Gross Motor function in pediatric onset *TUBB4A*-related Leukodystrophy: GMFM-88 performance and validation of GMFC-MLD in *TUBB4A*

Francesco Gavazzi[1]*, MD, PhD, Virali Patel[1]*, BS, Brittany Charsar[1]*, MD, PhD, Allan Glanzman[2], PT, Jacqueline Erler[1], BA, Anjana Sevagamoorthy[1], MD, MPH, Emma McKenzie[2], PT, Tracy Kornafel[2], PT, Elizabeth Ballance[2], PT, Samuel R.Pierce[2], PT, PhD, Michelle Teng[3], PhD, Brielle Formanowski[4], MS, Sarah Woidill[1], MS, Justine Shults[3], PhD, Evangeline Wassmer[5], MD, Davide Tonduti[6,7], MD, PhD, Francesca Magrinelli[8], MD, PhD, Geneviève Bernard[9,10,11] MD, MSc, FRCPc, MD, Marjo Van Der Knaap[12,13], MD, PhD, Nicole Wolf[12], MD, PhD, Laura Adang[1,14], MD, PhD, Adeline Vanderver[1,14], MD

*shared first authorship

[1]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[2]Department of Physical Therapy, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[3]Synaptixbio Ltd, Fermi Avenue, Harwell, Oxfordshire OX11 0QX
[4] Division of Neonatology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA
[5] Neurology Department , Birmingham Children's Hospital, Institute of Health and Neurodevelopment, Aston University, Birmingham, United Kingdom
[6] Unit of Pediatric Neurology, C.O.A.L.A (Center for Diagnosis and Treatment of Leukodystrophies), V. Buzzi Children's Hospital, Milan, Italy.
[7] Department of Biomedical and Clinical Sciences, L. Sacco University Hospital, Università degli Studi di Milano, Milan, Italy.
[8] Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom
[9] Departments of Neurology and Neurosurgery, Pediatrics and Human Genetics, McGill University, Montreal, Quebec, Canada
[10] Department Specialized Medicine, Division of Medical Genetics, McGill University Health Centre, Montreal, Quebec, Canada
[11] Child Health and Human Development Program, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada
[12] Department of Child Neurology, Amsterdam Leukodystrophy Center, Emma Children's Hospital, Amsterdam University Medical Centers, and Amsterdam Neuroscience, Cellular & Molecular Mechanisms, Vrije Universiteit, Amsterdam, The Netherlands
[13] Department of Integrative Neurophysiology, Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam, The Netherlands
[14] Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Corresponding author:
Francesco Gavazzi, MD, PhD
Email: gavazzif@chop.edu

Key words:
TUBB4A
GMFM-88
Leukodystrophy
GMFC-MLD
Gross Motor

Conflicts of interest:

AV receives grant and in-kind support for research from Eli Lilly, Gilead, Takeda, Illumina, Biogen, Homology, Ionis, Passage Bio, Orchard Therapeutics. AV serves on the scientific advisory boards of the European Leukodystrophy Association and the United Leukodystrophy Foundation, as well as in an unpaid capacity for Takeda, Ionis, Biogen and Illumina.

LAA is a consultant for Takeda, Biogen, and Orchard Therapeutics.

GB is/was a consultant for Passage Bio Inc (2020-2022) and Ionis (2019). She is/was a site investigator for the Alexander's disease trial of Ionis (2021-now), Metachromatic leukodystrophy of Shire/Takeda (2020-2021), Krabbe and GM1 gene therapy trials of Passage Bio (2021-now), Passage Bio GM1 natural history study (2021-now) and Adrenoleukodystrophy/Hematopoietic stem cell transplantation natural history study of Bluebird Bio (2019), a site sub-investigator for the MPS II gene therapy trial of Regenxbio (2021-now) and the MPS II clinical trial of Denali (2022-now). She has received an unrestricted educational grant from Takeda (2021-2022). She serves on the scientific advisory board of the Pelizaeus-Merzbacher Foundation, the Yaya Foundation Scientific and Clinical Advisory Council and is the Chair of the Medical and Scientific Advisory Board of the United Leukodystrophy Foundation. She is a member of the Vanishing White Matter Consortium, the H-ABC Clinical Advisory Board and the Chair of the POLR3-related (4H) Leukodystrophy Consortium. She is on the editorial boards of Neurology Genetics, Frontiers in Neurology – Neurogenetics, and Journal of Medical Genetics.

