VP.21

Baseline nutrition investigation in a Chinese cohort of pediatric patients with spinal muscular atrophy

S. Li, S. Liu, Y. Wu, Y. Liu, D. Tan, Y. Fan, C. Wei, H. Xiong
Peking University First Hospital, Beijing, China

Nutritional problem is frequently observed in pediatric patients with spinal muscular atrophy (SMA). In this study, we aimed to investigate the nutritional status in Chinese patients with SMA. Clinical data including the body weight, length, body mass index (BMI) and the levels of serum 25-hydroxy Vitamin D (25-OHD) of SMA patients from January 2022 to March 2022 were collected and analyzed. We used the Z-score (standard deviation) to analyze the BMI. The levels of serum 25-OHD were graded as follows: 75-250nmol/L for normal, 50-75nmol/L for insufficiency, less than 50nmol/L for deficiency. A total of 41 pediatric patients with SMA (8 case of SMA type 1, 20 case of SMA type 2, and 13 case of SMA type 3) with ages ranging from 12 months old to 15 years old were included. Nearly 25% of SMA patients showed nutritional problems. Malnutrition was observed in 50% (4/8) of SMA 1 patients, 10% (2/20) of SMA 2 patients and 15.3% (2/13) of SMA 3 patients; overweight was found in 5% (1/20) of SMA 2 patients and 15.3% (2/13) of SMA 3 patients. The 25-OHD deficiency was observed in 25% (2/8) of SMA 1 patients, 30% (6/20) of SMA 2 patients, and 38.5% (5/13) of SMA 3 patients. The 25-OHD insufficiency was found in 25% (5/20) of SMA 2 patients and 23.1% (3/13) of SMA 3 patients. This study showed that malnutrition was common in SMA 1 patients, 25-OHD deficiency or insufficiency was frequent among the three types of SMA. Disease management with adjusting the diet structure and more outdoor activities would improve the nutritional problems. In this study, we demonstrated the baseline nutrition situations in a Chinese cohort of pediatric patients with SMA.

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DMD – BIOMARKERS/OUTCOME MEASURES

FP.12

Application for primary endpoint qualification of the 95th centile of stride velocity (SV95C) in Duchenne muscular dystrophy

M. Annoussamy [1], D. Eggenspieler [1], A. Seferian [2], E. Mercuri [3], V. Straub [4], F. Muntoni [5], M. Scoto [5], M. Poleur [6], A. Daron [6], N. Butoianu [7], A. Mirea [8], N. Goemans [9], S. Previtali [10], M. Tulinius [11], A. Nascimento [12], P. Heydemann [13], M. Panzara [14], T. Singh [15], P. Strijbos [16], L. Servais [17]
[1] *SYSNAV, Vernon, France;* [2] *I-Motion Institute, Paris, France;* [3] *Universita' Cattolica del Sacro Cuore Roma, Roma, Italy;* [4] *John Walton Muscular Dystrophy Research Centre, Newcastle upon-Tyne, UK;* [5] *Great Ormond Street Hospital, London, UK;* [6] *University Hospital La Citadelle, Liège, Belgium;* [7] *Prof. Dr. Alexandru Obregia Clinical Hospital, Bucharest, Romania;* [8] *National Univ. Centre for Children Neurorehabilita, Bucharest, Romania;* [9] *UZ Leuven, Leuven, Belgium;* [10] *IRCCS Ospedale San Raffaele, Milano, Italy;* [11] *Drottning Silvias Barn Och Ungdomssjukhus, Göteborg, Sweden;* [12] *Hospital Sant Joan de Deu, Barcelona, Spain;* [13] *Rush University Medical Center, Chicago, USA;* [14] *Wave Life Sciences Ltd, Cambridge, USA;* [15] *Sarepta Therapeutics, Inc., Cambridge, USA;* [16] *F. Hoffmann-La Roche, Basel, Switzerland;* [17] *University of Oxford, Oxford, UK*

Qualification of a clinical outcome assessment (COA) by a health authority (HA) is the conclusion of a thorough process. Once qualified, the COA can be included in drug development pathways without needing a HA to reconsider and reconfirm its suitability and becomes a trusted tool for the community. In 2019, the 95th centile of stride velocity (SV95C) became the first wearable-derived digital COA qualified by the European Medicines Agency for use as secondary endpoint in pivotal trials in Duchenne muscular dystrophy (DMD). SV95C represents the speed of the fastest strides over a 50 to 180 hours recording period. When measured at the ankle with a suitable wearable device, it is a passively captured real-world digital COA that reflects the maximal ambulatory performance during normal daily living. The application based on data from 45 ambulant DMD patients older than 5 years contained assessments of reliability, external validity, minimal clinically important change, and responsiveness of the measure. Application for qualification as primary endpoint was submitted on February 24th, 2022. SV95C properties were studied in 125 ambulant DMD patients, aged 5 to 14, from 6 different natural history studies and clinical trials and from patients attending routine clinic appointments. In addition to confirming reliability, clinical relevance, and ability to detect decline overtime even in 5 to 7 years DMD patients, the application compared the statistical power with existing COA and assessed the ability to detect positive change. Content validity of SV95C was assessed through online surveys conducted in 92 patients or caregivers and 52 healthcare professionals trained to the wearable device used to record SV95C. Survey results confirmed the relevance of ambulation, walking speed and SV95C in DMD population. It also revealed that patients and caregivers recognize and value the use of a real-life based wearable device and would be willing to use such devices in clinical trials.

