

knowledge on movement and muscle activity was integrated in the design of the supportive devices. A passive trunk support device was developed and evaluated with 10 healthy men and 3 boys with DMD. A significant decrease in back muscle activity was seen when flexing the trunk with the use of the device, compared to without using the device. However, the variation was relatively large especially in the boys with DMD. A robotic setup was developed to evaluate different methods to control a robotic trunk supportive device for patients who have not enough muscle force to move. Control with a joystick and a force sensor in the device at chest level showed the fastest movement times, compared to control with force sensor below the feet and electromyography signals from the legs in 10 healthy participants. Measurements with 3 boys with DMD are ongoing. Both a passive and robotic head supportive device are designed and measurements are planned for mid 2018.

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## CONGENITAL MUSCULAR DYSTROPHIES

### P.323

#### Review of the natural history of mental development in Fukuyama congenital muscular dystrophy patients, based on a written questionnaire from their families

M. Shichiji, K. Ishigaki, T. Sato, A. Yamashita, S. Nagata  
*Tokyo Women's Medical University, Tokyo, Japan*

Fukuyama congenital muscular dystrophy (FCMD) is characterized by brain malformation caused by abnormal neurocyte migration, and presents with eye manifestations. Ninety percent of FCMD patients have the homozygote insertional mutation of the founder haplotype, and show typical progression of motor functional deficits. However, many patients with a heterozygote mutation show more severe motor and mental functional deficits. Although many prior reports on FCMD patients focused on the natural history of motor development, very few have referenced mental development. We surveyed 49 families of FCMD patients, who belonged to a patient's association, using a descriptive questionnaire. We classified our questions into 4 categories: 1) motor development, 2) social skills, 3) living skills and 4) language development. Forty-nine answers were collected, the median patient age was 7 years (range: 1.3 to 36 years). Twenty-eight patients had the homozygote mutation, 11 the heterozygote, and there was no answer for the other. All motor development milestones were delayed in all patients. Even though 80% of patients achieved single word communication, verbal development reflecting when the necessity for verbal communication arose, yielded a low evaluation in the social skill category. All patients achieved the skills needed for meal consumption more easily than other living skills such as changing their clothes. Many patients never obtained independent gait, while upper limb motions varied among patients. Furthermore, these motor function level affected their mental development. Communication with the others was also found to be an important factor for encouraging mental development. This study is a rare study focusing on the details of the mental development of FCMD. This survey is anticipated to help the families of FCMD patients as they strive to stimulate the development of their children.

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### P.324

#### Clinical characteristics and long-term course of selenoprotein N1 related myopathy in a large multi-centric cohort

A. Silwal<sup>1</sup>, M. Scoto<sup>1</sup>, D. Ridout<sup>2</sup>, A. Schmidt<sup>3</sup>, A. Laverty<sup>3</sup>, M. Henriques<sup>3</sup>, L. D'Argenzio<sup>1</sup>, M. Main<sup>1</sup>, R. Mein<sup>4</sup>, A. Sarkozy<sup>1</sup>, A. Manzur<sup>1</sup>, F. Al-Ghamdi<sup>5</sup>, C. Genetti<sup>5</sup>, F. Abel<sup>3</sup>, G. Haliloglu<sup>6</sup>, D. Ardici<sup>6</sup>, H. Topaloglu<sup>6</sup>, A. Beggs<sup>5</sup>, F. Muntoni<sup>1</sup>

<sup>1</sup>Dubowitz Neuromuscular Centre, London, UK; <sup>2</sup>Great Ormond Street ICH, London, UK; <sup>3</sup>Great Ormond Street Hospital, London, UK; <sup>4</sup>Guy's Hos-

pital, London, UK; <sup>5</sup>Boston Children's Hospital, Boston, USA; <sup>6</sup>Hacettepe University, Ankara, Turkey

