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1 Abstract

Background: Dravet Syndrome (DS) is a developmental and epileptic encephalopathy, characterized by drug resistant infantile onset seizures and cognitive and motor impairment. Walking problems progressively occur and crouch gait is frequently observed. Muscle weakness is hypothesized as contributing impairment. Yet, so far, no studies have performed strength measurements in patients with DS, most likely due to cognitive impairment.

Aims: To determine the feasibility and validity of strength measurements in the framework of gait analysis and to outline strength problems in patients with DS.

Methods: Manual muscle testing, dynamometry (hand grip strength and handheld dynamometry) and functional tests (underarm throwing, standing long jump, sit-to-stand, stair climbing) were performed in 46 patients with DS. Results were compared to age-related reference values from literature.

Results: Forty one percent (19/46) of the patients (aged 5.2-24.8 years, median: 15.8 years) accomplished all measurements and scored generally below the fifth percentile of norm values. The remaining 59 % (27/46) was not able to complete all strength assessment due to cognitive, behavioural and motor difficulties. Handheld dynamometry seemed most sensitive and specific to detect isolated muscle strength. Validity of the functional tests was controversial, as motor proficiency, balance and coordination may interfere.

Conclusion: Although measuring strength in patients with DS was challenging in the context of gait analysis, decreased muscle strength was observed in patients that could perform strength measurements. Handheld dynamometry is preferred over functional tests for future investigations of muscle strength and its interference with gait are required for better understanding of walking problems.

2 Introduction

Dravet Syndrome (DS) is a developmental and epileptic encephalopathy, primarily caused by mutations in the neuronal sodium voltage-gated channel type 1 alpha subunit encoding gene (*SCN1A*) [1]. The syndrome is characterized by drug resistant infantile onset seizures with cognitive impairment and progressive motor problems [2,3]. Walking difficulties become a major concern around adolescence, making many patients lean on others or use a wheelchair for longer distances [4,5]. The gait pattern is described as unstable and inefficient, with crouch gait observed in about 50 % of the patients [6,7]. Instrumented three-dimensional gait analysis (3DGA) has only recently been performed in this population [7] but is necessary for in-depth understanding of the nature of gait deviations [8–10]. To enhance clinical interpretation of the results, physical examination is generally expected to be part of 3DGA [9,11]. Assessment of muscle strength is a key element of physical examination, since muscle weakness is considered to be an important contributor to gait deviations such as crouch gait [10–14]. Previous studies

hypothesized a contribution of muscle weakness to gait deviations in DS, but were not able to perform strength measurements, due to low cognitive abilities of the participants [4,15].

Various methods to measure strength in paediatric populations are documented in literature [16]. During *manual muscle testing* (MMT), an assessor grades (0-5) the contraction against a manually administered resistance [17]. Although this method is widely performed in clinical practice as a quick assessment of specific muscle groups, MMT largely depends on evaluator's experience and its sensitivity to detect change over time is low [18–22]. *Dynamometry* objectively quantifies muscle strength and can be performed with relatively cheap and accessible instruments known as hand-held dynamometers (HHD) and hand grip strength devices (HGS). In HHD, the participant performs a maximum voluntary isometric contraction (MVIC) against a force transducer held perpendicular to the moving limb. Compared to the gold standard isokinetic testing, HHD can be considered a valid and reliable instrument for muscle strength assessment in a clinical setting [23]. In HGS, the participant holds the dynamometer to measure grip strength, which may be an indicator of total muscle strength [24]. As an alternative that is more motivating and closer to children's daily activities, *functional tests* are frequently used to estimate muscle strength. Aertssen et al. (2016) developed and validated the Functional Strength Measurement test battery (FSM), by selecting activities with strength as an important factor for successful performance, but low coordination requirements [25]. While HHD measures the isometric contraction of a muscle group around a single joint, functional tests indirectly estimate strength of multiple muscles combined around multiple joints. Concurrent validity of the FSM with HHD was therefore moderate in typically developing (TD) children [25].

Reliability and validity of the above mentioned methods are investigated in populations of children and adolescents with a TD [25–27], neurologic and orthopaedic disorders [19,22,28–30] and intellectual disabilities [31–33]. However, owing to the specific combination of motor and cognitive impairments, behavioural difficulties and seizures triggered by temperature rise and physical exercise [2], it remains unclear how feasible and valid the different tests are in a population with DS.

For thorough understanding of gait deviations and to enable appropriate interventions, insight in muscle strength in patients with DS is needed. However, no studies on muscle strength in DS have been reported so far. Therefore, the aim of this study is to determine how feasible strength measurements are in the framework of gait analysis in patients with DS and to detect strength problems. More specifically, we will attempt to perform *MMT*, *dynamometry* and *functional tests* in a group of patients with DS. We expect that not all participants will be able to perform the measurements. Comparison to normative reference values will reveal whether possible weakness can be detected. To investigate if functional tests offer a valid alternative to isometric strength tests, concurrent validity of the FSM compared to dynamometry will be assessed using correlation analysis. Preliminary explorative analysis will investigate whether gait deviations might be related to muscle weakness.

3 Methods

3.1 Study design and setting

This cross-sectional study was part of a project on gait disorders in patients with DS registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT03857451) and approved by the ethics committees of the Antwerp and Leuven University Hospitals (Belgian Registration Number B300201627079). Participants attended gait analysis sessions including physical examination of joint range of motion, alignment, muscle length and strength, at annual follow up at the Multidisciplinary Motor Centre Antwerp (M²OCEAN). The strength assessment protocol for the current study was performed as part of the physical examination between October 2018 and November 2019.

