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RESEARCH

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Acceptability, validity and responsiveness of inertial measurement units for assessing motor recovery after gene therapy in infants with early onset spinal muscular atrophy: a prospective cohort study

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Abstract

Background Onasemnogene abeparvovec gene replacement therapy (GT) has changed the prognosis of patients with spinal muscular atrophy (SMA) with variable outcome regarding motor development in symptomatic patients. This pilot study evaluates acceptability, validity and clinical relevance of Inertial Measurement Units (IMU) to monitor spontaneous movement recovery in early onset SMA patients after GT.

Methods Clinical assessments including CHOPINTEND score (the gold standard motor score for infants with SMA) and IMU measurements were performed before (M0) and repeatedly after GT. Inertial data was recorded during a 25-min spontaneous movement task, the child lying on the back, without (10 min) and with a playset (15 min) wearing IMUs. Two commonly used parameters, norm acceleration 95th centile ($\|A\|_{95}$) and counts per minute ($\|A\|_{CPM}$) were computed for each wrist, elbow and foot sensors.

Results 23 SMA-patients were included (mean age at diagnosis 8 months [min 2, max 20], 19 SMA type 1, three type 2 and one presymptomatic) and 104 IMU-measurements were performed, all well accepted by families and 84/104 with a good child participation (evaluated with Brazelton scale). $\|A\|_{95}$ and $\|A\|_{CPM}$ showed high internal consistency (without versus with a playset) with interclass correlation coefficient for the wrist sensors of 0.88 and 0.85 respectively and for the foot sensors of 0.93 and 0.91 respectively. $\|A\|_{95}$ and $\|A\|_{CPM}$ were strongly correlated with CHOPINTEND (r for wrist sensors 0.74 and 0.67 respectively and for foot sensors 0.61 and 0.68 respectively, p -values < 0.001). $\|A\|_{95}$ for the foot, the wrist, the elbow sensors and $\|A\|_{CPM}$ for the foot, the wrist, the elbow sensors increased significantly between baseline and the 12 months follow-up visit (respective p -values: 0.004, < 0.001 , < 0.001 , 0.006, < 0.001 , < 0.001).

Conclusion IMUs were well accepted, consistent, concurrently valid, responsive and associated with unaided sitting acquisition especially for the elbow sensors. This study is the first reporting a large set of inertial sensor derived data after GT in SMA patients and paves the way for IMU-based follow-up of SMA patients after treatment.

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Keywords Spinal muscular atrophy, Gene therapy, Inertial measurement unit, Neuromuscular disease, Infants, Wearable sensors, Quantitative movement analysis

Introduction

Spinal muscular atrophy (SMA) is an early onset severe genetic disease with degeneration of motoneurons [1]. Clinical severity is classified from type 0 (neonatal form) to type 4 (adult onset). In the natural course of the severe cases (SMA type 0 or 1), symptoms appear before 6 months of age and progressive muscle paralysis leads to flaccid quadriplegia and death by respiratory failure in the first 2 years of life [2, 3]. SMA severity is correlated with the number of *SMN2* copies and SMA type 1 patients have 2 to 3 copies of *SMN2* [4, 5].

Recently, gene therapy (GT) has changed survival and motor prognosis of SMA patients with prolonged survival without respiratory failure and motor improvement (instead of regression) with motor keystones acquisition (such as unaided sitting) and increase in clinical motor scores for most treated patients [6–10]. Despite positive impact on survival without respiratory failure, the motor function of symptomatic treated patients remains below normal development. A large proportion of treated patients could not walk after 2 years follow-up and required a spinal brace for orthopedic deformities [8, 9, 11–14]. Thus innovative therapies lead to new motor phenotypes and a precise description of these emerging motor trajectories is mandatory to monitor treatment outcomes.

Motor development of the children with SMA are usually evaluated by semi-quantitative motor scales, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOPINTEND) score being the most widely admitted [15]. Other scales such as the Hammersmith Infant Neurological Examination Sect. 2 (HINE-2) or the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) are also widely used [16–20] (see Supplementary Material 1 for clinical motor scores descriptions). These scores are operant to evaluate motor function in clinical trials [6–10] but they remain intrinsically subjective and may be prone to rater bias [21]. Compound muscle action potential (CMAP) is a neurophysiological biomarker obtained by distal supra-maximal stimulation on motor nerves that reflects indirectly the pool of functional motor-neurons. They are known to increase after treatment in SMA patients especially for the median CMAP [17, 18]. Motor scores and CMAPs may reflect the child's motor potential ('capacity') but do not provide an objective measure of movements performed in daily life ('performance').

Three-dimensional movement analysis provides objective measures [22, 23] however, it does not bridge the gap between laboratory and real-life. In the last decades, inertial measurement units (IMU) have become one of the best suited wearable technology to monitor movement in real life conditions [24] as they are small and lightweight and can be worn over long periods of time without necessitating a movement measurement laboratory. Accelerometric measurements have been performed in various age-ranges (from preterm [25] and infants [26–28] to elderly [29]) and in different clinical conditions including neuromuscular diseases in childhood such as SMA or Duchene disease [30, 31]. Several previous studies have shown that IMUs were well accepted by infants [24, 26, 32, 33] and were reliable and sensitive to change in children with neuromuscular diseases [30].

Before being able to monitor physical activity in ecological conditions, validation studies must be performed in semi-controlled conditions [30]. This is particularly true in infants, whose movements are greatly influenced by the caregivers movements or the daily life activity (e.g. hold on the parents arms, carried in a baby stroller, sat in an adapted seat or lying on the floor or a bed) [34]. Protocols concerning movement assessment with IMUs in infants or children with neuromuscular diseases are heterogeneous in terms of sensor's location, measurement duration and activity performed during the measure (imposed or spontaneous movement) [24].

IMUs provide three-dimensional acceleration, angular velocity and magnetic field at a classical sampling frequency of 100 Hz. In term of parameter extraction from raw signal, algorithms are again heterogeneous and computational details are not always publicly available and kept as intellectual property by device suppliers. Activity counts [35] and the amplitude of norm acceleration magnitude vector [36, 37] are two commonly used accelerometric parameters. To enhance comparability between studies, authors have provided publicly available algorithms. For example, Neishabouri et al. 2022 provided a ready to use Python package for activity count computation [35]. If these parameters have been validated especially in children with neuromuscular diseases (SMA and Duchene disease) [31, 38], no study tackled the specific issue of monitoring severe SMA infant's movement using IMUs, especially in the follow-up of GT or any other innovative therapy.

The present study aims at tackling this issue by evaluating acceptance, reliability (internal consistency),

concurrent validity and responsiveness of IMUs to monitor motor recovery after GT in early onset SMA infants on a semi controlled task using commonly reported and easy to compute IMU-parameters. Clinical relevance of the different IMU-parameters and sensor-placement is also evaluated with the association with patient-centered outcomes after GT. Based on encouraging previous results in the use of IMUs in infants [24, 26, 32, 33], we hypothesized that IMUs were acceptable, valid and clinically relevant. Based on clinical observation, we hypothesized that sensors placed on the weaker body parts (lower limbs and proximal sensors) would be of particular interest. Indeed, after GT, limbs with advanced paralysis were observed to regain spontaneous motor function. We hypothesized that detecting the appearance of movement in a paralyzed limb would provide key information on the disease evolution.

Method

Participants

All consecutive patients diagnosed with SMA between June 2019 and June 2023 and treated by GT (onasemogone abeparvovec) at Necker hospital were included in the study. GT indication was discussed in a bimensal national expert committee for all infants with SMA under 2 years at diagnosis and under 12 kg. Patients with severe respiratory impairment or bulbar signs, need for respiratory support or a profound motor deficit did not receive GT indication after thorough discussion by the committee and were not included in this study. Patients were excluded from the study if the IMU-based protocol could not be respected by the child (ability to crawl and flip without cooperation capacity).

GT was administered as a single dose in the intensive care unit. Specific biological monitoring and steroid prophylactic medication were carried out as recommended [7]. We did not add a minimum follow-up time as an inclusion criteria as the internal consistency and concurrent validity analyzes (see statistical analyses sub-section) do not require a minimum follow-up time.