Selenoprotein N1 related myopathies (SEPN1-RM), including congenital muscular dystrophy with rigid spine (RSMD1), multimincore disease (MmD), desmin-related myopathy with Mallory body-like inclusions and congenital fiber-type disproportion, are autosomal-recessive disorders caused by pathogenic variants in the *SELENON* gene. They are collectively characterized by early onset muscle weakness especially of the axial muscles, respiratory insufficiency often more severe and out of proportion to skeletal weakness, spinal rigidity and scoliosis. Here we present a detailed phenotypic review of 61 patients (2-58 years) with genetically confirmed SEPN1-RM, with long-term follow-up data for 25 of them. Mean age at onset was 2.2 years, with 47/61 patients presenting before age 2 years mostly with hypotonia, poor head/neck control and developmental delay. Over a mean follow up of 4.8 years, a decline from a mean of 33 to 27 on the 40 point Hammersmith ambulant motor scale was noted in 10/19 patients (range 0.7-14.1 years), with an estimated annual change in motor ability scores of -0.55, indicative of a slow motor decline. Ten children of the total cohort (16%) lost ambulation within the first two decades of life. 45/61 patients (74%) developed scoliosis at a mean age of 10.3 years and 18 (29%) patients underwent scoliosis surgery. Weight trends, available for 21 children, showed values below 2nd centile for 10, while nasogastric feeds and/or gastrostomy was needed in 6/61 children (10%). FVC trends, available for 20 children, showed an estimated % change per year of -2.04 (SE 0.46; p value < 0.001). Nocturnal ventilator support was required in 50/61 (82%) at a mean age of 13 years. This study expands our knowledge of the clinical phenotype and long-term course of SEPN1-RM, and highlights the importance of robust and consistent multi-disciplinary assessment and management to improving outcomes in these children.

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### P.325

#### Severe loss of semimembranosus muscle bulk is an early phenomenon in SEPN1-related muscle disorders: toward early recognition of early-onset muscle disorders by imaging

F. Munell<sup>1</sup>, D. Gomez-Andres<sup>1</sup>, A. Sanchez-Montañez<sup>1</sup>, L. Costa Comellas<sup>1</sup>, S. Ferrer-Aparicio<sup>2</sup>, P. Romero<sup>2</sup>, S. Quijano-Roy<sup>3</sup>, M. Olivé<sup>4</sup>

<sup>1</sup>Vall Hebron University Hospital, Barcelona, Spain; <sup>2</sup>Vall Hebron Research Institute, Barcelona, Spain; <sup>3</sup>Hôpital Raymond Poincaré, Garches, France; <sup>4</sup>IDIBELL-Hospital Bellvitge, Barcelona, Spain

Marked decrease in semimembranosus muscle bulk has been pointed out as the major hallmark in muscle imaging in SEPN1-related muscle disorders. However, it remained unclear whether this decrease in semimembranosus muscle bulk was present early in muscle development or it was a progressive phenomenon that mainly occurred during childhood. We present two new SEPN1-related muscle disorders and their imaging phenotype. Patient 1: a female patient was evaluated due to repetitive respiratory infections, hypotonia and gross motor delay. She was firstly evaluated in our center at 29 months. Lower limb MRI at 25 months show absence of semimembranosus muscle bulk and mild infiltration in sartorius and soleus. By exome sequencing, compound homozygous missense mutations in *SEPN1* (c.1379C>T; p.Ser460Phe) were found. Progressive restrictive respiratory disorder occurred with significant fatigability. At 6 year of age, she suffered a sudden death while sleeping. Patient 2: eleven month-old male patient was studied by progressive generalized hypotonia. Predominant neck extensor weakness was detected. Absence of semimembranosus muscle bulk was found at whole body muscle MRI. In addition, infiltration in gluteus maximum, sartorius, soleus and lumbar erector spine was detected. The imaging findings leads to *SEPN1* sequencing, which demonstrate compound heterozygous mutations (splice-site mutation c.404-1G>A and nonsense mutation c.1189C>T, p. Gln397\*). The early absence or significant loss of semimembranosus muscle bulk is diagnostic hallmark that is useful for early diagnosis of SEPN1-related muscle disorders. The specific, early involvement of semimembra-

nus could indicate a differential expression or role of SEPNI in this muscle.

