pact), Pompe Disease Symptom Scale (PDSS) and Pompe Disease Impact Scale (PDIS). These scales are simple self-report questionnaires based on daily or social activities that may be affected by the disease. The R-Pact consists of 18 items in order of increasing difficulty and the score for each item is defined as 0 = unable to perform, 1 = able to perform with difficulty, 2 = able to perform without difficulty[13]. The PDSS is based on 12 items with specific focus on fatigue, in which patients rate the severity of symptoms in the last 24 h from 0 to 10[14]. Nevertheless, the 15-item PDIS questionnaire provides a picture of mood and mobility-related activities over the previous 24 hours[9,14].

Digital health technology assessment

The RehaGait® system consists of three mobile inertial sensors (dimensions: 60 × 15 × 35 mm); each sensor comprises a 3-axis accelerometer (± 16 g), a 3- axis gyroscope (± 2000 °/s) and a 3-triaxial magnetometer (± 1.3 125 Gs). The sensors were attached to the lateral side of each shoe using special straps and at the level of the fifth lumbar spine segment close to the centre of mass to measure linear acceleration, angular velocity and the magnetic field at a sampling rate of 100 Hz[15].

Raw data were processed using Matlab R2022b (MathWorks, Natick, MA, USA). To analyse gait parameters the raw data of the IMU from the lower back was used. As stated in the method session, only variables with a percentage of missing data lower than 5% were considered. Outliers were defined by a value higher or lower than 3 standard deviations of the disease-specific group and were excluded from the analyses. As described in the references, the raw accelerometer and gyroscope data were processed to first detect the gait events[16,17]. Step time was defined as the time between two consecutive heel strikes, step time variabilities were calculated extracting standard deviation (SD) from all steps[18]. Step length was calculated as previously reported by Welzel and coauthors[19]. 6MWT-Fatigability was specifically evaluated by contrasting steps-4-104 with the last 100 steps detected during the 6 min walking test. Asymmetry was defined as the average absolute difference between left and right steps for each walking pass. The parameters included in the final analyses were duration of TUG, duration of turns, peak and mean angular velocities (in degrees per second), for the whole turning. Mean values from the clockwise and counterclockwise turns were used[20,21]. Postural transition digital assessment included PT duration, speed and angular velocity based on vertical displacement of the IMU placed on the low bac[16,22].

Statistical analysis

Differences in demographic and clinical parameters between participants with LO-GSDII and controls were not normally distributed and non-parametric tests adjusted for age and sex were used for all analyses. The sample size was calculated using the g*power 3.1.9.4 software, with a 0.05 alpha level, an 80% power (Cohen 1988), and an effect size of 0.85 to account for the small sample size and a 3:1 ratio. The model also accounted for the non-normal distribution between the groups, given the small sample size. Based on these assumptions, the number of calculated matched controls for eight patients was 24 subjects; the size was doubled in order to potentially expand the analyses on a subset of symptomatic vs. asymptomatic patients. For the secondary analyses focused on mildly affected/asymptomatic cases, a younger group of controls ($n = 21$, age 27 ± 1.9) was thus selected. All analyses were 2-tailed, and $p < 0.05$ was considered as statistically significant.

PT	Onset symptoms	Age at diagnosis	Genetic diagnosis		Age at start ERT	Age at assessment	*R*-PACT Scale	PDSS	PDIS	WGM Scale	GSGC score	TUG right foot (sec)	6MWT (m)
3	Mildly symptomatic (mild Fatigue)	16	c.−32-13T > G; c.2237G > A	Splice; Nonsense	17	19	33	2	1	0	4	7	530
2	Asymptomatic	18	c.[2481_2646del]; c.−32-13T > G	Deletion; Splice	20	21	35	6	2	0	4	9	470
1	Asymptomatic	2	c.32-13T > G; c.1670T > G	Splice; Missense	23	28	34	3	0	0	5*	10	420
7	Motor impairment 35 y.o.	36	c.−32-13T > G; c.−32-13T > G	Splice; Splice	37	48	35	12	2	2*	5*	7	555
5	Motor impairment 28 y.o.	29	c.−32-13T > G; c.2481 + 102_2646 + 31del	Splice; Large deletion	44	50	16	57	45	3*	16*	21*	300*
8	Motor impairment 40 y.o.	41	c.−32-13T > G; c.2237G > A	Splice; Nonsense	41	53	18	71	53	3*	15*	17*	281*
4	Motor impairment 36 y.o.	37	c.−32-13T > G; c.2237G > A	Splice; Nonsense	47	63	29	43	35	2*	9*	14*	405*
6	Motor impairment 53 y.o.	54	c.−32-13T > G; c.1927G > A	Splice; Missense	55	64	25	28	24	2*	10*	15*	420