Between June 2019 and June 2023, 23 consecutive patients were included in the study. No patient treated by GT was excluded at baseline.

Most patients had type 1 SMA (19/23), three had type 2 and one was a presymptomatic patient (sister of an index case in family). Age at diagnosis ranged from 3.1 to 20.9 months. Patient 6 is the only patient with respiratory impairment at inclusion necessitating nocturnal noninvasive ventilation. Other participant's baseline characteristics are represented in Table 1.

Clinical follow-up

Close clinical follow-up was performed for each participant at initial stage (M0) and at M1, M3, M6, M12, M18 and M24 after GT infusion. Clinical examination was performed by experimented pediatric neurologists (ID, CB) and clinical scores (CHOPINTEND, HINE2 and Bayley III [gross motor section] scores) were performed by specifically trained occupational therapists (ED, VLG, AH). Patients living far away from the follow-up center were seen only at initial stage, at M12 and at M24 (patients 4, 10, 15 and 19).

Compound muscle action potentials (CMAPS) were measured for the 4 principal nerves (median, ulnar, fibular and tibial) at M0, M6, M12, M18 and M24 by an experimented neurophysiologist (CG) as previously described [39].

IMU measurement

IMU measurements were performed at each follow-up evaluation at M0, M1, M3, M6, M12, M18 and M24.

Sensors (four synchronized tri-axial IMUs [accelerometer, gyroscope and magnetometer] wirelessly connected to a computer, Movella XSens[®] MTw, weight 16 g, dimension 47 × 30 × 13 mm, sampling frequency 100 Hz) were placed on both wrists and both feet, with anatomical references accordingly to previous IMU studies [24]. In addition, movements from the elbows were also monitored because muscular weakness in SMA affects predominantly proximal muscles. Sensors were firmly fixed to the body with single use cohesive bandages (Peha-Haft[®]). The elbow sensors were fixed just proximal to the elbow, at the posterior side on the distal part of the upper arm, so that the child's elbow movements did not alter the sensor positioning during the measurement. The wrist sensors were fixed at the posterior side of the arm distally and the foot sensors at the dorsal side of the feet. Sensors were strongly maintained in place by cohesive bandages. Spontaneous child movements measured in the study were not strong enough to cause sensor's displacement during the measurement.

In the case of infants' measurements it is important to avoid any caregivers' parasite movement [34]. In the present study, parasite accelerations provided by caregivers were avoided by asking parents to stimulate the child only vocally and visually without any physical contact during the measurement tasks. Video recordings were used to identify any physical parent/child contact. In case of prolonged parent/child contacts during the experiment, the recording segment was to be removed. In practice parents respected the directives and it was not necessary to remove any recording segments. This implied a relatively short measurement time in a semi-controlled

Table 1 Patients' baseline characteristics before gene therapy and IMU recordings moments during follow-up after gene therapy (last right column)

Patient number	Age at GT (month)	SMA type	S/MN2 copy number	Gender	Weight (kg)	Height (cm)	HINE2 score (/26)	CHOP-INTEND score (/64)	Bayley III score (/72)	Median CMAP (mV)	Ulnar CMAP (mV)	Fibular CMAP (mV)	Tibial CMAP (mV)	IMU recordings (months after GT)
1	10.2	1c	2	m	8.3	72	7	29	11	1.02	0.27	0.50	0.36	6, 12, 18
2	3.9	1b	2	m	6.1	61	2	15	2	0.04	0.00	0.00	0.00	3, 6, 12, 18
3	4.0	prespt	3	f	5.2	60	7	59	17	5.40	4.70	1.51	4.80	1
4	6.5	1c	3	m	8.9	78	7	29	4	0.31	0.00	0.15	0.53	12, 24
5	11.1	1c	3	f	7.1	70	8	30	13	1.10	0.40	2.60	1.68	0, 3, 6, 12, 18, 24
6	9.3	1b	2	m	8.7	71	2	25	3	0.35	0.24	0.00	0.28	0, 1, 3, 6, 12, 24
7	9.8	1c	3	f	7.1	69	7	38	11	0.78	0.35	0.46	1.10	0, 1, 3, 6, 12, 24
8	8.1	1c	2	f	9.1	75	5	36	10	2.53	0.35	0.70	1.80	0, 1, 3, 6, 12, 18, 24
9	9.0	1c	2	f	7.4	71	6	37	10	0.23	0.17	0.09	0.39	0, 1, 3, 6, 12, 18, 24
10	7.1	1b	2	m	8.5	66	2	26	2	0.22	0.24	0.07	0.76	0, 1, 12, 24
11	5.2	1b	2	f	7.0	66	2	29	6	0.29	0.18	0.00	0.18	0, 1, 3, 6, 12, 24
12	4.2	1b	2	f	8.5	61	2	17	4	0.19	0.22	0.00	0.00	0
13	3.8	1b	2	f	5.2	60	3	28	3	0.23	0.82	0.58	0.71	0, 1, 3, 12, 18, 24
14	12.5	2	3	f	9.0	76	8	43	13	4.50	0.84	1.07	1.57	0, 1, 3, 6, 12, 18, 24
15	5.4	1b	2	f	5.4	63	4	36	6	0.54	0.72	0.46	0.97	0, 1, 12, 24
16	9.0	1b	2	f	6.7	66	2	35	9	0.49	0.32	0.17	0.18	0, 12, 18
17	13.6	1c	3	m	11.3	82	5	42	13	3.00	1.10	1.07	1.39	0, 1, 3, 6, 12
18	4.6	1b	2	m	7.4	67	2	23	3	0.34	0.50	0.30	0.49	0, 1, 3, 6, 12
19	3.1	1b	2	f	5.2	60	2	30	3	0.12	0.05	0.05	0.17	0, 1, 3, 12
20	20.9	2	3	f	9.4	79	28	62	27	5.15	2.70	2.50	3.75	0, 3, 6, 12
21	15.7	2	3	f	10.4	80	18	58	31	4.80	3.40	2.14	0.98	0, 1, 6
22	4.4	1b	2	m	5.1	60	2	29	-	0.45	0.15	-	0.60	0, 3, 6, 12
23	4.0	1b	2	f	6.3	63	2	34	3	0.56	0.00	0.55	0.20	0, 1, 6
24	2.6	1a	2	f	4.3	58	2	38	5	0.52	-	1.23	0.55	0, 3
25	13.1	2	3	m	9.3	75	10	50	17	3.40	2.16	1.27	0.57	1

Prespt.: presymptomatic patient; IMU: Inertial Measurement Unit; SMA: Spinal Muscular Atrophy; TC/HC: thoracic/head circumference ratio; CMAP: compound muscle action potential; S/MN2: Surviving Motor Neuron 2; GT: gene therapy; CHOPINTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2: Hammersmith Infant Neurological Examination Section; Bayley-III: Bayley Scales of Infant and Toddler Development, Third Edition, gross motor section. Additional information concerning HINE2, CHOPINTEND and Bayley III scores can be found in Supplementary Material 1

environment in a dedicated room at the hospital. To evaluate if external stimulation had an influence on the IMU-parameters, measurements with and without playset were performed. The measurement protocol and set up is represented on Fig. 1.

One measurement included 3 distinct acquisitions.

- Acquisition 1: participant lying on the back wearing 4 IMUs on both wrists and both feet without a playset for 10 min.
- Acquisition 2: participant lying on the back wearing 4 IMUs on both wrists and both feet with a playset (SOLINI® reference 171,803, see Supplementary material 2) for 10 min.
- Acquisition 3: participant lying on the back wearing 4 IMUs on both wrists and both elbows with a playset for 5 min.

The total measurement duration was 25 min.

To control the readiness of the child to participate, the time of the evaluation, the duration since last meal and the duration since last sleep was systematically registered. Tolerance and participation of the child was evaluated with Brazelton scale. Brazelton 4 and 5 (respectively “awake, alert state” and “alert but fussy state”) were considered as good participation and Brazelton states 3 and 6 (respectively “drowsy state” and “cry”) were considered as

poor participation. For Brazelton states 1 and 2 the measures were postponed by 1 h to allow a better participation of the child.