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### P.326

#### Minimal clinically important difference for the Motor Function Measure in patients with congenital muscular dystrophy and congenital myopathy

L. Le Goff<sup>1</sup>, M. Fink<sup>2</sup>, G. Norato<sup>2</sup>, P. Rippert<sup>1</sup>, K. Meilleur<sup>2</sup>, A.R. Foley<sup>2</sup>, M. Jain<sup>2</sup>, M. Waite<sup>2</sup>, S. Donkervoort<sup>2</sup>, C. Bönnemann<sup>2</sup>, C. Vuillerot<sup>1</sup>

<sup>1</sup>Hospices Civils de Lyon, Bron, France; <sup>2</sup>National Institutes of Health, Bethesda, USA

To determine the minimal clinically important difference (MCID) for the motor function measure (MFM-32) in congenital muscular dystrophy and congenital myopathy patient an observational, retrospective, multicentric study was conducted on 85 congenital muscular dystrophy or congenital myopathy patients, aged 5 to 22 years at the national institute of neurological disorders and stroke of the national institutes of health and 2 French departments of paediatric physical medicine and rehabilitation. Data were collected if at least 2 MFMs were performed (MFM1 and MFM2) within 8 to 36 months of each other and if during MFM2 parents or patients were asked to provide their perceived change in functional status or strength since MFM1. Patients were divided in 3 groups according to their overall assessment of disease evolution: deterioration, stability or improvement. Absolute score changes between MFM1 and MFM2 total score (TS) and each subscore (D1, D2 and D3) were calculated for each patient. The mean score change of each group of patient reported disease evolution was provided and then groups were compared to determine if the difference was statistically significant. The MCID was calculated. Mean scores changes for D1, D2 and TS improved for patients reporting improvement (respectively  $2.4 \pm 5.6$ ;  $2.1 \pm 13.3$  and  $2.5 \pm 7.2$ ) and declined for patients reporting deterioration ( $-3.2 \pm 8.1$ ;  $-1.3 \pm 15.7$  and  $-1.3 \pm 7.2$ ) or stability ( $-1.2 \pm 7.4$ ;  $-2.2 \pm 10.5$  and  $-1.5 \pm 10$ ). The mean score for D3 was stable or improved in all patients, even if they reported an overall deterioration. The MCID was consecutively calculated for D1, D2 and TS. When designing clinical trials in congenital onset neuromuscular diseases, the use of MCID for MFM should be considered as a chief outcome measure to determine if a given intervention effects not only statistically significant change but also clinically meaningful improvements.

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### P.327

#### A model for dominant-mutated collagen VI-related disorder and allele-specific gene silencing therapy

S. Noguchi, M. Ogawa, I. Nishino

National Institute of Neuroscience, NCNP, Tokyo, Japan

Primary collagen VI-related disorders (Col6-RD) due to mutations in *COL6A1*, *COL6A2* and *COL6A3* lead to either a severe Ullrich congenital muscular dystrophy or a milder Bethlem myopathy. Col6-RD is characterized clinically by muscle weakness, respiratory failure, proximal joint contracture, and scoliosis, and pathologically by marked variation in fiber size, scattered muscle necrosis and regeneration, and increased endomysial fibrosis and adipogenesis. Recently, we established mouse models ( $\Delta 50$  mouse) of an autosomal dominant form of Col6-RD by 50-bp deletion in *Col6a1* gene, which causes the in-frame deletion of whole exon 9 in *Col6a1* transcript. In this study, we further analyzed the phenotypes of the  $\Delta 50$  mouse models and conducted the allele specific silencing therapy toward the muscle-retained mesenchymal progenitor cells (MPCs). We analyzed muscle pathology of  $\Delta 50$  mice chronologically on aging. Muscles from  $\Delta 50$  mice showed enhanced fibrosis from young ages with morphological changes of mesenchymal progenitor cells.  $\Delta 50$  mice represented the unique spatial localization of collagen VI aggregates near MPCs, which was different from that of per-

lecan. The efficacy of designed siRNAs for allele-specific gene silencing was measured by *in vitro* luciferase assay on artificial reporter gene constructs. We identified an siRNA which is highly effective and specific to a product from the mutated allele. By treatment with this siRNA, collagen VI localization was recovered around MPCs. Thus, dominant-mutation in *Col6a1* made unique features of collagen VI aggregates in muscles. Allele specific gene silencing by siRNA would be promising therapeutic application for autosomal dominant Col6-RD.