Funding:

AV, LA, and FG were supported by U54TR002823 from the NIH, NINDS and NCATS.

LAA supported by the NIH under Award Number K23NS114113.

GB has received a Clinical Research Scholar Junior 1 award from the Fonds de Recherche du Quebec – Santé (FRQS) (2012-2016), New Investigator Salary Award from the Canadian Institutes of Health Research (2017-2022) and Senior Clinical Research Scholar award from the FRQS (2022-2025).

FM is supported by the Edmond J. Safra Foundation.

ABSTRACT

TUBB4A pathogenic variants are associated with a spectrum of neurologic impairments including movement disorders and leukodystrophy. With the development of targeted therapies, there is an urgent unmet need for validated tools to measure mobility impairment.

Our aim is to explore gross motor function in a pediatric-onset *TUBB4A*-related leukodystrophy cohort with existing gross motor outcome tools.

Gross Motor Function Measure-88 (GMFM-88), Gross Motor Function Classification System (GMFCS-ER), and Gross Motor Function Classification-Metachromatic Leukodystrophy (GMFC-MLD) were selected through face validity. Subjects with a confirmed clinical and molecular diagnosis of *TUBB4A*-related leukodystrophy were enrolled. Participants' sex, age, genotype, and age at disease onset were collected, together with GMFM-88 and concurrent GMFCS-ER and GMFC-MLD. Performances on each measure were compared. GMFM-88 floor effect was defined as total score below 20%.

A total of 35 subjects participated. Median performance by GMFM-88 was 16.24% (range 0–97.31), with 42.9% (n=15) of individuals performing above the floor. GMFM-88 Dimension A (Lying and Rolling) was the best performing dimension in the GMFM-88 (N=29 above the floor). All levels of the Classification Scales were represented, with the exception of the GMFC-MLD level '0.' Evaluation by GMFM-88 was strongly correlated with the Classification Scales (Spearman Correlations: GMFCS-ER:GMFM-88 r=0.90; GMFC-MLD:GMFM-88 r=0.88; GMFCS-ER:GMFC-MLD: r=0.92).

Despite overall observation of a floor effect, the GMFM-88 is able to accurately capture the performance of individuals with attenuated phenotypes. GMFM-88 Dimension A shows no floor effect. GMFC-MLD shows a strong correlation with GMFCS-ER and GMFM-88, supporting its use as an age-independent functional score in *TUBB4A*-related leukodystrophy.

INTRODUCTION

TUBB4A pathogenic variants result in a spectrum of neurologic disorders, including Hypomyelination with Atrophy of the Basal ganglia and Cerebellum (H-ABC), isolated hypomyelination, and whispering dysphonia (formerly DYT4 dystonia). Pediatric onset cases are characterized by leukoencephalopathy (*TUBB4A*-related leukodystrophy) (1-5). The developmental phenotypes of a pediatric population carrying heterozygous disease-causing *TUBB4A* variants were recently characterized, demonstrating different developmental trajectories based on genotype and age at disease onset (6). Gross motor skills are prominently affected across the spectrum of *TUBB4A*-associated disorders, particularly in the pediatric population, with many children never gaining the ability to walk, or losing ambulation before the end of the first decade (6).

Despite the prevalence of motor impairment in pediatric-onset *TUBB4A*-related leukodystrophy, there are currently no studies on standardized measures to characterize the motor phenotype of affected individuals. The Gross Motor Function Measure-88 (GMFM-88) is an assessment that was originally designed to measure changes in gross motor function in a pediatric population with cerebral palsy (CP) (7) and evaluation of the efficacy of interventions in CP (8). This tool has since been widely applied across a range of medical conditions such as characterization of functional abilities (9). The performance of GMFM-88 has been shown to strongly correlate with that of the Gross Motor Classification System (GMFCS-ER) scale, which is an age-dependent ordinal measure of gross motor function among children with CP (10). While the GMFM-88 and GMFCS-ER have been validated for use in conditions with static gross motor functions such as the CP, its use in a population with changing gross motor function in the form of deterioration over time

remains to be validated. Additionally, a modified version of the GMFCS-ER, called the GMFC-MLD an age-independent tool, has been adapted and validated for use in children with metachromatic leukodystrophy (11). The GMFC-MLD can capture changes in gross motor function in the context of clinical trials (12), and has been shown to have high inter-rater reliability with application in children who are 18 months or older (11). However, this scale remains to be validated for use in *TUBB4A*-related leukodystrophies.