Parameter computation

IMU-based parameters were computed on the norm of the free acceleration (acceleration without gravity given by the sensors) as follows:

$$a(t) = \sqrt{a_x(t)^2 + a_y(t)^2 + a_z(t)^2}$$

a_x , a_y and a_z being the free accelerations (acceleration without gravity) given by the sensors in tri-axial coordinates of the sensor frame, t being the time.

Xsens® MTw sensors provide two acceleration outputs: the acceleration in the sensor’s frame which includes the gravity component in it and the free acceleration which is the acceleration sensed by the IMU without the gravity component expressed in the Earth-reference frame. Free acceleration is obtained by 3D angular velocity, 3D acceleration and 3D earth magnetic field combined with Xsens® sensor fusion algorithms. We ensured that magnetic field was not disturbed by ferromagnetic material. A 3D calibration measurement was performed before each measurement for the four sensors as recommended by the device supplier.

We computed following parameters:

Acquisition nbr.	Nbr. of IMU	IMU's position	Duration (min)	Playset	Child's position
1	4	Wrist x 2 Foot x 2	10	no	lying on the back
2	4	Wrist x 2 Foot x 2	10	yes	lying on the back
3	4	Wrist x 2 Elbow x 2	5	yes	lying on the back

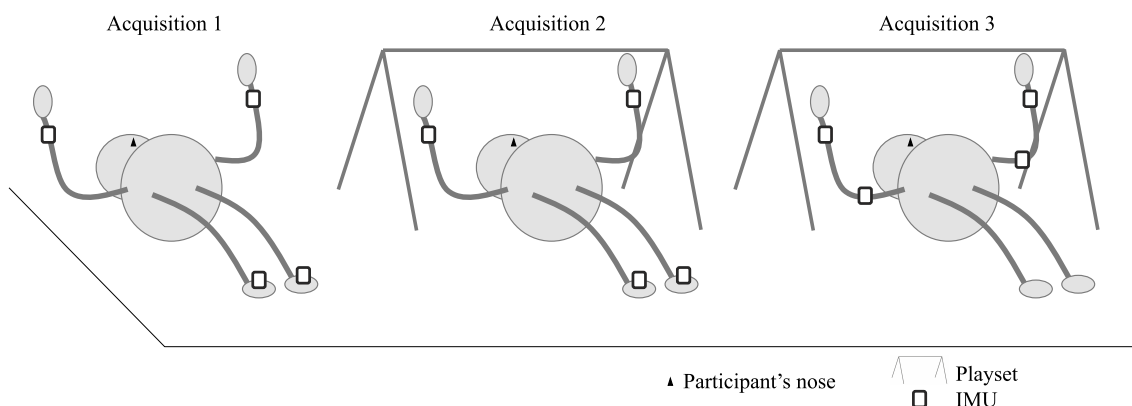


Fig. 1 Schematic representation of the IMU-measurement protocol. One measurement was made of 3 acquisitions. Acquisition 1: participant lying on the back wearing 4 IMUs on both wrist and both feet without a playset for 10 min (left illustration). Acquisition 2: participant lying on the back wearing 4 IMUs on both wrist and both feet with a playset for 10 min (middle illustration). Acquisition 3: participant lying on the back wearing 4 IMUs on both wrist and both elbows with a playset for 5 min (right illustration). The total measurement duration was 25 min. IMU: Inertial Measurement Unit

- Norm acceleration 95th centile ($\|A\|_{95}$). The computation process is simple and reproducible. The statistic 95th centile is a measure of the children's peak performance outliers excluded, representing the higher values of accelerations the wearer is able to produce over the 10 or 5 min acquisitions [31, 38].
- Counts per minute computed on the norm acceleration ($\|A\|_{CPM}$). Counts per minute are widely used in actimetric studies and allow comparison of our results with literature. To increase comparability, we used the open Python library *agcounts* version 0.2.0 function *get_counts* by Neishaboury et al. 2022 [35] with 60 s epochs length. The mean values of the counts of the 60 s epochs over the 10 or 5 min acquisitions were taken.

For each parameter, we computed the mean value of the right and the left sensors. Hence, we obtained four parameters for each acquisition: two (i.e. $\|A\|_{95}$ and $\|A\|_{CPM}$) for the wrist sensors and two for the foot sensors in acquisition 1 and 2; two for the wrist sensors and two for the elbow sensors in acquisition 3.

The raw norm acceleration and the movement counts obtained for one typical severe SMA infant over a

24 months follow-up period for the wrist and the foot sensors of acquisition 1 are represented on Fig. 2. Corresponding parameters $\|A\|_{95}$ and $\|A\|_{CPM}$ are also represented using horizontal dashed lines on Fig. 2. Note the visual increase of the norm of the acceleration and of the computed parameters with time.

Statistical analysis

The definition for reliability, internal consistency, concurrent validity and responsiveness are those previously given in COSMIN study consensus statement [40, 41].

Internal consistency analysis (reliability analysis)

Reliability of IMU-parameters in semi-controlled tasks has already been established through test/retest experiments [30], thus no test-retest experiment was performed.

It is established that IMU recordings are variable within a day as a function of the daily life activities [42]. As our recording protocol is short, we oriented our study design to evaluate if the IMU-parameters were impacted by external stimulation. External stimulation was provided by the use or not of a playset, and measurement with and without playset were performed. IMU-parameters

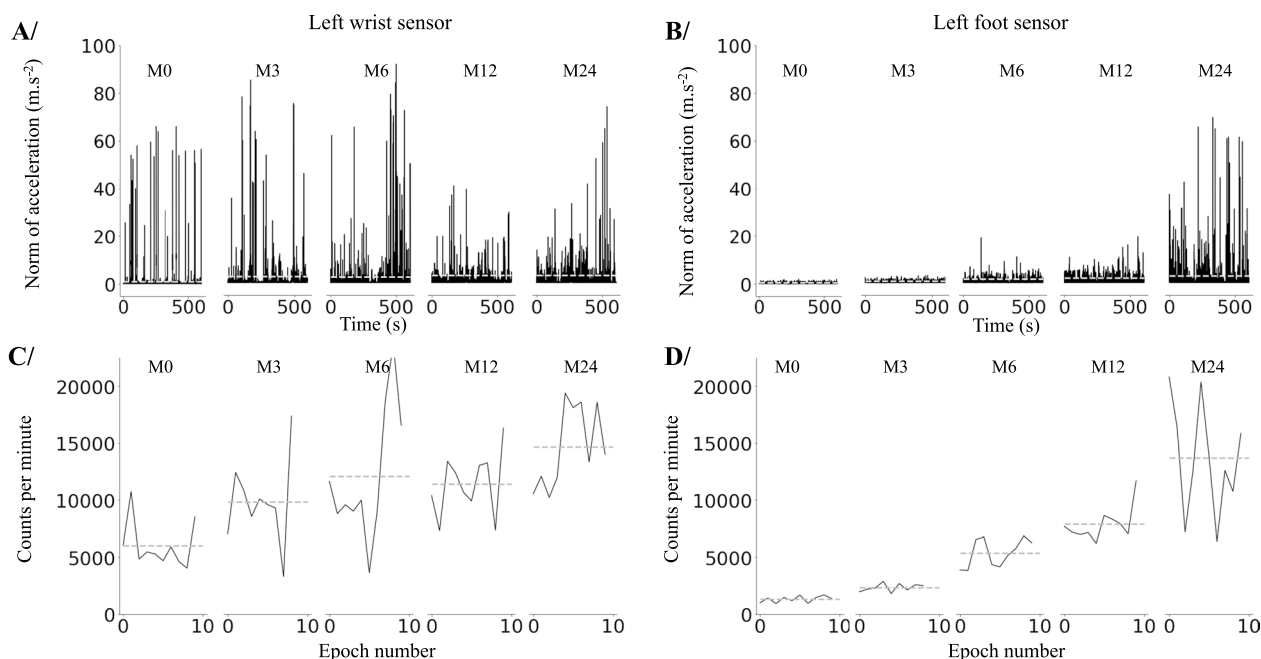


Fig. 2 Typical norm acceleration raw data as a function of time for acquisition 1 for one SMA type 1 infant before gene therapy (M0) and 3, 6, 12 and 24 months (M3, M6, M12, M24) after gene therapy for the left wrist sensor (**A**) and for the left foot sensor (**B**). Sampling frequency is 100 Hz. Corresponding movement counts computed for the norm acceleration with Neishaboury et al. 2022 [35] open Python library with 60 s epochs length for the left wrist sensor (**C**) and for the left foot sensor (**D**). The horizontal grey dashed lines represent the norm acceleration 95th centile for each measurement (M0, M3, M6...) in graphic **A** and **B**/ and the mean of movement counts for each measurement (M0, M3, M6...) in graphic **C** and **D**/. Note the visual increase of the norm of the acceleration and of the computed parameters with time. IMU: Inertial Measurement Unit; SMA: spinal muscular atrophy

obtained from acquisition with and without a playset were compared (intra-protocol robustness of the measure). The Interclass Correlation Coefficient (ICC) between acquisition 1 (without playset) versus acquisition 2 (with playset) of a same measurement for wrist and foot sensors were computed.