Table 1. Clinical characteristics of LO-GSDII included in the study. *indicates values considered abnormal at individual levels according to the cut-off of specific scales and test (see references for specific cut offs of validated scale). Abbreviations: GSGC, gower, chair score; R-PACT, Rasch-Built Pompe-specific activity scale; PDIS, Pompe disease impact scale; PDSS, Pompe disease symptom scale; TUG, timed up and go test; WGM, Gardner-Medwin-Walton scale; 6MWT, 6-minute walking test.

Parameter	LO-GSDII patients ($n = 8$)	Healthy controls ($n = 52$)	*P*-value
Walking normal speed			
Step counts (n)	578 (± 136.34)	710 (± 56.59)	**0.02**
Step time (s)	0.67 (± 0.28)	0.51 (± 0.38)	< **0.001**
Step time variability (s)	0.07 (± 0.03)	0.04 (± 0.01)	< **0.001**
Step asymmetry	0.02 (± 0.01)	0.01 (± 0.10)	0.27
Step Length	0.61 (± 0.14)	0.69 (± 0.07)	**0.05**
Turning during TUG			
Angle of turns (grades)	179.52 (± 16.02)	183.25 (± 26.10)	0.58
Duration turning (sec)	2.33 (± 0.58)	2.22 (± 0.58)	0.17
Angular velocity (rad/s)	79.83 (± 20.31)	90.76 (± 16.55)	**0.02**
Peak angular velocity (rad/s)	176.79 (± 43.23)	213.25 (± 36.62)	**0.01**

Table 2. Digital health technology assessment evaluating walking and turning in LO-GSDII compared to matched control subjects. The assessment evaluated gait and turning parameters. Abbreviations: TUG, timed up and go test.

Results

Eight LO-GSDII patients (mean age 43 years, Female 3/8, 37%), five symptomatic and three mildly affected/asymptomatic and 52 matched controls (mean age 44 years, female 38%) entered the study (Table 1).

The five symptomatic patients presented heterogeneous motor impairment, as scored by clinical scales and 6MWT. Out of the three mildly affected/asymptomatic patients, only one was diagnosed because of mild fatigability during adolescence, while the other two were asymptomatic at diagnosis (incidental finding of hyperCKemia, diagnosis in first grade relative). Asymptomatic patients at diagnosis later started ERT due to magnetic resonance imaging of muscle fatty substitution. At the clinical scale and timed test, all mildly affected/asymptomatic subjects scored within the normal range except one patient with borderline GSGC score. Differences in digital parameters have been summarized in Tables 2, 3 and 4.

In the walking task, LO-GSDII patients exhibited a lower number of steps with a longer step time, shorter step length and increased step time variability, compared to controls (Supplementary Fig. 1, Table 2). The comparison between the first and last 100 walking bouts showed similar trends in patients and controls during the 6MWT task (Table 3).

In the turning task, LO-GSDII patients exhibited lower angular and peak velocities, and a slightly higher turning duration, than controls. In the postural transition task during TUG, LO-GSDII patients showed a longer duration of standing. Moreover, in the Five Times sit-to-stand Test, they showed lower extension maximal velocity during the standing up phases and a longer duration of the standing phases between the transitions (Supplementary Fig. 1, Table 4). Clinical scores correlated significantly with peak angular velocity of turning, sit to stand duration of the Five Times sit-to-stand Test and number of steps of the 6MWT (Supplementary Fig. 1).

Parameter	LO-GSDII patients ($n=8$)	Healthy controls ($n=52$)	*P*-value
Step time	+3.12	+1.90	0.425
Stance time	+3.44	+1.91	0.180
Double Limb Support	+3.10	+2.21	0.358
Step Time Variability	+2.90	+1.35	0.201
Asymmetry	+3.20	+1.47	0.159

Table 3. Variation of walking parameters in LO-GSDII compared to age matched control subjects (%) between the first and last steps (4-104 vs. last 100 steps detected) during the 6MWT.