The purpose of this study is to describe the gross motor functions in pediatric *TUBB4A*-related leukodystrophy through the administration and validation of the GMFM-88, GMFCS-ER, and GMFC-MLD in a cohort of affected individuals.

METHODS

Patient recruitment and enrollment.

All subjects were enrolled from the Myelin Disorders Biorepository Project (MDBP), an IRB-approved protocol, at the Children's Hospital of Philadelphia. Individuals with a pediatric onset (<21 years) and a confirmed molecular and clinical diagnosis of *TUBB4A*-related leukodystrophy were included. All MDBP-enrolled subjects meeting the above criteria with functional motor assessments performed between 1/1/2017 - 5/12/2022 were included in the final analysis. For each encounter, the following information was collected: genotype, chronological age at the time of GMFM-88 administration, sex, and the age at disease onset (6). The GMFM-88 assessments were administrated by licensed physical therapists (13).

Data storage and integrity.

Study data was managed on the Research Electronic Data Capture (REDCap) database hosted at the Children's Hospital of Philadelphia (14, 15). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Motor assessment description, face validity, and administration

Outcome selection. GMFM-88, GMFCS-ER, and GMFC-MLD were selected by an international group of disease experts (MvdK, GB, AV, FG, BC), and a parent advocate (MT) through a process of face validity. The minimum rate of agreement for approval was set at 80%.

GMFM-88. The Gross Motor Function Measure-88 is a tool that evaluates the gross motor abilities of a pediatric population through the administration of 88 motor items, scored by ordinal criterion achievement, each with specific item-based criterion that fits the following high-level categories: 0- not initiated, 1- initiated, 2- partially completed, 3- successfully completed. This assessment comprises of five dimensions: (i) A- Lying and Rolling; (ii) B- Sitting; (iii) C- Crawling and Kneeling; (iv) D- Standing; (v) E- Walking, Running, and Jumping (13). The GMFM-88 raw scores for each dimension are calculated as a percentage. The total score is derived from the average of the 5-dimension scores. As the GMFM-88 floor and ceiling effects are not clearly defined in the literature, we defined the floor effect (performance in the lowest register of scores) as 20% or less of the total score, and the ceiling effect (performance in the highest register of scores) as 90% or more of the total score.

Classification System Assessments. The GMFCS-ER (16, 17) and the GMFC-MLD were used to define clinical severity. The GMFCS-ER is composed of 5-levels with 'I' representing normal

function and ‘V’ representing complete impairment, while the GMFC-MLD is composed of 7-levels, with ‘0’ representing no neurologic impairment and ‘6’ representing severe neurologic involvement, with no head control.

Outcome administration. Administration of the GMFM-88 was performed by licensed physical therapists. Thirty-four assessments were conducted in person, while one was performed remotely based on a validated methodology for its administration (18). Neurologic severity scores (GMFCS-ER, GMFC-MLD) were assigned by trained child neurologists based on retrospective review of the medical documentation from the time of administration of the GMFM-88. GMFCS-ER and GMFC-MLD scores were obtained for individuals of any age.

Inter and intra-rater reliability were computed for both GMFCS-ER and GMFC-MLD. Intra-rater reliability was assessed by having a provider re-score the medical documentation one month apart, while inter-rater reliability was evaluated through blinded dual (FG and AV) scoring of each medical encounter. The scores were assigned for 34/35 encounters (97.15%). One subject (2.85%) had no medical notes available at the time of the GMFM88 administration, therefore neurologic severity assessment could not be performed for that encounter.

Statistical Analysis

The data was summarized using counts and proportions for categorical variables and, mean, standard deviation (SD), median, range (minimum to maximum values) and interquartile range (IQR) for continuous variables. Descriptive statistics using two-sided t-test was performed with a p=value of <0.05 to determine statistical significance. Tests for correlation such as Spearman’s Rank Correlation and Pearson’s Rank Correlation were performed to compare GMFM-88 with the Classification Systems (GMFCS-ER and GMFC-MLD). A correlation range of 0.00-0.19 is considered very weak, a correlation range of 0.20-0.39 is considered weak, a correlation range of

0.40-0.59 is considered moderate, a correlation range of 0.60-0.79 is considered strong, and a correlation range of 0.80-1.00 is considered very strong. Intra-rater and inter-rater reliability were calculated using Cohen's Kappa (κ) statistics (19). All the analsysis were performed using Prism GraphPad.