As the IMUs may not have negligible weight (16 g) for infants with poor motor function, the effect of the presence or not of an elbow sensor on the wrist sensor parameters was evaluated. The IMU-parameters from the wrist sensors obtained from acquisition with and without the elbow sensors were compared. The ICCs between acquisition 2 (without elbow sensors) versus acquisition 3 (with elbow sensors) of a same measurement for wrist sensors were computed.

Concurrent validity analysis

Concurrent validity of IMU-based parameters was evaluated with the correlation with gold-standards evaluating the motor function of the patients (i.e. CHOPINTEND and median CMAP) with Pearson correlation coefficient. Correlation between age, clinical scores (CHOPINTEND, HINE2, Bayley), CMAPs (median, ulnar, fibular, tibial) and IMU-based parameters ($||A||_{95}$ and $||A||_{CPM}$ for the foot, the wrist, the elbow sensors) were also computed with the Pearson correlation coefficient. Significant p-values for the correlations were set <0.0001 after Bonferroni correction because multiple tests were performed.

All patients were included in the internal consistency and concurrent validity analysis.

Responsiveness analysis

Responsiveness of the IMU-parameters was evaluated by comparing $||A||_{95}$ and $||A||_{CPM}$ for foot (acquisition 1), wrist (acquisition 1) and elbow (acquisition 3) sensors represented in mean and standard deviation at baseline before gene replacement therapy (M0) and at the 12 month follow-up visit (M12) with a paired student t-test (p-value for significance set at 0.05). For this analysis, only patients with an available IMU-measurement at M0 and M12 were included.

Additionally, the correlations between the differences between M0 and M12 for IMU-parameters ($||A||_{95}$ computed on the wrist-sensors in acquisition 1, on the foot-sensors in acquisition 1, on the elbow-sensors in acquisition 3 and for $||A||_{CPM}$ computed on the wrist-sensors in acquisition 1, on the foot-sensors in acquisition 1, on the elbow-sensors in acquisition 3) and the difference between M0 and M12 for the CHOPINTEND score were evaluated using Pearson correlation coefficient.

Clinical relevance analysis

Means of $||A||_{95}$ and $||A||_{CPM}$ computed on the foot (acquisition 1), the wrist (acquisition 1) and the elbow (acquisition 3) sensors were compared with a paired student t-test (p-value for significance set at 0.05) at baseline and at M12.

The association of IMU-parameters and the acquisition of 30 s unaided sitting (a patient centered outcome) was evaluated using the area under the ROC curve (comparison between a continuous variable i.e. IMU-based parameters, motor scores and CMAPs) and compared with the area under the ROC curve of the motor scores (CHOPINTEND score, Bayley III motor score and HINE2 score) and CMAPs (median, ulnar, fibular and tibial).

Results

Participants

Clinical follow-up and acceptability of the 25-min measuring task was good

A total of 104 IMU-measurements were performed with a median of 4 by patient (min 1, max 7). Exact IMU-measurement moments (M0, M1, M3, M6...) for each patient are given in Table 1. Patients 1, 2, 3 and 4 had already received GT before the study's start and were included after GT infusion that is why first measurements are missing. Patient 3 was the presymptomatic patient. She had normal motor development. Six months after GT, she was excluded because she had acquired crawling and did not respect the protocol. Patient 12 died from severe adverse event one month after therapy. Only patient 3 and 12 were excluded from the study. Patients 4, 10, 15 and 19 lived far away from the follow-up center and came every 6 months for the visit. Thirteen patients out of 23 had 24 months follow-up and 6/23 had 12 months follow-up. Other (4/23) had less than 12 months follow-up.

At baseline, the motor development of patient 20 nearly exceeded parameters of the CHOPINTEND score (62/64) so the CHOPINTEND score was not performed in the follow-up for this patient. Patient 13, 14 and 15 stagnated at high scores on CHOPINTEND score during the follow-up (as it is often observed in SMA infants after GT [7]) at respectively 62, 56 and 58/64 so the CHOPINTEND score at the M24 visit was no longer performed for these patients. Altogether, 104 IMU-measurements were available: 98 with CHOPINTEND score and 63 with CMAP evaluations. Fifteen patients had available IMU-measurements at M0 and M24. Fourteen patients had available IMU-measurements and CHOPINTEND scores at M0 and M24.

IMU-measures were well tolerated in most cases. 84/104 measures were performed with good participation

(Brazelton states 4 and 5) of the child and 20/104 with poor participation (Brazelton states 3 and 6). Participation of the child to the measurement could be influenced by tiredness or hunger. Online Fig. 1 shows the repartition of the IMU-measurements as a function of daytime, duration since last nap and duration since last meal. Repartitions were quite heterogeneous in our data set. In some occurrences, some children could initially try to oppose the installation of the sensors, but in all cases eventually forgot or accept their presence.

IMU-parameters were consistent between acquisitions of the same IMU-measurement; $\|A\|_{95}$ and $\|A\|_{CPM}$ were strongly correlated with each other

All 104 IMU-measurements were included for the internal consistency analysis. External stimulation (the presence of the playset or not) had little impact on $\|A\|_{95}$: the consistency of the measure between acquisition 1 (without playset) and acquisition 2 (with playset) was good to excellent with an ICC of 0.88 for the $\|A\|_{95}$ computed on the wrist sensors and 0.93

for the $\|A\|_{95}$ computed on the foot sensors as shown on Fig. 3. For $\|A\|_{CPM}$, ICCs were similar but slightly lower: 0.84 for wrist sensors and 0.91 for foot sensors for acquisition 1 versus 2. The presence or not of the elbow sensor had limited impact on the $\|A\|_{95}$ computed on the wrist sensor even if the ICCs were slightly lower: an ICC of 0.83 was found when comparing $\|A\|_{95}$ computed on the wrist sensors in acquisition 2 versus in acquisition 3. For $\|A\|_{CPM}$, ICCs were similar: 0.83 for wrist sensors for acquisition 2 versus 3 as shown on Fig. 3. Altogether, external stimulation had limited impact on the wrist and foot parameters and the presence of the elbow sensor had also limited impact on the wrist parameters. Also, internal consistency was better (higher ICCs) for the foot sensors than for the wrist sensors.

$\|A\|_{95}$ and $\|A\|_{CPM}$ were strongly correlated with each other (r for Pearson correlation for wrist sensors 0.96 [p-value $2e-56$] and for foot sensors 0.95 [p-value $1e-55$] for acquisition 1 and for elbow sensors 0.97 [p-value $1e-66$] for acquisition 3) as shown on Table 2.