3.2 Participants

Patients diagnosed with DS and a confirmed *SCN1A* mutation were recruited through the department of child neurology at the Antwerp University Hospital and the parent organization of the Netherlands and Flanders 'Stichting Dravetsyndroom Nederland/Vlaanderen'. Exclusion criteria were the occurrence of a severe epileptic seizure within 24 hours before the assessment and comorbidities of other neurological and/or orthopaedic disorders not related to DS.

3.3 Data collection

3.3.1 Demographics

Body mass (kg) and height (mm) were measured using a digital scale with stadiometer. Body mass index (BMI) and BMI-for-age z-scores were calculated using WHO growth references in R (v 4.0.0, package 'anthro' and macro 'WHO2007', R Foundation, Vienna, Austria). Scores were classified as 'underweight', 'normal', 'overweight' or 'obese' according to De Onis et al. (2010) [34]. Dominant sides for upper (writing) and lower (kicking a ball) limb were indicated by the parents. Levels of intellectual disability (ID) were estimated by the treating physician as mild, moderate or severe and supported by cognitive test scores if available [35]. From patient records, information was obtained on age at first seizure, current epileptic seizures and onset of independent walking. Using the windows of achievement as defined by the World Health Organization [36], age of independent walking was classified as delayed (> 17.5 months) or normal.

3.3.2 Manual muscle testing

Knee extensor muscle strength (grade 0-5) was assessed by manual muscle testing according to Daniels and Wortingham's technique [17]. As all patients were able to move the limb against gravity, the test was performed with the participant in sitting position. The 'make' method was used: the assessor applied resistance against concentric muscle contraction with the hand placed distally on the tibia. The amount of resistance was graded from 3+ (minimal) to 5 (maximal).

3.3.3 Dynamometry

The HGS (kg) was assessed using a Jamar® hydraulic hand dynamometer (Patterson Medical, IL, USA) in standardized position (table 1) adopted from Ploegmakers et al. 2013 with the handle in second position unless this was not comfortable for the participant [37,38]. Four muscle groups' MVIC's (Newton) were measured using a MicroFET2® hand-held dynamometer (Hoggan Scientific, UT, USA). More specifically, elbow flexors, elbow extensors, hip flexors and knee extensors were tested in standardized positions with the device most distally on the moving limb, adopted from Beenakker et al. (2001) [39] (table 1). The 'make' method was used: the assessor held the device stationary and asked the participant to push as hard as possible against the force transducer. After giving the 'Ready? Start!' signal, the assessor counted out loud to five in order to encourage the participant to gradually achieve maximum force.

Muscle group	**Participant position**	**Device**	**Device position**
Hand grip strength	Sitting, shoulder adducted, elbow 90° flexed	Jamar ®	In hand, second position*
Elbow flexors	Supine, shoulder adducted, elbow 90° flexed, forearm supinated	MicroFET ®	Flexor surface of forearm, just proximal to wrist
Elbow extensors	Supine, shoulder adducted, elbow 90° flexed, forearm supinated	MicroFET ®	Extensor surface of forearm, just proximal to wrist
Hip flexor	Supine, hip 90° flexed, knee fully relaxed, foot not supported	MicroFET ®	Anterior surface of thigh, just proximal to knee
Knee extensors	Sitting, knee 90° flexed	MicroFET ®	Anterior surface of shank, just proximal to knee

Table 1: Standardized positions for the muscle groups tested using hand-held dynamometry. *adapted to first or third position if not comfortable for participant

3.3.4 Functional tests

Out of the original eight items of the FSM [25], only four were performed in order to reduce protocol duration: standing long jump (SLJ, cm), underarm throwing (UT, cm), stair climbing (SC, number of steps during 30 sec) and sit to stand (STS, number of repetitions during 30 sec). All tests were performed according to the FSM protocol by Aertssen and Smits-Engelsman (2012) [40] with three adaptations. First, in order to reduce protocol duration and physical exertion, the warm-up protocol and practice trials were not performed. Second, for safety reasons, alternating steps was not required, and slight arm support was allowed for SC. Third, to assure correct performance of STS, participants had to fold their hands during the performance and touch a drawing on the wall while standing.

