Organised by:

PACTALS
Pan-Asian Consortium for Treatment and Research in ALS

CNNS
CLINICAL NEUROPHYSIOLOGY NEUROMUSCULAR SECTION

PACTALS 2023

Royale Chulan Kuala Lumpur, Malaysia

Pre-Congress
14th September 2023

Congress
15th-16th September 2023

ABSTRACT E-BOOK

Supported by:

INTERNATIONAL ALLIANCE OF ALS/MND ASSOCIATIONS

MND Malaysia

Malaysia Convention & Exhibition Bureau

Meet in Malaysia

Malaysia Truly Asia

Contents

Basic Science
OB001

GENETIC LINK AND CAUSAL INFERENCE BETWEEN LIPIDS, APOLIPOPROTEINS, STATINS, AND AMYOTROPHIC LATERAL SCLEROSIS

Kailin Xia[1], Yajun Wang[1], Ninghao Huang[2], Gan Zhang[1], Lu Tang[1], Linjing Zhang[1], Tao Huang[2], Dongsheng Fan[1]

[1] *Department of Neurology, Peking University Third Hospital, Beijing 100191, China*

[2] *Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100871, China*

[3]

INTRODUCTION

Growing evidence showed a close association between lipid and apolipoproteins metabolism in amyotrophic lateral sclerosis (ALS). However, the genetic mechanism and causal association behind the altered lipid or apolipoprotein levels and ALS remains elusive, as well as the potential effect of lipid-lowering drugs on the disease. Therefore, we performed a genetic correlation analysis, a multivariable mendelian randomization analysis (MVMR), and a drug target MR to study whether lipid and apolipoprotein metabolism and ALS are genetically associated.

METHODS

We obtained the largest European-based GWASs data for TG, HDL-C, LDL-C, ApoA1, ApoB, and ALS and employed linkage disequilibrium score regression analysis to assess the genetic correlation of lipids and ALS. Univariable MR, MVMR, and drug target MR were adopted to verify and further study whether lipids and apolipoproteins are independently causal risk factors for ALS and the effect of LDL-C-lowering targets (*ACLY, HMGCR, PCSK9*, and *NPC1L1*) on ALS.

RESULTS

We found positive genetic correlations between ALS and HDL-C (rg=0.068, P=0.027) and ApoA1 (rg=0.091, P=0.013). In the primary univariable MR, we found the elevated LDL-C [OR (95%CI)= 1.1 (1.024, 1.181), P=0.009], HDL-C [OR (95%CI)= 1.073 (1.005, 1.146), P=0.035], ApoA1 [OR (95%CI)=1.08 (1.01, 1.156), P=0.025] and ApoB [OR (95%CI)=1.081 (1.009, 1.158), P=0.027] were risk factors for ALS, which was not observed in the MVMR models including TG, HDL-C and LDL-C or TG, ApoA1 and ApoB. The genetic variation within the *ACLY* gene window suggested that genetically predicted reduced activity of *ACLY* (a new target of statins) may decrease the risk of developing ALS [OR (95%CI)=0.099 (0.012, 0.854), P=0.035].

CONCLUSION

A genetic correlation between HDL-C and ALS was identified. Genetically predicted elevated levels of HDL-C, LDL-C, and their apolipoproteins were associated with the risk of developing ALS dependently. MR analysis supports that using ACLY inhibitors may decrease ALS.

Basic Science
OB002

UBIQUITIN PROTEASOME DYSFUNCTION IN FATAL AND NON-FATAL MOTOR NEURON DISEASE: LESSONS LEARNED FROM THE PERIPHERAL NERVOUS SYSTEM.

***Anthony N Cutrupi*[1,2], *Ramesh Narayanan*[1,2], *Alexandra Boyling*[1,2], *Gonzalo Perez-Siles*[1,2], *Bianca Grosz*[1,2], *Kaitao Lai*[1,5], *Garth A Nicholson*[3], *Steve Vucic*[2,4], *Marina L Kennerson*[1,2,3].**

(1) *Northcott Neuroscience Laboratory, ANZAC Research Institute SLHD, Sydney, Australia;*
(2) *Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia;*
(3) *Molecular Medicine Laboratory, Concord Repatriation General Hospital, Sydney, Australia;*
(4) *Brain and Nerve Research Centre, Concord Repatriation General Hospital, Sydney, Australia*
(5) *Ancestry & Health Genomics Laboratory, Charles Perkins Centre, School of Medical Sciences, University of Sydney, Australia*

INTRODUCTION

The ubiquitin-proteasome system (UPS) is a one of the major intracellular proteolytic pathways involved in maintaining cellular proteostasis. Dysfunction in the UPS is associated with a spectrum of motor neuron disorders (MND) ranging from non-fatal distal hereditary motor neuropathy (dHMN) to the invariably fatal amyotrophic lateral sclerosis (ALS). It is established that there are several clinicogenetic commonalities between dHMN and ALS and evidence showing that both display significantly connected and overlapping biological processes. We've previously reported a novel mutation in a dHMN family (DHMN1: OMIM %182960) involving partial duplication of the ubiquitinprotein E3 ligase gene (*UBE3C*) resulting in a novel gene-intergenic fusion transcript (*UBE3CIF*). Here, we show how iPSC-derived neuronal models can be combined with *in vivo* animal models to unravel the mechanisms underpinning UPS dysfunction in MND.