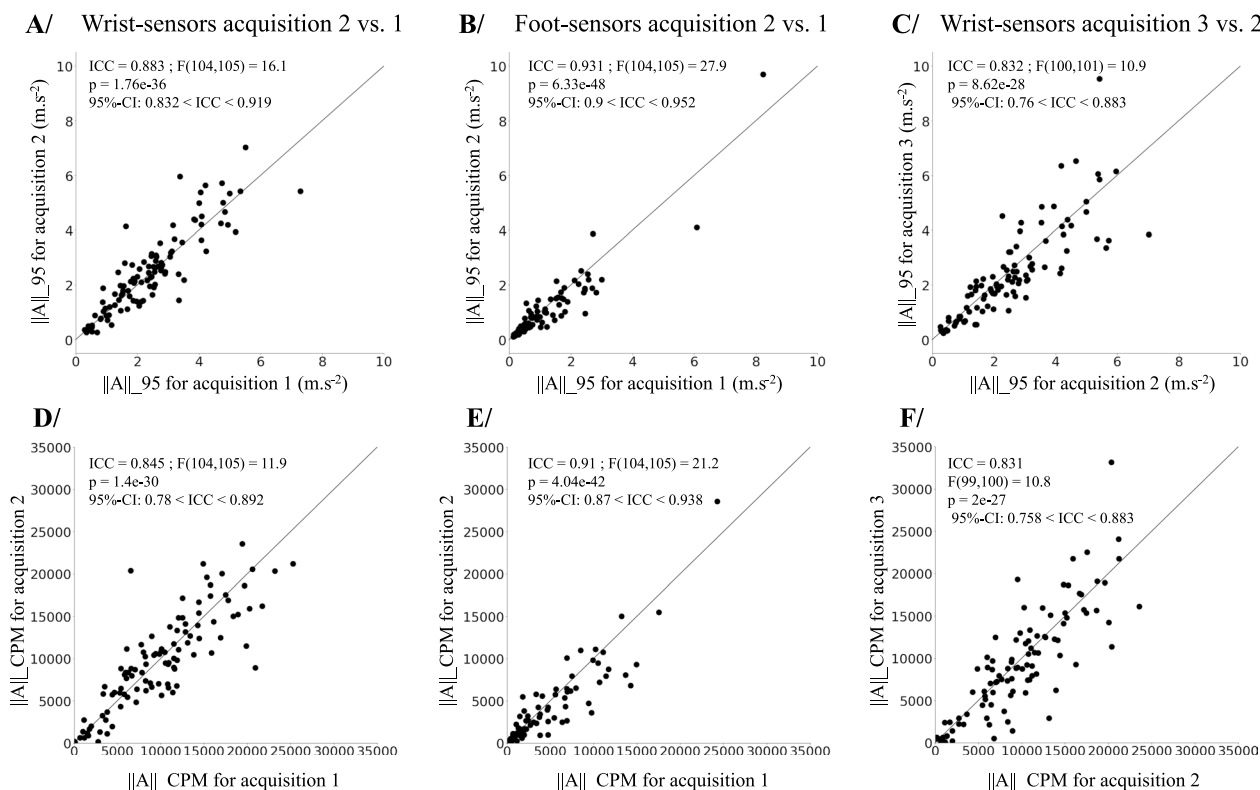


Fig. 3 Internal consistency between $\|A\|_{95}$ computed on the wrist sensors (A) and on the foot sensors (B) between acquisition 1 (without playset) and acquisition 2 (with playset) and for the wrist sensor between acquisition 2 and acquisition 3 (with playset and with elbow sensors) (C). Internal consistency between $\|A\|_{CPM}$ computed on the wrist sensors (D) and on the foot sensors (E) between acquisition 1 (without playset) and acquisition 2 (with playset) and for the wrist sensor between acquisition 2 and acquisition 3 (with playset and with elbow sensors) (F). ICC are given for each plot. All 104 IMU-measurements were included in this analysis. ICC: interclass correlation coefficient. $\|A\|_{95}$: Norm acceleration 95th centile; $\|A\|_{CPM}$: Mean counts per minute computed on the norm acceleration

Table 2 Correlations between IMU-parameters ||A||₉₅ versus ||A||_{CPM} on all sensors of all acquisitions of all 104 IMU-measurements

	A _{CPM} - wrist - acqu. 1	A _{CPM} - wrist - acqu. 2	A _{CPM} - wrist - acqu. 3	A _{CPM} - foot - acqu. 1	A _{CPM} - foot - acqu. 2	A _{CPM} - elbow - acqu. 3
A ₉₅ - wrist - acqu. 1	0.96	0.88	0.80	0.63	0.53	0.78
A ₉₅ - wrist - acqu. 2	0.81	0.96	0.83	0.63	0.56	0.80
A ₉₅ - wrist - acqu. 3	0.73	0.82	0.96	0.66	0.60	0.93
A ₉₅ - foot - acqu. 1	0.49	0.51	0.54	0.95	0.93	0.54
A ₉₅ - foot - acqu. 2	0.38	0.43	0.45	0.86	0.97	0.44
A ₉₅ - elbow - acqu. 3	0.71	0.78	0.91	0.65	0.59	0.98

The numbers are the Pearson correlation coefficients. Bold numbers represent statistically significant correlation with p values < 0.0001. Bold italic cells show Pearson correlation coefficient > 0.80. Note the high correlations between ||A||₉₅ versus ||A||_{CPM} when computed on the same sensors

Abbreviations: IMU – Inertial Measurement Unit. SMA – Spinal Muscular Atrophy. ||A||₉₅ – Norm acceleration 95th centile. ||A||_{CPM} – Mean counts per minute computed on the norm acceleration signal

Thus, in the results, observations made for ||A||₉₅ will also be valid for ||A||_{CPM}.

Concurrent validity: IMU-parameters were correlated with motor scores (CHOPINTEND score, Bayley III motor score and HINE2 score) and CMAPs (median, ulnar, fibular and tibial)

All 104 IMU-measurements were included for the concurrent validity analysis: 98 were available with CHOPINTEND scores and 63 with CMAP evaluations. CHOPINTEND score was strongly correlated with ||A||₉₅ and ||A||_{CPM} computed on the wrist sensors for acquisition 1 (r 0.74 p-value 1e-17 and r 0.67 p-value 1e-13 respectively) and also when they were computed on the foot sensors for acquisition 1 (r 0.61 p-value 7e-11 and r 0.69 p-value 2e-14 respectively) even if the correlation was slightly weaker than for the wrist sensors (Fig. 4 and Table 3). ||A||₉₅ and ||A||_{CPM} were also correlated with median CMAP for the wrist sensors for acquisition 1 (r 0.59 p-value 4e-5 and r 0.56 p-value 1e-4 respectively) and for the foot sensors for acquisition 1 (r 0.58 p-value 8e-7 and r 0.61 p-value 1e-7 respectively) as shown on Fig. 4 and Table 3.

||A||₉₅ and ||A||_{CPM} were also correlated with age for the wrist sensor of acquisition 1 (r 0.59 p-value 2e-11 and r 0.53 p-value 6e-9 respectively) and the foot sensors of acquisition 1 (r 0.34 p-value 3e-4 and r 0.50 p-value 6e-8 respectively) as shown on Fig. 4 and Table 3. Correlations were better (higher correlation coefficient and lower p-values) for wrist sensors than for foot sensors.

All 3 clinical scores (CHOPINTEND score, Bayley III motor score and HINE2 score) showed comparable correlations with accelerometric parameters (||A||₉₅ and ||A||_{CPM} on the foot, wrist and elbow sensors). Ulnar and fibular CMAPs showed slightly lower correlations with accelerometric parameters than median and tibial

CMAPs with lower correlation coefficients and higher p-values as shown on Table 3.

Altogether, ||A||₉₅ and ||A||_{CPM} computed on the foot sensors in acquisition 1 showed lower correlations with clinical scores (CHOPINTEND score, Bayley III motor score and HINE2 score) than those computed on the upper limbs sensors (wrist and elbow) as shown on Table 2.

Responsiveness: ||A||₉₅ and ||A||_{CPM} increased significantly between the baseline and the 12 month visit after GT for all 3 sensor locations (foot, wrist and elbow)

Fifteen patients had measurement at baseline and at the 12 month visit and were included in the responsiveness analysis. ||A||₉₅ for the foot, the wrist, the elbow sensors and ||A||_{CPM} for the foot, the wrist, the elbow sensors increased significantly between baseline before GT and the 12 month follow-up visit (respective p-values: 0.004, < 0.001, < 0.001, 0.006, < 0.001, < 0.001) as shown on Fig. 5. Note that the difference was stronger here for the parameters computed on the upper limb sensors (wrist and elbow) than those computed on the foot sensors (p-values were higher).