Parameter	LO-GSDII patients ($n=8$)	Healthy controls ($n=52$)	*P*-value
Single Task sit to stand (during TUG)			
Sit to Stand Duration (sec)	3.13 (±0.87)	2.01 (±0.42)	<**0.001**
Angle (grades)	50.45 (±15.77)	43.45 (±10.71)	0.069
Extension max velocity (cm/s)	75.76 (±16.42)	83.87 (±21.84)	0.415
Flexion max velocity (cm/s)	119.73 (±51.58)	149.51 (±45.31)	0.091
Repeated 5-chair stand			
Stand to Sit duration (sec)	2.23 (±1.08)	1.42 (±0.38)	<**0.001**
Angle Stand To Sit (grades)	44.40 (±18.48)	37.4 (±11.6)	0.20
Extension max velocity (cm/s)	70.38 (±21.87)	94,35 (±35.56)	**0.05**
Flexion max velocity (cm/s)	95.21 (±29.60)	104.72 (±34.10)	0.06

Table 4. Postural transition parameters in LO-GSDII compared to control subjects (Means (±standard deviations)). The task has been assessed one single time and repeated 5 times separately-according to the short physical performance battery protocol.

Parameter	aLO-GSDII patients ($n=3$)	Healthy controls ($n=21$)	*P*-value
Walking normal speed			
Step counts (n)	640.33 (±27.4)	708.23 (±56.59)	0.121
Step time (s)	0.56 (±0.02)	0.51 (±0.04)	0.101
Step time variability (s)	0.06 (±0.03)	0.03 (±0.01)	**0.001**
Step asimmetry	0.01 (±0.01)	0.01 (±0.01)	0.737
Step Length	0.54 (±0.13)	0.68 (±0.06)	**0.001**

Table 5. Walking parameters in asymptomatic LO-GSDII (aLO-GSDII) patients compared to younger matched controls. *Abbreviations:* TUG, timed up and go test.

Mildly affected/asymptomatic LO-GSDII subjects exhibited higher step time variability and lower step length, compared to age-matched controls, whereas no significant differences in the number of steps and step time were detected (Table 5). In turning and sit-to-stand tasks, a trend towards reduced peak and normal angular speed and longer task duration was observed (Supplementary Tables 1 and 2).

Discussion

LO-GSDII is a debilitating, progressive disorder that imposes significant challenges on affected individuals and their families[23,24]. Characterized by insidious onset and gradual progression, LO-GSDII primarily affects the skeletal and respiratory muscles, leading to increased morbidity and decreased quality of life[23,24]. In this context, the development and implementation of robust outcome measures is essential for accurately tracking disease progression, evaluating therapeutic efficacy, and ultimately improving patient care and outcomes.

One of the foremost needs of LO-GSDII outcome measures is their sensitivity to detect subtle changes over time. LO-GSDII progresses slowly, and often the incremental decline in muscle strength or respiratory function can be missed by less sensitive measures[25,26]. Tools that can capture these minute changes are useful for early intervention and for assessing the true impact of therapeutic strategies. Without such sensitivity, we risk underestimating the disease's progression and overestimating the efficacy of interventions.

To date, outcome measures used in Pompe Disease, as derived from clinical trials, include functional tests such as the 6-minute walk test (6MWT) and the timed up-and-go (TUG) test, alongside assessments of activities of daily living (ADLs), respiratory function assessments (forced vital capacity), and patient-reported outcomes (PROs) able to detect patients' perceptions of their own health, symptoms, and the impact of the disease on daily life[7,27–30].

As new therapies emerge, outcome measures must evolve to capture their specific impacts. This adaptability ensures that the measures remain relevant and continue to provide meaningful data that reflects the benefits or limitations of novel treatments.

Digital parameters obtained by DHTs have recently demonstrated their validity as outcome measures in several conditions, including movement disorders and Duchenne muscular dystrophy[10–13]. In LO-GSDII, only one preliminary study has been conducted in this area using FitBit OneTM data to track the number of steps taken by moderately and severely affected patients[14]. The study showed a reduction in total step count in LO-GSDII, with a reasonable correlation with disease severity and disease duration.