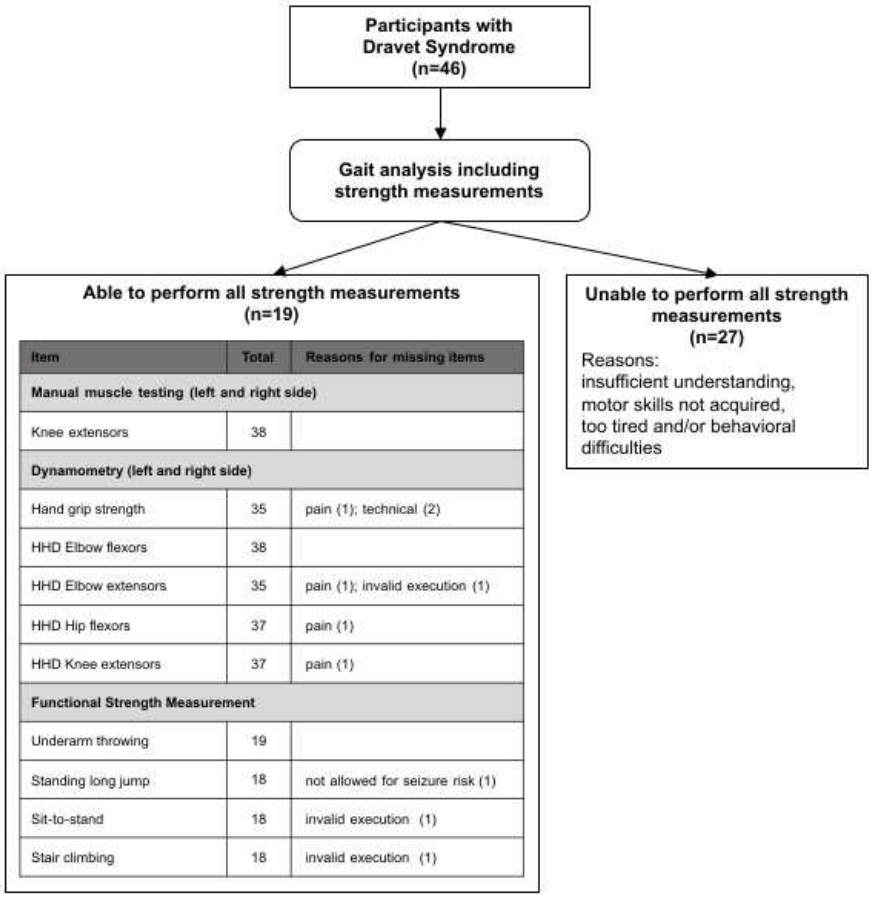
3.3.5 Instrumented gait analysis

The instrumented gait analysis protocol has previously been described in detail [41,42]. Briefly, the lower body Vicon Plug-in Gait model was used to obtained 3D lower limb kinematics. To obtain a summary index of overall gait pathology, Gait Profile Score (GPS) was calculated based on the nine relevant joint angular time profiles as well as separately for kinematics in the sagittal (GPS_Sg), coronal (GPS_Co)

and transversal (GPS_Tr) plane [43]. Higher GPS values indicate a larger deviation from normal gait kinematics (Appendix A). Using the GPS, gait was classified as normal (<6.94°), mildly impaired (≥ 6.94°), and impaired (≥ 8.10°), based on the mean GPS (5.78°) +1 SD (1.16°) and +2 SD (2.32°) of typical developing children (reference database of 60 children with mean age= 10.55 ± 3.87 years).

3.4 Procedure

Measurements were executed in the order mentioned above. Two trials per side for dynamometry and three trials for FSM were performed, starting from the first correct execution. The highest value was used for analysis. In order to prevent fatigue, STS and SC were only performed once. All tests were performed by the same assessor (MSc, physiotherapist). Verbal encouragement was given. Total duration of the strength assessments was around 30 minutes, influenced by the patient's behaviour and understanding of the tasks. Patients who were unable to correctly perform all measurements, were omitted from further analysis. Patients who were able to perform tests in all three categories, but could exceptionally not complete specific items (e.g., pain because of wound on location of HHD device, execution interrupted before 30 sec were complete) were retained as 'able to perform all strength measurements' (figure 1). Observations on challenges or reasons of invalid performance were noted.



Item	Total	Reasons for missing items
Manual muscle testing (left and right side)		
Knee extensors	38	
Dynamometry (left and right side)		
Hand grip strength	35	pain (1); technical (2)
HHD Elbow flexors	38	
HHD Elbow extensors	35	pain (1); invalid execution (1)
HHD Hip flexors	37	pain (1)
HHD Knee extensors	37	pain (1)
Functional Strength Measurement		
Underarm throwing	19	
Standing long jump	18	not allowed for seizure risk (1)
Sit-to-stand	18	invalid execution (1)
Stair climbing	18	invalid execution (1)

Figure 1: Data collection procedure. All participants performed strength measurements after gait analysis. Patients who were unable to perform all strength measurements were omitted from further analysis. Reasons for omission and for missing items in further analysis are reported. HHD, handheld dynamometry

3.5 Statistical analyses.

Strength measurement outcomes were plotted against available age-related reference values (5th, 50th and 95th percentile) available in literature: HGS paediatric values by Ploegmakers et al (2013) [38] and adult values by Peters et al. 2011 [44], HHD paediatric by Beenakker et al. (2001) [39] and adult by Douma et al. (2014) [45] and FSM paediatric by Aertssen and Smits-Engelsman (2012) [40].

Visual inspection and formal tests (Shapiro-Wilk) highlighted normal distribution of the data. To test the hypothesis that FSM validly measured muscle strength, Pearson correlation coefficients were calculated between FSM and dynamometry items. As there was a wide age range and heterogeneity in body composition, confounding effects of height and BMI were expected. Therefore, partial correlations were calculated between FSM and dynamometry items, controlling for height and BMI. Additionally, Pearson and partial correlations were also calculated between HGS and the four other dynamometry items, to confirm if HGS was an indicator of total muscle strength. Since a small number of missing values occurred, complete case analysis was used. Finally, explorative analysis using Pearson correlations as well as partial correlations (controlling for height and BMI) between dynamometry items and GPS scores was performed to test the hypothesis that gait deviations are related to muscle weakness. All statistical analyses were performed in IBM SPSS® software (v26.0, IBM Corp, Armonk, NY, US)

4 Results

Out of 46 participants, 19 patients (19/46, 41 %) with DS aged 5.2 to 24.8 years (median 15.8 years) were able to complete all strength measurements (figure 1 and table 2). Twenty-seven patients (27/46, 59 %) aged 3.0 to 26.1 years (median 8.4 years) were not able to complete all strength assessments due to a combination of disturbed cognitive functioning, motor skills and behaviour. More specifically, they did not understand the instructions, were not skilled to jump or throw, were too tired and/or not willing to cooperate. No seizures occurred during the assessments. Younger age and lower levels of ID were more frequent in participants unable to complete the assessments, while gender and BMI were evenly distributed. More children showed an impaired gait pattern in the group unable to complete the strength assessments (table 2).