None of the differences between M0 and M12 for IMU-parameters (||A||₉₅ computed on the wrist-sensors in acquisition 1, on the foot-sensors in acquisition 1, on the elbow-sensors in acquisition 3 and for ||A||_{CPM} computed on the wrist-sensors in acquisition 1, on the foot-sensors in acquisition 1, on the elbow-sensors in acquisition 3) were significantly correlated with the difference between M0 and M12 for the CHOPINTEND score for the 14 patients who had available IMU-parameters and CHOPINTEND scores for M0 and M12. Nevertheless, even though not significant, a trend of correlation was observed between IMU-parameters difference and CHOPINTEND score difference between M0 and M12. Of

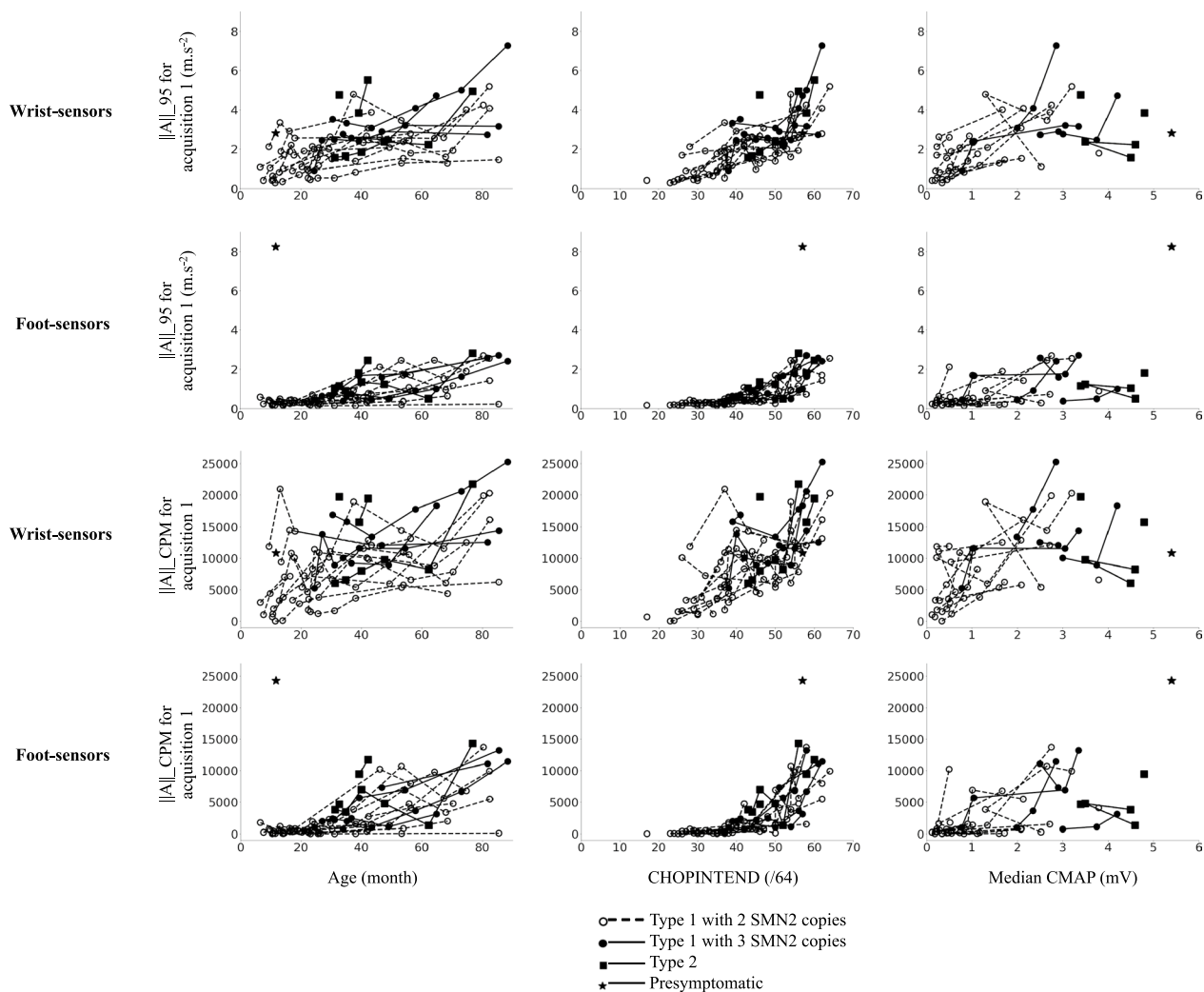


Fig. 4 $\|A\|_{95}$ (6 top plots) and $\|A\|_{CPM}$ (6 bottom plots) as a function of age (left column), CHOP-INTEND score (middle column) and median CMAP (right column) for wrist (first and third lines) and foot sensors (second and fourth lines). Points of the same patient are linked by lines. Dashed lines with empty circles represent SMA type 1 patients with 2 *SMN2* copies, continuous lines with filled circles represent SMA type 1 patients with 3 *SMN2* copies, squares with continuous lines represent SM1 type 2 patients and stars with continuous lines represent the presymptomatic patient. A hundred and four IMU-measurements were available with the age of the patients (left column). Ninety-eight IMU-measurements were available with CHOPINTEND (middle column). Sixty three IMU-measurements were available with CMAP evaluations (right column). SMA: Spinal Muscular Atrophy; $\|A\|_{95}$: Norm acceleration 95th centile; $\|A\|_{CPM}$: Mean counts per minute computed on the norm acceleration; CMAP: compound muscle action potential

note, this trend was more marked for foot-sensors (lower p-values) than for upper limb sensors (Online Fig. 2).

Clinical relevance: IMU-parameters were significantly higher for the wrist sensors versus elbow sensors and elbow sensors versus foot sensors; elbow and foot sensors were more strongly associated with unaided sitting than wrist sensors

Among the 15 patients with available IMU-parameters at M0 and M12, the mean of $\|A\|_{95}$ for the wrist sensors was significantly different at M0 versus the mean of the

foot sensors and versus the mean of the elbow sensors. In contrast, the mean of $\|A\|_{95}$ for the foot sensors was not different from the mean of $\|A\|_{95}$ for the elbow sensors at M0. At M12, all previously significant differences remained and were more marked (lower p-values and greater differences between means) and a significant difference appeared between the mean of $\|A\|_{95}$ for the foot and the elbow sensors as shown on Table 4.

As shown on Online Fig. 3, $\|A\|_{95}$ showed stronger association with 30 s unaided sitting than CHOPINTEND especially for the elbow and foot sensors with

Table 3 Correlations between IMU- parameters versus age, motor scores (CHOPINTEND score, Bayley III motor score and HINE2 score) and CMAPs (median, ulnar, fibular and tibial)

	Age	CHOP-INTEND score	Bayley III motor score	HINE2 score	median CMAP	ulnar CMAP	fibular CMAP	tibial CMAP
A ₉₅ - wrist - acqu. 1	0.59	0.74	0.69	0.70	0.59	0.50	0.61	0.57
A _{CPM} - wrist - acqu. 1	0.53	0.67	0.60	0.62	0.56	0.47	0.55	0.56
A ₉₅ - foot - acqu. 1	0.34	0.61	0.56	0.55	0.58	0.64	0.36	0.66
A _{CPM} - foot - acqu. 1	0.50	0.69	0.66	0.66	0.61	0.58	0.39	0.69
A ₉₅ - elbow - acqu. 3	0.65	0.78	0.72	0.74	0.71	0.61	0.63	0.68
A _{CPM} - elbow - acqu. 3	0.62	0.74	0.70	0.72	0.69	0.59	0.67	0.63

The numbers are the Pearson correlation coefficients. Bold numbers represent statistically significant correlation with p values < 0.0001

IMU: Inertial Measurement Unit; SMA: Spinal Muscular Atrophy. ||A||₉₅ - Norm acceleration 95th centile. ||A||_{CPM}: Mean counts per minute computed on the norm acceleration signal; CMAP: compound muscle action potential