RESULTS

Study population.

A total of 35 subjects participated in motor outcome assessments. Of the 35 patients, 19 were male (54.3%), and 16 were female (45.7%). At the time of the GMFM-88 administration and classification system assessment, the mean chronologic age of patients was 8.36 years (SD 5.17). Descriptive demographic information is included in **Table 1**.

Motor performance

In our pediatric *TUBB4A*-related leukodystrophy cohort, a range of gross motor performance was observed both in the total score and within each dimension of the GMFM-88 (**Figure 1**). As the difficulty associated with a motor task increased (Dimension A to E), there was an increase in the proportion of the cohort who demonstrated a floor effect. No ceiling effect was observed. (**Table 2**).

Correlations (Pearson R Coefficient) between the GMFM-88 and age at evaluation (R=-0.09, 2-tail p-value =0.59) and length of disease (R=-0.11, 2-tail p-value =0.52) were not significant; while age at disease onset (R =0.36, 2-tail p-value =0.04) showed a significant association. There was no sex-based difference in GMFM-88 total score performance (males: median 13.61, IQR 7.79; females: median 16.74, IQR 4.84)

Neurologic Severity Scales

Overall, 34/35 individuals (97.15%) had GMFCS-ER and GMFC-MLD scores derived from medical notes concurrent with the date of GMFM-88 administrations. All levels of the Neurologic Classification Systems were represented in the cohort, with the exception of the GMFC-MLD level '0.' The GMFCS-ER intra-rater reliability showed agreement in 32/34 observations (94% rate of agreement, Weighted Kappa 0.954, 95% CI 0.79-1.00); the GMFC-MLD intra-rater reliability showed agreement in 32/34 observations (94% rate of agreement, Weighted Kappa 0.97, 95% CI 0.81-1.00).

The GMFCS-ER had an inter-rater reliability agreement in 32/34 observations (94% rate of agreement, Weighted Kappa 0.955, 95% CI 0.78-1.00); while the GMFC-MLD had an inter-rater reliability agreement in 33/34 observations (97% rate of agreement, Weighted Kappa 0.99, 95% CI 0.88-1.00).

Correlation of motor outcomes

GMFM-88 total percentage and dimension scores demonstrated a strong inverse correlation with GMFCS-ER (Spearman's Rank Correlation Coefficient -0.90, 2-tail p-value <.0001) and GMFC-MLD (Spearman's Rank Correlation Coefficient -0.89, 2-tail p-value <.0001) (**Figure 2A, 2B, Table 3**). Similarly, the correlation between GMFCS-ER and GMFC-MLD was very strong (Spearman's Rank Correlation Coefficient 0.96, 2-tail p-value <.0001), **Figure 2C**.

DISCUSSION

The identification of functional motor outcomes in a rare disease pediatric population presents unique challenges. As previously described in the literature, the description of motor function might be challenging in individuals with motor decline in the pediatric age group, since

standardized tools are not always able to capture changes over time due to floor effects (19). Conversely, in a population with heterogeneous developmental trajectories, it is also necessary to identify tools that can capture the entire spectrum of function in disorders with heterogeneous phenotypes. Previous work has shown that subjects with disease-causing *TUBB4A* variant can have variable developmental trajectories as well as a variable rate of motor skill loss (6), suggesting the need for tools with the ability to discriminate across a broad range of functional levels, particularly those at the lower range of developmental skills.

The GMFM-88 is a tool originally developed to evaluate change over time in children with CP, a non-progressive condition. Due to its relatively limited item bank and weighted subdimension averaging, this assessment particularly targets individuals with moderate to high motor function. In a population characterized by profound motor limitations, floor effects may limit the use of the GMFM-88 in its entirety. While we observed a floor effect in more than half of the population using the total score (Figure 1), Dimension A (which represents floor-based skills) was able to differentiate gross motor performance within the more severely affected individuals, without a floor effect. Thus, analysis of dimension-based performance may better represent the functional skills of individuals with a more severe disease phenotype (associated with a lack of acquisition of motor milestones, or a progressive loss of previously acquired motor competencies), while the overall GMFM-88 appears to be of appropriate use in individuals with attenuated phenotypes, as no floor or ceiling effect was observed.