To our best knowledge, ours is the first study to use a comprehensive DHT assessment to study motor impairment in LO-GSDII. The results of this small pilot study may be relevant for the research community, which is still searching for reliable outcome measures[2,6,14,25,26]. It shows a wide range of alterations in mobility among both fully symptomatic and mildly affected/asymptomatic subjects.

Considering the total number of LO-GSDII subjects, significant changes in the walking task (lower number of steps, longer step time, shorter step length, and increased step time variability), turning task (lower angular and peak velocities, and slightly higher turning duration), and postural transition task (longer duration of standing) were observed compared to controls. A significant correlation with clinical scores was found for peak angular velocity of turning, sit-to-stand duration of the Five Times sit-to-stand Test, and number of steps of the 6MWT.

Interestingly, our study went further to evaluate mildly affected or asymptomatic LO-GSDII patients in a supervised setting, focusing on a wider range of components, namely walking, turning, and postural changes. Gait analysis in this subgroup of subjects showed reduced step length and increased variability, despite normal scores on clinical scales and timed motor tests. Overall, the variability of walking parameters in LO-GSDII was slightly increased but substantially like the control group between the first and last 100 steps. This may suggest that the differences in walking parameters are related to a stable deficit undetectable by routine scores rather than fatigability. Turning and postural transition tasks also revealed subtle changes that could be related to axial muscle weakness, even though they did not reach statistical significance in this subgroup.

Our findings demonstrate that digital motor metrics potentially have the capacity to detect subtle motor impairments in individuals with mild or asymptomatic Pompe disease, including those not identified by conventional clinical scales. Digital metrics may provide a richer and continuous readout of motor performance that could enhance disease monitoring and – if supported byu longitudinal studies- progression tracking. In conditions such as Pompe disease, where early therapeutic intervention can modify the course of the disease, digital health assessments could serve as valuable tools to facilitate more timely and personalised treatment decisions. These tools have the potential to reduce the frequency of invasive or time-consuming procedures by offering reliable remote assessments, thereby improving patient care and potentially reducing healthcare burden[31,32].

However, while digital metrics show significant promise, a critical next step will be establishing clinically meaningful thresholds that define when a detected digital change reflects true disease progression or necessitates clinical action. Furthermore, it should be noted that our cross-sectional data is not sufficiently comprehensive in terms of capturing the evolution of the disease. Ongoing Longitudinal studies are essential to validate the prognostic value of digital assessments, determine their sensitivity to change over time, and define their role in guiding treatment decisions.

The small number of subjects remains the main limitation of this study, although we have demonstrated the validity of DHT assessment even with a limited sample size and high heterogeneity of motor involvement. The sensitivity of promising digital markers such extension max velocity in 5-times raising from chair, angular velocity in turning transitions and step alterations in length, time and time variability will be investigated on a larger on-going longitudinal study. We would also extend these measures to unsupervised settings, which are known to be more effective and sensitive to detect multiple symptoms in different conditions, as demonstrated in Parkinson's disease, multiple sclerosis, and even healthy aging[17,33].

Notwithstanding this limitation, our preliminary results suggest that wearable technologies can identify subtle walking abnormalities also in mildly affected or asymptomatic patients not otherwise evident by usual clinical evaluation. They may have important implications for management, follow-up, and treatment decisions in clinical practice. Importantly, our results suggest that DHT deserve to be evaluated as a promising outcome measure for clinical trials.

Data availability

The raw data supporting the conclusions of this article will be made available by the correspondent author, without undue reservation.

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Author contributions

A.Pi., B.L., A.R., C.Z., W.M., A.Pa. and M.F. contributed to the conception and design of the study; A.Pi, B.L., A.R., C.Z., C.H., R.R., J.G., S.C.P, E.O., L.F., L.P., W.M and A.Pa. contributed to the acquisition and analyses of data; A.Pi., B.L., A.R., C.Z., C.H., R.R., F.C., B.R., S.D., W.M., A.Pa and M.F contributed to drafting the text; A.Pi., A.R., C.Z., C.T., C.H. and R.R contributed to statistical analyses. All authors read and approved the final manuscript.

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Declarations

Competing interests

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Consent statement

The Ethics Committee approved the Brescia Hospital's research protocol (NP 3710). Written informed consent was obtained from all participants.

Additional information

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