When patients were able to perform all tests, correct execution still proved to be challenging. Ten items were missing, merely owing to circumstances than patient ability (figure 1). We observed difficulties to perform selective movements during HHD and balance problems during FSM. Frequent observations per test item are presented in table 3.

Strength measurement outcomes of patients with DS and reference values of TD children and, if available, adults are presented in table 2. All tests showed poor strength in patients with DS. Even adolescents and young adults performed below the fifth percentile of TD children. This trend was

observed in analytical as well as functional strength measurements, with HHD elbow extension and FSM UT as exceptions.

Significant Pearson correlations between FSM and dynamometry were only found for UT. Pearson correlations between HGS and the four HHD items were all significant. When controlling for height and BMI, partial correlations between UT and dynamometry were only significant for elbow flexors (both sides) and extensors (dominant side). Other significant partial correlations were found for STS with elbow flexors (both sides), elbow extensors and HGS (dominant side), and for HGS with elbow flexors and knee extensor (dominant side). The significant partial correlation coefficients ranged from .57 to .73 (table 4).

Explorative correlation analysis between dynamometry and gait showed significant positive correlations between HGS and GPS (both sides) and GPS_Tr (both sides). GPS_Tr also correlated significantly with knee extensor strength of the dominant side. When controlling for height and BMI, however, significant negative correlations were found between hip flexors and GPS (non-dominant side) and GPS_Tr (both sides) (table 5).

	Complete strength assessment (n = 19)	**Unable to complete strength assessment (n = 27)**
Age		
3-4 years	0 (0 %)	5 (19 %)
5-7 years	4 (21 %)	8 (30 %)
8-11 years	4 (21 %)	6 (22 %)
12-17 years	6 (32 %)	3 (11 %)
18-26 years	5 (26 %)	5 (19 %)
Sex		
Male	11 (42 %)	13 (52 %)
Female	8 (58 %)	14 (48 %)
BMI classification		
Underweight	6 (32 %)	5 (19 %)
Normal	7 (37 %)	17 (63 %)
Overweight	5 (26 %)	5 (19 %)
Obese	1 (5 %)	0 (0 %)
ID level		
Mild	8 (42 %)	5 (19 %)
Moderate	8 (42 %)	9 (33 %)
Severe	3 (16 %)	13 (48 %)
Age at first seizure		
Mean (sd) in months	5.45 (2.30)	5.46 (2.04)
Epileptic Seizures		
No information	1	7
Free of seizures	5 (26%)	5 (25%)
Mild	6 (32%)	8 (40%)
Moderate	5 (26%)	1 (5%)
Severe	3 (16%)	6 (30%)
Independent walking		
Mean (sd) in months	17.3 (4.0)	20.9 (9.1)
Delayed/ Normal	9/9	13/6
Gait		
No information	1	5
Normal	4 (21%)	0 (0%)
Mildly impaired (1 sd)	6 (32%)	4 (18%)
Impaired (2 sd)	8 (42%)	18 (82%)

Table 2: Characteristics of patients able and unable to complete strength assessment. BMI, body mass index; ID, intellectual disability; sd standard deviation

Test item	Frequent observations	
	Complete strength assessment (n = 19)	**Unable to complete strength assessment (n = 27)**
Manual muscle testing		
MMT Knee extensors	Participants tended to combine with hip flexion and/or backward trunk lean	Not cooperative; Did not understand the instruction to move against resistance
Dynamometry		
Hand grip strength	Device was heavy for small children; Participants wanted to turn device inwards to look on scale	Not cooperative; Did not understand the instruction to squeeze
HHD Elbow flexors	None	Not cooperative; Did not understand the instructions for correct execution
HHD Elbow extensors	Participants tended to combine with forearm pronation and/or shoulder anteflexion	Not cooperative; Did not understand the instructions for correct execution
HHD Hip flexors	None	Not cooperative; Did not understand the instructions for correct execution
HHD Knee extensors	Participants tended to combine with hip extension	Not cooperative; Did not understand the instructions for correct execution
Functional Strength Measurement		
Underarm throwing	Loss of balance after throwing.	Not cooperative; Did not understand the instructions for correct execution: overarm or side throwing; Did not understand “as far as possible”
Standing long jump	Loss of balance after landing; Difficulties jumping and landing with both feet simultaneously	Not cooperative; Not able to jump; Did not understand the instructions for correct execution: not standing still before jump; Did not understand “as far as possible”
Sit-to-stand	Participants tended to lift feet up when seated	Not cooperative; Did not understand “as many as possible”: abnormally slow or did not persevere for 30 sec
Stair climbing	Alternating steps was not required; Slight arm support for safety was allowed	Not cooperative; Required more help than slight support; Did not understand “as many as possible”: abnormally slow or did not persevere for 30 sec

Table 3: frequent observations of the execution and challenges for the different test items in patients able and unable to complete strength assessment. HHD, hand-held-dynamometry