METHODS

Western blot was used to assess UBE3C and UBE3C-IF protein expression. Transfection of *UBE3CIF* in HeLa cells was carried out by lipofection. Transgenic *C.elegans* expressing *UBE3C-IF* in GABAergic motor neurons were generated to model the functional consequences of *UBE3C-IF in vivo.*

RESULTS

DHMN1 iPSC-sMN harbouring the *UBE3C-IF* transcript show a significant reduction of UBE3C protein levels. Overexpression of *UBE3C-IF* in HeLa cells recapitulates observed reduction of UBE3C. *C. elegans* expressing the *UBE3C-IF* transcript show neuronal synaptic transmission deficits. Furthermore, the transgenic animals are susceptible to heat stress which may implicate defective protein homeostasis in DHMN1 pathogenesis.

CONCLUSION

Our results highlight the utility of iPSC-derived neuronal models combined with *in vivo* models in unravelling the biology associated with UPS dysfunction in MND. These methods and techniques will be expanded to mutations in UPS genes causing fatal MND such as *UBQLN2.*

Understanding the molecular pathology of the spectrum of MND involving these biological processes will guide research to potential common therapeutic targets and intervention strategies.

Basic Science
OB003

TDP-43 ACCUMULATIONS APPEAR IN INTRAMUSCULAR NERVE BUNDLES OF ALS PATIENTS.

Takashi Kurashige[1, 2], Hiroyuki Morino[2, 3], Tomomi Murao[1], Yuishin Izumi[4], Tomohito Sugiura[1], Kazuya Kuraoka[5], Hideshi Kawakami[6], Tsuyoshi Torii[1], Hirofumi Maruyama[2]
[1]Department of Neurology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Kure, Japan
[2]Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan
[3]Department of Medical Genetics, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan
[4]Department of Clinical Neuroscience, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan
[5]Department of Diagnostic Pathology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Kure, Japan
[6]Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima
University, Hiroshima, Japan
[7]Department of Neurology, National Hospital Organization Hiroshima-nishi Medical Center, Ohtake, Japan

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) shows progressive muscle weakness and atrophy caused by neuronal death associate with TAR DNA-binding protein 43 (TDP-43). Meanwhile, Awaji and Gold Coast criterion include an electrophysiological aspect but not a pathological aspect. The Gold Coast criteria enables us to diagnose spinal onset ALS patients and needs to allow for a specific diagnosis including a pathological aspect. Here, we aimed to characterize the histopathology of peripheral axons in muscles of ALS patients.

METHODS

The post-mortem study included 10 sporadic ALS (SALS) patients with TDP-43 pathology and 12 patients with non-ALS disease. The muscle biopsy cohort considered 450 patients, and enrolled 114 as without family history of ALS or other neuromuscular diseases and not diagnosed with muscle diseases at biopsy. They ensure clinical follow-up in minimum one year. Exclusions were as follows: 51 for not screening clinical records after biopsy, 282 diagnosed with muscular diseases, and 3 harboring known causative genes of ALS. Muscle tissues were evaluated by histochemistry and immunohistochemical analysis.

RESULTS

Ten SALS patients exhibited axonal phosphorylated TDP-43 (pTDP-43)-positive accumulations in intramuscular nerve bundles; 12 non-ALS patients did not. Among the muscle biopsy cohort, 71 patients exhibited intramuscular nerve bundles; 43 did not. Of the former, 33 presenting pTDP-43-positive nerve bundles were later diagnosed with ALS. The remaining 38 showed no pTDP43-positive bundles and did not develop ALS. Among those without evident nerve bundles, 3 were later diagnosed with ALS. Among ALS patients in the biopsy cohort, 9 having pTDP-43-positive bundles showed only lower motor neuron symptoms at biopsy.

CONCLUSIONS

Axonal pTDP-43 accumulations might be characteristic for ALS patients. As such findings precede clinical fulfillment of the Gold Coast criteria, TDP-43 in nerve bundles might be a novel diagnostic biomarker for ALS.

Clinical
OC001

QUANTITATIVE FASCICULATION INTENSITY ANALYSIS COULD IMPROVE DIFFERENTIATION BETWEEN AMYOTROPHIC LATERAL SCLEROSIS AND MIMICS

Mingsheng LIU, Yi LI, Jingwen LIU, Liying CUI
Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

INTRODUCTION

Muscle ultrasound (MUS) has been proven a sensitive tool in detecting fasciculation in patients with Amyotrophic lateral sclerosis (ALS). The aim of this study was to explore the quantitative intensity of fasciculation in differential diagnosis of ALS.

METHODS

One hundred and thirty-nine patients with ALS and 61 patients with peripheral neuropathy were recruited prospectively. MUS and muscle strength was investigated on 16 limb muscles. The intensity of fasciculation in each muscle was classified into 0 to 4 grades.