While an earlier age at disease onset is weakly correlated with the GMFM-88 performance, chronologic age, and disease duration at the time of assessment did not show a clear connection with the motor performance. This might be due to the fact that, while an earlier disease onset is associated with a lower probability of acquisition of developmental milestones, it is known that at

later stages of life, children with later disease onset can lose motor abilities previously acquired (6). The cohort of this study is comprised of individuals with a significant length of disease, with the potential loss of motor abilities already acquired. Further studies will be needed to determine the utility of the GMFM-88 as a tool for potential evaluation of the pediatric *TUBB4A*-related leukodystrophy closer to a child's disease onset, as well as to show longitudinal motor change.

In this study, the performance of the GMFCS-ER and the GMFC-MLD were compared to the GMFM-88 by both total score and individual dimensions. Inter-rater and intra-rater reliability showed an appropriate level of agreement between blinded scores, and both tools showed a strong correlation with each other and with the GMFM-88 (total score and individual dimensions) in *TUBB4A*-related leukodystrophy. Additionally, the application of these functional scales to perform assessments retrospectively using existing medical records can supplement our understanding of neurologic trajectories (11, 20). One major challenge of the GMFCS-ER is the inability to compare performance across age brackets, thus limiting its use when applied longitudinally, as it was originally created to evaluate a population with static functional abilities in the context of CP. Conversely, the GMFC-MLD can be used to assess function in all individuals across time. Due to its strong correlation with the GMFM-88 performance, and its intrinsic age-independent scoring methodology, we suggest the use of the GMFC-MLD scale in individuals with pediatric *TUBB4A*-related leukodystrophy.

Our study was limited by the rarity of *TUBB4A*-related leukodystrophy and the small cohort of individuals enrolled. This study selected a pediatric population with leukodystrophy, with potential ascertainment bias towards younger, more severely affected individuals. Finally, the selected measures restricted this study to a pediatric onset cohort, although *TUBB4A*-related leukodystrophy can manifest across the lifespan. Additionally, enrollment was biased to

encompass those able to travel for evaluation. Finally, all measures were performed at a single site. Additionally, this cohort lacked sufficient racial diversity, which will need to be addressed by specific diagnostic strategies to improve access to available genetic testing in underrepresented minorities. Future studies should be multicentric and include approaches to improve equity, which can include the improved availability of remote administration of measures (18) for those individuals unable to travel. Despite these limitations, our cohort represents a global pediatric population, and we anticipate that our findings will be generalizable.

In summary, children affected by *TUBB4A*-related leukodystrophy demonstrate a range of gross motor function. This was captured using the prospective measure GMFM-88 in combination with two classification scales: GMFCS-ER (an age-dependent classification system) and the GMFC-MLD (an age-independent score). The GMFM-88 is able to describe the gross motor function of individuals with an attenuated phenotype when considered in its entirety. GMFM-88 dimensions exploring lying and rolling (e.g. Dimension A) show promising application in the description of individuals with more severe disease manifestations. The GMFCS-ER and the GMFC-MLD both were able to classify across the heterogeneous abilities of this population.

There was strong agreement between all motor tools in the *TUBB4A*-related childhood-onset leukodystrophy population, and both functional scores have an extremely high rate of agreement when independently scored by two pediatric neurologists. We anticipate that the longitudinal application of these tools will enable the definition of clinically coherent motor phenotypes in this population and the evaluation of future therapeutic options.

Figure Legends

Figure 1. Performance of the study cohort on the GMFM-88. 20/35 subjects (57.1% of the cohort) presented GMFM-88 total score below 20. Each individual is represented by a single dot.

Figure 2: Performance on the GMFM-88 is strongly inversely correlated with GMFCS-ER and GMFC-MLD scores while GMFCS-ER and GMFC-NLD scores are strongly correlated. **A.** GMFM-88 and GMFCS-ER present a very strong inverse correlation (Spearman's Rank Correlation Coefficient -0.90, 2-tail p-value <.0001. **B.** GMFM-88 and GMFC-MLD present a very strong inverse correlation, comparable with what observed with GMFCS-ER (Spearman's Rank Correlation Coefficient -0.89, 2-tail p-value <.0001). **C**.Correlation between gross motor function scales: GMFCS-ER and GMFC-MLD. Scores were assigned retrospectively using medical records current with research assessments. Performance on the two classification systems were strongly correlated (Spearman's Rank Correlation Coefficient 0.96, 2-tail p-value <.0001).