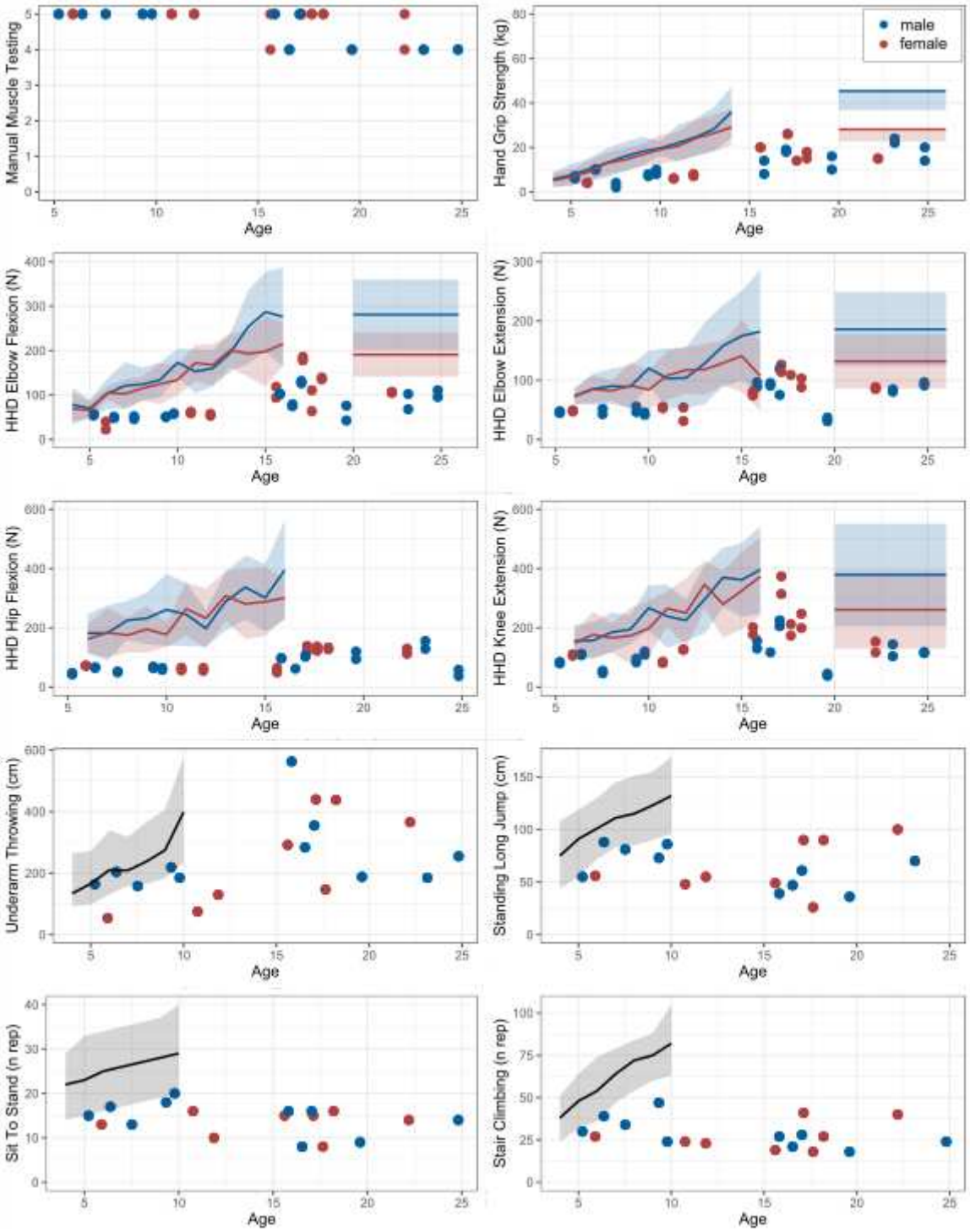


Figure 2: Strength of participants (n=19) with Dravet Syndrome compared to reference values. Lines represent P50 and shaded areas P5 to P95 of age-related reference values in typically developing children and adults, by Ploegmakers et al (2013) [38], Peters et al. 2011 [44], Beenakker et al. (2001) [39], Douma et al. (2014) [45] and Aertssen and Smits-Engelsman (2012) [40]. Red colours stand for female participants, blue for male, grey for both sexes. HHD, hand-held dynamometry; n rep, number of repetitions

	Pearson r (*P*-value)					Partial correlation controlling for height and BMI (*P*-value)				
	UT	**SLJ**	**STS**	**SC**	**HGS**	**UT**	**SLJ**	**STS**	**SC**	**HGS**
DOMINANT SIDE (n=14)										
HGS	.76**	.25	.16	.10		.40	-.03	.64*	.09	
	(.002)	(.39)	(.57)	(.74)		(.19)	(.94)	(.02)	(.78)	
Elbow flexors	.81**	.38	.25	.22	.94**	.65*	.26	.73**	.35	.71**
	(<.001)	(.19)	(.39)	(.44)	(<.001)	(.02)	(.41)	(.008)	(.27)	(.009)
Elbow extensors	.80**	.39	.27	.32	.84**	.64*	.25	.61*	.46	.37
	(<.001)	(.17)	(.36)	(.27)	(<.001)	(.02)	(.43)	(.03)	(.13)	(.24)
Hip flexors	.73**	.39	.01	.25	.67**	.26	.52	.25	.47	-.33
	(.003)	(.17)	(.98)	(.38)	(.008)	(.42)	(.08)	(.44)	(.12)	(.29)
Knee extensors	.68**	.41	.25	.24	.88**	.44	.24	.57	.29	.65*
	(.008)	(.14)	(.38)	(.42)	(<.001)	(.16)	(.45)	(.053)	(.35)	(.02)
NON-DOMINANT SIDE (n=15)										
HGS	.58*	.16	-.04	.01		.05	.25	.44	.15	
	(.02)	(.56)	(.89)	(.96)		(.88)	(.42)	(.13)	(.62)	
Elbow flexors	.75**	.24	.01	.12	.87**	.57*	.43	.59*	.41	.33
	(.001)	(.40)	(.97)	(.67)	(<.001)	(.04)	(.14)	(.04)	(.17)	(.27)
Elbow extensors	.69**	.06	-.01	.10	.67**	.48	-.04	.34	.24	-.21
	(.005)	(.84)	(.97)	(.72)	(.006)	(.09)	(.89)	(.26)	(.42)	(.49)
Hip flexors	.56*	.13	-.27	.05	.69**	.00	.27	-.12	.23	-.14
	(.03)	(.65)	(.33)	(.87)	(.004)	(1.00)	(.37)	(.70)	(.45)	(.66)
Knee extensors	.57*	.23	.11	.12	.79**	.40	.21	.55	.25	.42
	(.03)	(.41)	(.70)	(.68)	(<.001)	(.18)	(.49)	(.051)	(.41)	(.15)