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FP.13

Diffusion-tensor MRI captures increased diameter and size heterogeneity of skeletal muscle fibres in Becker muscular dystrophy, as verified by histology

D. Cameron [1], T. Abbassi-Daloii [1], L. Heezen [1], N. van de Velde [1], Z. Koeks [1], T. Veeger [1], M. Hooijmans [2], J. Verschuuren [1], M. van Putten [1], A. Aartsma-Rus [1], V. Raz [1], P. Spitali [1], E. Niks [1], H. Kan [1]
[1] *Leiden University Medical Centre, Leiden, Netherlands;* [2] *Amsterdam University Medical Center, Amsterdam, Netherlands*

Interventions for muscular dystrophies (MDs) seek to preserve functioning muscle tissue, prior to its replacement with fat and fibrosis—which reflect disease progression. To test such interventions, imaging biomarkers should focus on muscle inflammation, degeneration and regeneration—hallmarks of MDs that represent disease activity. One consequence of these processes is a variation in fibre size, which precedes fat replacement and can be probed using diffusion-tensor MRI (DT-MRI). Here we use advanced DT-MRI to non-invasively quantify muscle fibre size in Becker MD patients and controls and compare to histology. We scanned 13 BMD patients—age 20-59yrs—and 9 male controls—23-65yrs—on a 3T MRI system. DT-MRI was applied in the calf and fibre diameter was measured per muscle via the random permeable barrier model. For comparison, tibialis anterior biopsies from 38 BMD patients were sectioned and stained with laminin, along with samples from 15 male controls. Laminin images were segmented to give measures of fibre size. Between individuals, DT-MRI fibre diameters were larger and more variable in BMD than in controls: mean (SD) = 68(31) vs 59(19)μm, respectively, p=0.03. Further, DT-MRI fibre size differences were observed between muscles in both groups ($p \leq 0.002$). DT-MRI fibre size agreed with laminin fibre size: measured as mean (SD) = 72.5(7.9) in BMD vs 63.2(6.9)μm in controls, p=0.006 . Per sample, BMD patients also showed more variation in laminin fibre size than controls: mean variance (SD) = 34.2(7.9) vs 21.4(6.9)μm, $p \ll 0.001$. Our study is the first to explore DT-MRI fibre size measures in Becker muscular dystrophy. We show larger, more variable muscle fibre diameters in BMD versus controls, in agreement with histology data from the same cohort. DT-MRI offers a non-invasive alternative to muscle biopsies for characterising and monitoring muscle changes, and could represent a valuable biomarker for future clinical trials in Becker and Duchenne muscular dystrophies.

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FP.14

Dystrophin and satellite cell quantification in Duchenne and Becker muscular dystrophies

S. Nicolau, T. Vetter, E. Frair, A. Bradley, K. Flanigan
Nationwide Children's Hospital, Columbus, USA

The dystrophinopathies are a group of muscular dystrophies stemming from mutations in the *DMD* gene. We have developed a series of sensitive and reproducible dystrophin and satellite cell quantification methods in order to better define associations between dystrophin expression and disease severity, as well as the molecular mechanisms of mutations in the N-terminal region of dystrophin. In a pilot study of 18 dystrophinopathy patient muscle biopsies, we employed western blot, capillary western immunoassay, and automated quantitative immunofluorescence analysis to quantify dystrophin expression and Pax7-positive satellite cells. Among 9 patients with a Duchenne muscular dystrophy phenotype, the mean dystrophin protein level by capillary western was 1.8% of normal. These biopsies displayed a mean of 6.8% immunofluorescence staining intensity of individual fibers and 26% dystrophin positive fibers (PDPF). This high PDPF reflects the use of a sensitive cutoff to improve the discriminating power of the assay at low expression levels. By contrast, patients with intermediate or Becker muscular dystrophy had 11% dystrophin expression by capillary western and 70% PDPF. Several truncating mutations in the first 4 exons of DMD were associated with milder phenotypes and significantly higher dystrophin expression (16% by capillary western and 79% PDPF), in keeping with activation of an internal ribosome entry site in exon 5. There was poor overall correlation between Pax7-positive satellite cell count and dystrophin expression. Analysis of individual muscle fibers however demonstrated that fibers with one or more adjacent Pax7-positive satellite cells had a lower mean dystrophin expression, indicating concentration of satellite cells around dystrophin-deficient fibers. This study lays the groundwork for a