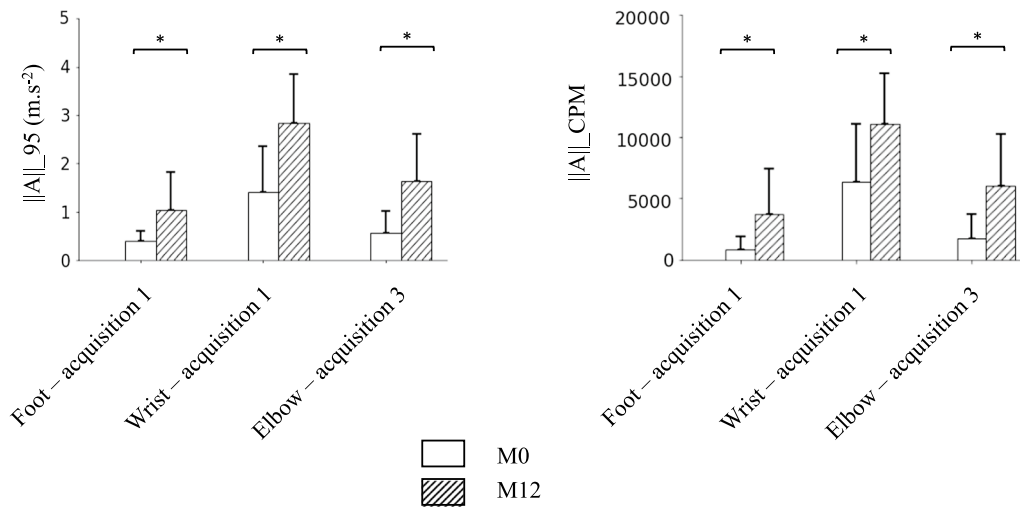


Fig. 5 ||A||₉₅ and ||A||_{CPM} for foot (acquisition 1), wrist (acquisition 1) and elbow (acquisition 3) sensors represented in mean and standard deviation for 15 patients with available data at baseline before gene replacement therapy (M0) and the 12 month follow-up visit (M12). * for p-values < 0.05 (paired student t-test). ||A||₉₅: Norm acceleration 95th centile. ||A||_{CPM}: Mean counts per minute computed on the norm acceleration

Table 4 ||A||₉₅ for foot (acquisition 1), wrist (acquisition 1) and elbow (acquisition 3) sensors represented in mean and standard deviation for 15 patients with available data at baseline before gene replacement therapy (M0) and the 12 month follow-up visit (M12)

		A ₉₅ - wrist - acqu. 1 (m/s ²)	A ₉₅ - foot - acqu. 1 (m/s ²)	A ₉₅ - elbow - acqu. 3 (m/s ²)	p-value wrist vs. foot	p-value wrist vs. elbow	p-value foot vs. elbow
M0	mean	1.40	0.38	0.55	0.0003	0.0002	0.06
	std	0.96	0.22	0.46			
M12	mean	2.83	1.03	1.63	<.00001	<.00001	0.006
	std	1.02	0.78	0.97			

P-values for a paired student t-test are represented by bold numbers when < 0.05. Note the significant difference between ||A||₉₅ for the foot versus the elbow sensors not present at M0 that appeared at M12

IMU: Inertial Measurement Unit; SMA: Spinal Muscular Atrophy. ||A||₉₅: Norm acceleration 95th centile; ||A||_{CPM}: Mean counts per minute computed on the norm acceleration signal; CMAP: compound muscle action potential; Std: standard deviation

areas under the curve for elbow sensors of 0.91 and 0.90 respectively and for foot sensors of 0.90 and 0.90 respectively versus 0.89 for CHOPINTEND. Bayley III score had the best AUC of 0.94. All 104 IMU-measurements were included in this analysis.

Discussion

This study reports originally on the psychometric properties of IMU-based assessment of motor recovery in early onset SMA patients after GT. IMU acceptance was high. $||A||_{95}$ and $||A||_{CPM}$ computed on a 25-min semi-controlled task showed high internal consistency, moderate to high concurrent validity (correlations with CHOPINTEND and median CMAPs) and excellent responsiveness. Moreover, these parameters were associated with the ability to stay 30 s sitting unaided, especially for those sensors placed on the body parts with the most marked motor deficit (foot and elbows).

Acceptance and feasibility of the measure

Our measurement protocol was widely well accepted and tolerated by children and their families (83% of infants' showed a good level of participation and none of the parents refused the test), even if measurements were performed in children from 3 months to 2 years which covers a wide range of developmental ages and behaviors. The presymptomatic child with normal psychomotor milestones did not respect the protocol from 6 months of age and was excluded at that time. In contrast, the protocol showed to be well adapted to all other more severe SMA patients who rested lying in a supine position for 25 min. None of them were able to flip and crawl at the time of the test. Therefore, the presented semi-controlled protocol seems to be adapted to infants with a spectrum of development and severity explored in this study but might not be adapted for healthy infants over 4 months of age or for less severe SMA children.

Internal consistency of IMU-parameters

IMUs have already been shown to be a valid tool to measure every-day motor activity in children with neuromuscular disease [30] using parameter such as norm acceleration 95th centile [31]. Nevertheless, validation studies are lacking concerning the infant population [43]. The present study adds strong arguments towards their validity in the precise clinical situation addressed here i.e. measuring motor recovery after GT in severe SMA infants. The good ICC observed between acquisition 1 (measure without a playset) and acquisition 2 (measured with a playset) and between acquisition 2 and acquisition 3 shows strong consistency to external stimulations. We observed better ICCs on the foot than on the wrist sensors. We hypothesize that foot-movements were weaker

and thus more stereotypical than movements from the wrists and thus maybe less affected by participation of the child and by external stimulation. Furthermore, the calculated accelerometric parameters are easy to compute but relatively coarse and not analytical, as they do not account for the axes of the sensors and aggregate the data between the left and right sides. This likely does not fully capture the complexity of upper-limb movements and lower the upper-limb sensors' reliability.

Concurrent validity of IMU-parameters

On the other hand, the correlation of IMU-parameters with age, gold standard clinical scores (i.e. CHOPINTEND, HINE2 and Bayley III) and neurophysiological biomarkers (i.e. median CMAP) was striking. We hereby show strong correlation between a short ecological measure and a functional score which validates the IMU-parameters to evaluate motor function. The correlations with motor scores were better for IMU-parameters computed on the upper limb sensors (wrist or elbow) than those computed on the foot sensors. This might be explained by the non-linear relation between IMU-foot parameters and the motor scores. Indeed, as shown on Fig. 4, foot parameters remain near 0 for CHOPINTEND scores under 40/64 and increase quickly for CHOPINTEND score above 40/64. Probably, CHOPINTEND score and foot parameters are two items that do not measure the same reality: CHOPINTEND score is a global evaluation of the acquisitions of the child whereas foot parameters measure specifically the degree of lower limb paralysis and with great accuracy.

Responsiveness

IMU-parameters computed on all sensor locations (foot, wrist and elbow) showed excellent responsiveness by increasing significantly between baseline before GT and the 12 month follow-up visit. This difference was more significant for the upper limb sensors (wrist and elbow) than for the foot sensors. This result might reflect a profound reality of motor recovery in SMA after GT: weaker body segments (i.e. lower limbs) might have lower recovery potential than stronger ones (i.e. upper limbs). This observation is in line with previous observations reporting that less affected nerves (i.e. median nerve) had better recovery potential in CMAP than more affected nerves (i.e. fibular nerve) [39] and that a conserved motor function at treatment is of good prognosis [8, 9, 11–14]. However, this result has also to be taken carefully as internal consistency was proved to be lower in upper limbs sensors, the higher difference observed for upper limbs might also be due to measurement errors. The correlations between the difference between M0 and M12 for IMU-parameters versus the difference between M0

and M12 in the CHOPINTEND score were non-significant for all of the IMU-parameters tested. This might be due to the small amount of number points. Nevertheless we observed better associations for the foot sensors parameters (p -values were lower) than for upper-limb parameters (Online Fig. 2). The poorer results observed for upper limb parameters shows that responsiveness of upper limb parameters might suffer from their lower reliability.