Table 4: Pearson correlations between dynamometry and functional strength measurement items and partial correlations, controlling for height and weight. n, number of complete cases; SLJ, standing long jump; UT, underarm throw; STS sit to stand; SC, stair climbing; **P*<.05; ***P*<.01

	Pearson r (*P*-value)				Partial correlation controlling for height and BMI (P¬-value)			
	GPS	**GPS_Sg**	**GPS_Co**	**GPS_Tr**	**GPS**	**GPS_Sg**	**GPS_Co**	**GPS_Tr**
	DOMINANT SIDE (n=14)							
HGS	**0.62***	0.30	-0.17	**0.69***	0.39	0.24	-0.20	0.37
	(.01)	(.26)	(.52)	**(.003)**	(0.17)	(0.41)	(0.48)	(0.18)
Hip flexors	-0.01	-0.03	-0.17	0.04	-0.47	-0.13	-0.19	**-0.66****
	(.96)	(.92)	(.52)	(.87)	(0.09)	(0.66)	(0.52)	**(0.01)**
Knee extensors	0.38	0.11	-0.00	**0.55***	0.24	0.14	0.34	0.19
	(.14)	(.67)	(.99)	**(.03)**	(0.40)	(0.62)	(0.24)	(0.51)
	NON-DOMINANT SIDE (n=15)							
HGS	**0.50***	0.30	0.20	**0.51***	0.38	0.15	0.28	0.39
	(.04)	(.23)	(.43)	**(.04)**	(0.17)	(0.59)	(0.31)	(0.15)
Hip flexors	0.10	0.11	-0.06	-0.17	**-0.61**	-0.22	-0.15	**-0.72**
	(.71)	(.68)	(.83)	(.52)	**(0.02*)**	(0.44	(0.60)	**(0.003**)**
Knee extensors	0.38	0.15	0.31	0.45	0.41	0.49	0.39	0.23
	(.14)	(.56)	(.22)	(.07)	(0.13)	(0.07)	(0.15)	(0.42)

Table 5: Pearson correlations between dynamometry and gait parameters and partial correlations, controlling for height and BMI. n, number of complete cases; HGS, hand grip strength; GPS, gait profile score; GPS_Sg, gait profile score in sagittal plane; GPS_Co, gait profile score in coronal plane; GPS_Tr, gait profile score in transversal plane; **P*<.05; ***P*<.01

5 Discussion

This study aimed to determine how feasible and valid strength measurements are in the framework of gait analysis in patients with DS and to outline strength problems in patients with DS. Feasibility was low, as only 41 % of the participants (19/46) were able to perform MMT, dynamometry (HGS and HHD) and FSM items (UT, SLJ, STS, SC). Muscle weakness was confirmed, with measurement outcomes generally situated below the fifth percentile of typically developing children.

The context of gait analysis increased the challenge of strength assessments. As good collaboration during gait analysis was prioritized, strength assessments were performed at the end of the session. Patients may have been tired of the demanding cooperation during gait analysis and passive clinical examination. Feasibility and performance may improve when tests are administered in an isolated context with warming up and practice time. During gait analysis sessions on the other hand, an easy-to-administer test that offers an estimation of strength, adequate to understand its interference with gait, is needed. It is not recommended to perform the complete protocol used in this study, but to select test items based on feasibility, validity and sensitivity to detect strength problems.

5.1.1 Feasibility

Low feasibility was expected from the clinical image of DS with cognitive, motor and behavioural problems [2,46 - 48]. Nevertheless, almost half of the participants over the age of five proved to be able to complete strength assessment. Completion rates improved slightly with age, highlighting the role of cognitive and motor development. Low cognitive functioning [47] made it hard for patients to understand the instructions of starting position, correct movement execution and restrictions of compensatory movements. Behavioural difficulties occurred [47], in most cases manifesting themselves already before strength assessment, namely when collaboration was lacking during gait analysis and passive physical examination. It was generally a combination of problems that prevented participants to perform the tests, rather than one main reason.

Although instructions of HHD were expected to be difficult to understand for patients with ID, the tactile feedback of the device against the participant's limb and the resistance of the examiner may have enhanced its feasibility. However, selective contraction of the investigated muscle group appeared challenging. It remains unclear whether this indicated purely compensation strategies or impaired selective motor control in patients with DS. For HGS, the heaviness of the device and position of the scale was a disadvantage. More child-friendly designed dynamometers exist such as a 'bulb' type dynamometer, with acceptable reliability [49]. Nevertheless, Jamar type hydraulic dynamometers are widely available and showed better reliability than 'bulb' type [49].

The FSM appeared an engaging method to assess strength, but correct execution was challenging, required more time to practice and good understanding of the instruction "as far/fast as possible". Motor

deficits and developmental delays [48] interfered with the FSM, as it was a prerequisite that participants had acquired the motor skill and were able to learn how to correctly perform the test, strongly reducing the feasibility in patients with DS.