REFERENCES

1. van der Knaap MS, Naidu S, Pouwels PJ, Bonavita S, van Coster R, Lagae L, et al. New syndrome characterized by hypomyelination with atrophy of the basal ganglia and cerebellum. AJNR Am J Neuroradiol. 2002;23(9):1466-74.
2. Simons C, Wolf NI, McNeil N, Caldovic L, Devaney JM, Takanohashi A, et al. A de novo mutation in the beta-tubulin gene TUBB4A results in the leukoencephalopathy hypomyelination with atrophy of the basal ganglia and cerebellum. Am J Hum Genet. 2013;92(5):767-73.
3. Curiel J, Rodriguez Bey G, Takanohashi A, Bugiani M, Fu X, Wolf NI, et al. TUBB4A mutations result in specific neuronal and oligodendrocytic defects that closely match clinically distinct phenotypes. Hum Mol Genet. 2017;26(22):4506-18.
4. Duncan ID, Bugiani M, Radcliff AB, Moran JJ, Lopez-Anido C, Duong P, et al. A mutation in the Tubb4a gene leads to microtubule accumulation with hypomyelination and demyelination. Ann Neurol. 2017;81(5):690-702.
5. Lohmann K, Wilcox RA, Winkler S, Ramirez A, Rakovic A, Park JS, et al. Whispering dysphonia (DYT4 dystonia) is caused by a mutation in the TUBB4 gene. Ann Neurol. 2013;73(4):537-45.
6. Gavazzi F, Charsar BA, Williams C, Shults J, Alves CA, Adang L, et al. Acquisition of Developmental Milestones in Hypomyelination With Atrophy of the Basal Ganglia and Cerebellum and Other TUBB4A-Related Leukoencephalopathy. J Child Neurol. 2021:883073821000977.
7. Russell DJ, Avery LM, Rosenbaum PL, Raina PS, Walter SD, Palisano RJ. Improved scaling of the gross motor function measure for children with cerebral palsy: evidence of reliability and validity. Physical therapy. 2000;80(9):873-85.
8. Gillespie CS, George AM, Hall B, Toh S, Islim AI, Hennigan D, et al. The effect of GMFCS level, age, sex, and dystonia on multi-dimensional outcomes after selective dorsal rhizotomy: prospective observational study. Childs Nerv Syst. 2021;37(5):1729-40.
9. Adang L, Gavazzi F, De Simone M, Fazzi E, Galli J, Koh J, et al. Developmental Outcomes of Aicardi Goutières Syndrome. J Child Neurol. 2020;35(1):7-16.
10. Palisano RJ, Hanna SE, Rosenbaum PL, Russell DJ, Walter SD, Wood EP, et al. Validation of a model of gross motor function for children with cerebral palsy. Physical therapy. 2000;80(10):974-85.
11. Kehrer C, Blumenstock G, Gieselmann V, Krageloh-Mann I. The natural course of gross motor deterioration in metachromatic leukodystrophy. Dev Med Child Neurol. 2011;53(9):850-5.
12. Beschle J, Döring M, Kehrer C, Raabe C, Bayha U, Strölin M, et al. Early clinical course after hematopoietic stem cell transplantation in children with juvenile metachromatic leukodystrophy. Mol Cell Pediatr. 2020;7(1):12.
13. Russell DJ, Rosenbaum PL, Wright M, Avery LM. Gross Motor Function Measure (GMFM-66 and GMFM-88) User's Manual. 2nd ed: Wiley; 2013.
14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.

15. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
16. Palisano RJ, Avery L, Gorter JW, Galuppi B, McCoy SW. Stability of the Gross Motor Function Classification System, Manual Ability Classification System, and Communication Function Classification System. Dev Med Child Neurol. 2018;60(10):1026-32.
17. Wood E, Rosenbaum P. The gross motor function classification system for cerebral palsy: a study of reliability and stability over time. Dev Med Child Neurol. 2000;42(5):292-6.
18. Gavazzi F, Adang L, Waldman A, Jan AK, Liu G, Lorch SA, et al. Reliability of the Telemedicine Application of the Gross Motor Function Measure-88 in Patients With Leukodystrophy. Pediatr Neurol. 2021;125:34-9.
19. Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. Anesth Analg. 2018;126(5):1763-1768.
20. Adang LA, Gavazzi F, Jawad AF, Cusack SV, Kopin K, Peer K, et al. Development of a neurologic severity scale for Aicardi Goutières Syndrome. Mol Genet Metab. 2020;130(2):153-60.