Our results interestingly show that IMU-parameters of the lower limbs were significantly lower than those of the upper limbs and that proximal IMU-parameters were significantly lower than distal ones. This difference was more marked at M12 than at M0 confirming the previous observation that weaker body segments might have lower recovery potential than stronger ones as we observe an accentuation of the differences. This is coherent with the pathophysiology of the disease and the clinical observations, because the loss of motor neurons will lead to the impossibility of motor improvement in territories with poor stock of cells, while those with better preservation after treatment will increase their function if they not only survive but also develop further with collateral sprouting and active reinnervation which may account for years.

Clinical relevance of IMU-parameters

Association between an IMU-parameters with the acquisition of unaided sitting was as good as those of motor scores and CMAPs. We hypothesize that IMU-parameters might be able to reflect patient-centered performances and could be useful as clinical trial outcome measures. Interestingly, association of IMU results with motor milestones (acquisition of 30 s unaided sitting) was stronger for sensors placed on body parts with the most severe motor deficit in SMA (elbows and feet). This association was the strongest for the elbow sensors (but no knee sensors were used so no proximal lower limbs were explored). This might be due to the fact that proximal sensors better reflect axial tonus. As a consequence of our results, it seems important for future accelerometric studies in SMA infants to integrate proximal and lower limb sensors, even if those locations do not show the highest amplitudes and are not the more commonly used in literature [24].

Of note, the measurement on the elbows was done only at the third acquisition of the protocol i.e. at the end of a 25-min test that can create muscular fatigability in severe SMA infants. We hypothesize that measuring a parameter in a state of muscular fatigue might increase the accelerometric parameter's relevance to show the real muscle strength of an SMA infant.

Accelerometric norms for IMU-parameters

Accelerometric studies concerning infants are relatively scarce. A review in 2020 on physical activity as measured by accelerometry listed only 5 five studies concerning children less than 12 months of age (43). Normative values for that age-range are rare. Prioireschi et al. 2017 [42] reports physical activity measured by IMU in a sample of infants from South Africa but the comparison with our study is hard to perform as measuring protocol, IMU-parameters and clinical condition of children differ. Reported values for physical activity evaluated by counts per minute vary greatly in that age range from 144 [44] to 1758 [45] counts per minute for sensors placed on the ankles and 1758 [45] to 2580 [46] counts per minute for sensors placed on the wrist. Our results show higher extreme values (for the wrist sensors for the 104 measurements min 15 max 25,283 counts per minute mean 10,013). This can be explained by our protocol that measures activity only during short phases of intense motor activity. To enhance comparability of our study with others we used a published open-source Python package to compute our parameter [35]. Finally, we also report $||A||_{95}$, a parameter that we show very correlated with counts per minute which with a simple computation process. We insist of the importance of showing raw data in publications and data processing steps as precisely as possible.

Study's limitations

Our study has several limitations. First, though the IMU-dataset presented here is remarkable by the specificity of the patients measured, the number of patients and the long duration of the follow-up, we report several missing data due to the time needed to implement the measurement protocol after GT start in France (patients 1 to 4 were included after GT infusion) and because some patient living far away from the follow-up center had part of their follow-up visits in a local follow-up center in which the IMU protocol was not implemented. This might harm the validity analysis and the power of our study.

Finally, our IMU-parameters were computed on a short movement task. Authors have recommended a minimum of 72 h wear-time for reliable IMU-parameters computation in uncontrolled conditions [45]. This might increase importantly the variability of the IMU-parameters presented here [47]. One of the objectives of this study was to prepare longer ambulatory IMU-measurements which might have an even better clinical relevance for the follow-up of SMA patients. The problem of caregiver's parasite movements in this population will always be present [34]. An alternative way forward might be to keep

the current protocol and try that parents can perform it at home several time within a day/week. The protocol should also be adapted to the patient's developmental keystone and include sitting and grasping tasks for the patients who acquired independent sitting.

Conclusion

Altogether, the present study validates the use of IMUs to monitor motor recovery in severe SMA patients after an innovative therapy (GT). The IMU-parameters $\|A\|_{95}$ and $\|A\|_{CPM}$ have shown to be internally consistent, concurrently valid, responsive and associated with patient centered endpoints. IMU technique is not attempting to replace current follow-up procedures, but the present work shows that IMU technique is consistent with the existing scores and provides a certain degree of objectivity that enriches the usual individual follow-up. We hypothesize that longer whole-day measurement might diminish parameter variability and enhance sensitivity of this promising technique and will make them complementary to clinical scales to detect slight motor changes to be used as endpoints in clinical trials as it is the case for stride length 95th centile in Duchene disease. Such measurements could also play a key role in deciding on a new treatment line or in monitoring rehabilitation progress. We believe that the results presented here will be of major interest for these future developments [47].

Abbreviations

IMU	Inertial measurement unit
SMA	Spinal muscular atrophy
$\ A\ _{95}$	Norm acceleration 95th centile
$\ A\ _{CPM}$	Mean counts per minute computed on the norm acceleration signal
CMAP	Compound muscle action potential
ICC	Interclass correlation coefficient
AUC	Area under the curve
ROC	Receiver operating characteristic
TC/HC	Thoracic/head circumference ratio
CHOPINTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
HINE-2	Hammersmith Infant Neurological Examination Section
Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12984-024-01477-9>.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3. Online Fig. 1: histogram representing the repartition of the 104 IMU-measurements as a function **A/** daytime, **B/** duration since last sleep and **C/** duration since last meal.

Supplementary Material 4. Online Fig. 2: Difference between the M12 visit (12 months follow-up) and the M0 visit (baseline) for $\|A\|_{95}$ (3 top plots) computed on the wrist-sensors on acquisition 1 (left plot), on the foot-sensors on acquisition 1 (middle plot), on the elbow-sensors on acquisition 3 (right plot) and for $\|A\|_{CPM}$ (3 bottom plots) computed

on the wrist-sensors on acquisition 1 (left plot), on the foot-sensors on acquisition 1 (middle plot), on the elbow-sensors on acquisition 3 (right plot) as a function of the difference between the M12 visit and the M0 visit for the CHOPINTEND score. Fourteen patient had available data for CHOPINTEND and IMU-parameters at M0 and M12 and are shown on the plots. $\|A\|_{95}$ —Norm acceleration 95th centile. $\|A\|_{CPM}$ —Mean counts per minute computed on the norm acceleration.

Supplementary Material 5. Online Fig. 3: **A/** ROC curves for 5 selected representative variables with highest AUC values evaluating the association with 30 s unaided sitting acquisition at the time of the variable evaluation. **B/** AUC values for the association between parameters and the acquisition of 30 s unaided sitting at the given measure. Parameter with a star (*) are the one with the best AUC that were selected to be plotted on the left ROC curves. All 104 IMU-measurements were included in this analysis. IMU—Inertial Measurement Unit. SMA—Spinal Muscular Atrophy. $\|A\|_{95}$ —Norm acceleration 95th centile. $\|A\|_{CPM}$ —Mean counts per minute computed on the norm acceleration signal. CMAP—compound muscle action potential. AUC—area under the curve. ROC—receiver operating characteristic.

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Author contributions

RB, BT, LO, DR, PPV, NV and DR conceptualized the study. RB, CB, ED, VLG, AH, CG and ID participated in the clinical follow-up of the patients and contributed to the data collection. RB, BT, MC and LO performed the formal data analysis. RB, BT and MC wrote the original draft. SB, SQR and ID reviewed and wrote the final version of the manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials

In order to protect patients' privacy under the French regulation (CNIL—Commission nationale de l'informatique et des libertés), the dataset supporting the conclusions of this research is available upon reasonable request to the corresponding author (RB).

Declarations

Ethics approval and consent to participate

This study was registered on clinical trial (NCT04833348). The study protocol was approved by a national ethical review boards (Comité de Protection des Personnes [Ref protocol CNRIPH: 20.12.29.48438 – IMUSMA study]) and study procedures were conducted according to the principles outlined in the Declaration of Helsinki. All parents or guardians provided written informed consent after thorough explanations of the study goals and procedures were given.

Consent for publication

All the authors provided their consent for publication of the present version of the manuscript.

Competing interests

The authors declare no competing interests.

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