5.1.2 Validity

To investigate validity, MMT, HGS and FSM were compared to HHD, as this method could serve as a reference standard for muscle strength [23]. Grade four of MMT was only given to adolescents and young adults, even though HHD of the knee extensors also revealed lower scores compared to age-related norm values in younger children. It cannot be excluded that MMT overestimated strength in young participants due to its subjective character: in paediatric populations, the assessor grades relative to what they expect as a maximum examiner-imposed resistance possible for the participant's age. It has been suggested that HGS can serve as an indicator of general muscle strength [24], but partial correlations revealed that HGS could predict strength of some, but not all muscle groups. Low validity of the FSM to measure muscle strength was detected by the absence of a correlation between three items (SLJ, STS and SC) and HHD. Although HHD outcomes tended to increase with age, SLJ, STS and SC scores of adolescents with DS remained on the level of young children. Higher partial correlations were observed between UT and dynamometry of the upper limb, indicating that this item validly assessed underlying muscle strength. Balance and coordination deficits may interfere with FSM, especially SLJ and SC [31]. These findings are partly in line with previous literature. The FSM proved to be a valid assessment of muscle strength with minimal demand of balance and coordination in TD children [25], but correlated significantly with balance tests in children with mild ID [31]. Feasibility and reliability were lower in children with moderate and severe ID [32].

5.1.3 Strength problems

In order to detect strength problems in DS and to assess the sensitivity of the different methods, comparison with reference values was performed. Since all included scores on MMT showed the ability to contract muscles against resistance, clear muscle weakness was not detected, suggesting that strength is only mildly decreased in patients with DS. As was expected MMT was not sensitive enough to reflect smaller variations within this range [18–21]. In circumstances where an assessor needs to form a quick idea of muscle strength for clinical purposes, MMT may be adequate. However, to document strength for objective analysis of its relationship with gait parameters and to detect change over time, MMT does not suffice [18,50].

Dynamometry has a higher sensitivity to objectively detect differences with reference values. Patients with DS showed poor HGS compared to age-related norms. Comparison of HHD with norm values available in literature is complicated due to variations in devices, methods and positions of participant and examiner. A major difference was the use of the 'make' method in this study and the 'break' method in the studies by Beenakker et al. (2001) [39] and Douma et al. (2014) [45]. We preferred the 'make' method

as it was supposed to be more reliable and easier to understand for children with cognitive and neurological problems [12,28,51]. However, studies that collect normative values usually prefer the 'break' method: the examiner overcomes the participant's maximum strength. The peak value is higher in 'break' tests, as eccentric muscle contractions occur at the moment the limb gives way [51,52]. Comparison with reference values plotted on figure 2 should therefore be made with caution. Forces during 'break' test are between 1.03 and 1.6 times higher than during 'make' tests in healthy adults [51,52]. Applying this as a correction to figure 2 would bring the observed values closer to the norm values, yet the participants would still score below average. HGS may be appropriate as an indicator of general muscle strength and enables monitoring over time and comparison with norm values. But since strength of specific lower limb muscles is of interest during gait analysis, additional information could be obtained using HHD, standardized methods and examiner experience are essential.

Comparing FSM to normative values, revealed decreased functional strength. This method also proved sensitive to detect differences with TD. These differences may not only reflect decreased muscle strength, but also impaired capacity to optimally employ muscle strength during functional tasks.

For reasons mentioned above, individual scores should be interpreted with caution. On a group level, the results suggested that muscle strength in DS is decreased compared to TD children and healthy adults. This was in line with studies in populations with ID in general, showing lower levels of physical fitness and muscle strength [31–33,53,54], associated with gait deviations [55]. It remained unclear whether reduced strength in DS solely resulted from lower levels of physical activity due to seizure risks and motor problems, or if pathophysiology of sodium channel dysfunction may have played a role [56]. Future investigations might consider the use of ultrasound measurements, sensory neurography or sensory evoked potentials to differentiate between neuropathy [55], myopathy or muscle volume loss by inactivity. Interventions targeting muscle strength and physical fitness may be indicated to improve gait and functional mobility in patients with DS [12,56].

5.1.4 Muscle strength and gait deviations

Significant correlations were observed between HHD and the parameters quantifying the amount of gait pathology. The positive correlations between HGS and gait pathology are most likely related to age as a confounding factor, since older children are stronger but also show more gait deviations [4, 41]. Interestingly, negative correlations are found between hip flexor strength and gait pathology, primarily in the sagittal plane. Limited hip flexor strength might compromise hip power generation and thereby negatively affect step length, cadence and speed [57]. Increased pelvis rotation is a well-known compensation for this, which can explain the correlation with GPS_Tr. Furthermore, pelvic instability can also be related to strength of hip musculature, thus explaining these negative correlations. Since no correlations were found with gait pathology in the sagittal plane, we could not confirm previously formulated hypotheses that development of crouch gait is related to muscle weakness [4]. However, a

major limitation in this regard is that the group of children where strength measurements could not be performed, showed a more deviant gait pattern with probably a higher prevalence of crouch.

Even though the primary aim of this study was not to explain gait pathology by muscle weakness, the results confirm the presence of gait abnormalities that are possibly linked to reduced muscle strength. From a clinical point of view, instrumented gait analysis in combination with objective strength assessment will provide insights allowing to distinguish primary problems, e.g., reduced step length due to muscle weakness, from compensations e.g., increased pelvic rotation, knowledge that is imperative to design an adequate rehabilitation program.

5.1.5 Limitations

This study did not investigate reliability of the measurements, which can be considered a limitation. For practical reasons, strength tests could only be performed once. In order to ensure the highest reliability, all tests were performed by the same assessor. A second limitation was poor generalizability of the results to the general population with DS, due to the low completion rates, especially in young children and more severe ID. Furthermore, comparison to normative values should ideally be performed following the exact same method and taking into account age, sex and body composition [30].