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### P.328

#### Pneumothorax in Ullrich congenital muscular dystrophy

Y. Arahata<sup>1</sup>, A. Ishiyama<sup>1</sup>, M. Ogawa<sup>2</sup>, S. Noguchi<sup>2</sup>, R. Tanaka<sup>3</sup>, E. Takeshita<sup>1</sup>, Y. Shimizu-Motohashi<sup>1</sup>, H. Komaki<sup>1</sup>, Y. Saito<sup>1</sup>, I. Nishino<sup>2</sup>

<sup>1</sup>National Center Hospital, Kodaira, Japan; <sup>2</sup>National Institute of Neurosci, Kodaira, Japan; <sup>3</sup>Ibaraki Children's Hospital, Ibaraki, Japan

Pneumothorax (PT) is a rare complication of Ullrich congenital muscular dystrophy (UCMD). To determine the clinical characteristics of UCMD with PT and the histological features of lung tissue in mice with a *Col6a1* dominant mutation. Among 25 UCMD patients treated at NCNP hospital, 4 (16%) developed PT. Case 1 was a 16-year-old girl who had received noninvasive positive-pressure ventilation (NPPV) since age 11 years. At age 16 years, she was admitted to the hospital due to chest pain and dyspnea. Chest CT revealed PT, and she was successfully treated with oxygen therapy without recurrence for six months. Case 2 was a 29-year-old man treated with thoracoscopic surgery for tension PT at age 13 years. He had used NPPV since age 16 years and had 8 recurrences of PT. Case 3 was a 29-year-old woman who had received NPPV since from the age of 15 years. At age 23 years, she had 9 episodes of PT, concurrent with menstruation. She died of tension PT at the last recurrence. Case 4 was a 9-year-old girl who had received NPPV since age 7 years. At age 9 years, she was transferred to the hospital because of emesis and decreased consciousness level. She was in shock status on arrival and died despite resuscitative efforts. Postmortem CT revealed PT and free air in the abdomen. Of the 4 patients with UCMD, 3 first developed PT in teens or earlier (median, 14.5 years), 2 had recurrences, and 2 had fatal outcomes. In the lung tissue of mice, localization of collagen VI was different between *Col6a1* mutated and wild-type mice, particularly in the visceral pleura. NPPV use may not always lead to PT. Structure abnormality of the visceral pleura in lung of UCMD patient may lead to pleural fragility and PT. PT can be a complication of UCMD even in the early stage.

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### P.329

#### CALLISTO: a phase I open-label, sequential group, cohort study of pharmacokinetics and safety of omigapil in LAMA2 and COL6-related dystrophy patients

A.R. Foley<sup>1</sup>, M. Leach<sup>1</sup>, G. Averion<sup>1</sup>, Y. Hu<sup>1</sup>, P. Yun<sup>1</sup>, S. Neuhaus<sup>1</sup>, D. Saade<sup>1</sup>, C. Arevalo<sup>1</sup>, M. Fink<sup>1</sup>, J. DeCoster<sup>1</sup>, C. Mendoza<sup>1</sup>, O. Mayer<sup>2</sup>, R. Hausmann<sup>3</sup>, D. Petraki<sup>3</sup>, K. Cheung<sup>4</sup>, C. Bönnemann<sup>1</sup>

<sup>1</sup>National Institutes of Health, Bethesda, USA; <sup>2</sup>CHOP, Philadelphia, USA; <sup>3</sup>Santhera Pharmaceuticals, Pratteln, Switzerland; <sup>4</sup>Columbia University, New York, USA

The anti-apoptotic compound omigapil demonstrated inhibition of GAPDH-Siah1-mediated apoptosis in muscle with concomitant improved weight and locomotor activity in the *LAMA2*-related dystrophy (*LAMA2*-RD) mouse model (*dyw/dyw* mouse). Studies of omigapil in the *COL6*-related dystrophy (*COL6*-RD) mouse model (*Col6a1*-/- mouse) demonstrated decreased apoptosis, in particular of the diaphragm muscle. A phase I open-label, sequential group, cohort study of omigapil in *COL6*-RD or *LAMA2*-RD patients aged 5-16 years conducted at the NIH with objectives: 1. to establish the pharmacokinetic (PK) profile of omigapil at a range of doses, using a novel adaptive algorithm, SAVOR (stochastic approximation with virtual