6 Conclusion

The feasibility of a strength measurement battery of MMT, dynamometry and FSM in the context of gait analysis was low in patients with DS due to cognitive, behavioural and motor impairments. Nearly half of the participants with a minimum age of five years were able to complete the strength assessment consisting of MMT, dynamometry and functional tests. The context of gait analysis increased the challenge of strength assessment and required an easy-to-administer test that provides a sensitive and quantitative estimate of muscle strength. These requirements were best met by HHD of specific lower limb muscles. From the FSM items, UT may assess upper limb strength and STS may predict general strength, while SLJ and SC could not validly measure muscle strength. Motor proficiency, balance and coordination might interfere with functional tests. Comparison of strength outcome to age norms, suggested decreased muscle strength in patients with DS. Explorative analysis revealed some relations between strength and gait pathology, but future investigations are imperative to unravel a potential causal relationship.

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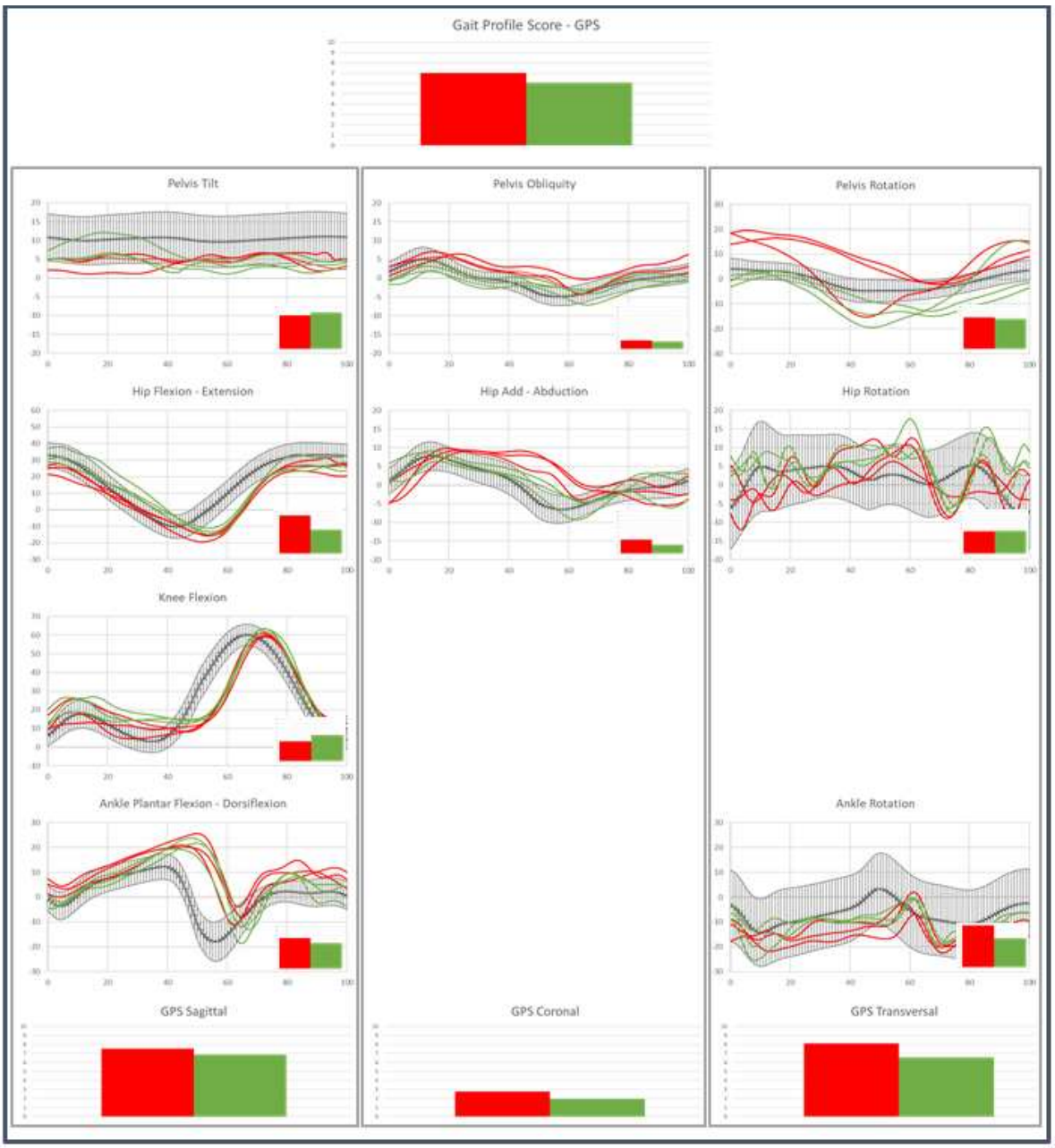
9 Appendix A - The Gait Profile Score



Appendix A: The Gait Profile Score (GPS) - The figure represents nine relevant kinematic joint angular time profiles (from 0% to 100% of gait cycle) of a 15-year-old boy with Dravet syndrome showing 3 representative left strides in **red**, 3 representative right strides in **green** compared to normal reference values (mean ± 1 standard deviation) in **grey**. The GPS (represented in the top bar chart for left side and right side) is a summary index of overall gait pathology. It is calculated by quantifying the amount of deviation of these nine kinematic angular time profiles from the mean of a reference database using the root mean-squared error method and is expressed in degrees. The GPS is calculated by averaging the root mean squared errors of the selected nine kinematic profiles. In addition to the GPS, we also calculated a similar index of gait pathology separately for the sagittal (average RMSE of pelvis tilt, hip, knee and ankle flexion and extension), coronal (average RMSE of pelvis obliquity and hip add & abduction) and transversal plane (average RMSE of pelvis, hip and foot rotation) - more information in Baker et al. 2009 [43]