RESULTS

The maximal fasciculation Grade of limb muscles was higher than grad 2 in 84.9% patients with ALS and 9.8% patients with peripheral neuropathy($p<0.01$). Median (P25, P75) of overall fasciculation score of 16 limb muscles were 29(15, 41) in ALS and 3 (0,8) in peripheral neuropathy. The sensitivity and specificity in diagnosis of ALS were 80.6% and 93.4% for total fasciculation score of limbs (cut-off value 14). When MRC were 4 and 5, 42.3% and 24.1% muscles showed fasciculation grade≥3 in ALS, while only 1.7% and 0% in peripheral neuropathy.

DISCUSSION

Quantitative fasciculation intensity analysis could improve the differential diagnosis of ALS.

Clinical
OC002

PROGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS FOLLOWING TRACHEOSTOMY IN SOUTH KOREA

Seok-Jin CHOI[1, 2], Jong-Su KIM[2], Yoon-Ho HONG[3], Jung-Joon SUNG[1]
Center for Hospital Medicine, Seoul National University Hospital, Seoul, Republic of Korea
Department of Neurology, Seoul National University Hospital, Seoul, Republic of Korea
Department of Neurology, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea

INTRODUCTION

Tracheostomy-invasive ventilation (TIV) is one of the treatment options utilized for a small subset of amyotrophic lateral sclerosis (ALS) patients to aid in ventilator support and airway management. The objectives of this study were to describe and identify factors that impact the prognosis of Korean patients with ALS undergoing TIV therapy.

METHODS

In this nationwide cohort study, the Korean National Health Insurance Database was utilized to enroll newly diagnosed ALS patients between January 2012 and December 2017. A minimum follow-up period was set to be three years from the time of diagnosis, with available followup data up to December 2020. The survival time between the TIV group and the non-TIV group was compared using propensity score matching analysis, and prognostic factors were assessed within the TIV group.

RESULTS

The study involved 3,484 ALS patients, with a mean age of 62.4 (11.9) years and 60.4% male. Of these, 1,230 (35.3%) underwent TIV while 2,254 (64.7%) did not. Within the TIV group, 26.0% of tracheostomy was performed as an emergency procedure following endotracheal intubation. After propensity score matching (1:1), there was no significant difference in survival time between the two groups (28 [13-50] vs. 25 [12-44] months, P=0.057). Cox regression analysis revealed that older ages (HRs for 40s-50s-60s-70s-80s or older, 3.89-3.83-5.30-6.78-8.40; P<0.005 for all), low income (HR 1.28; 95% CI 1.09-1.52; P=0.003), gastrostomy (HR 0.57; 95% CI 0.50-0.66; P<0.001), and supportive care service (HR 0.43; 95% CI 0.32-0.59; P<0.001) were independent predictors of mortality.

CONCLUSION

Currently, tracheostomy was being implemented in more than one-third of Korean ALS patients, and over a quarter of them was performed as an emergency procedure following endotracheal intubation. However, tracheostomy did not increase survival time in Korean ALS patients. These findings underscore the importance of shared decision-making regarding tracheostomy and end-of-life supportive care for ALS patients.

Clinical
OC003

DEFINING THE CORE WHITE-MATTER DISEASE SIGNATURE OF ALS THROUGH STATE-OF-THE-ART DIFFUSION-WEIGHTED IMAGING AND FIXEL-BASED ANALYSIS

Sicong TU[1], Arkiev D'SOUZA[1], Colin MAHONEY[1], William HUYNH[1], Chenyu WANG[1], Feando CALAMANTE[1], Matthew KIERNAN[1]
[1]Brain and Mind Centre, The University of Sydney, Sydney, Australia

INTRODUCTION

Developing an MRI signature of ALS is significantly impacted by data quality and subsequent analysis pipeline(s). Tensor-based modelling of standard clinically acquired diffusion-weighted imaging (DWI) signal as a single Gaussian component can result in counterintuitive and conflated mixed-fibre orientation signals of white-matter (WM) abnormality. We employed a state-of-the-art multi-shell DWI acquisition and fixel-based analysis (FBA) to define the core WM disease signature of ALS.

METHODS

54 participants (37 ALS; 17 Control; age-education matched) were prospectively recruited from the Forefront MND Clinic, following clinical diagnosis, and underwent an MRI scan (3T GE MR750; 32 channel head-coil; T1; DWI: 140 directions, b-value=700/1000/2800, 8xb0). Whole-brain FBA was performed using MRtrix3 to assess WM fibre-density (FD), cross-section (FC), and their combination (FDC). ALSFRS-R total score, disease duration, and disease progression rate were calculated for all patients.

RESULTS

Significant age-related FD reduction in the foix and tail of the corpus callosum was observed in the ALS cohort (FWE, $p<0.01$). Localised disease associated reduction in FD was observed in the body of the corpus callosum and diffusely along the corticospinal tracts (CST) extending into intersecting parieto-occipital-pontine fibers, relative to controls (FWE, $p<0.01$). Notably, reduced FD integrity across all FBA identified disease-affected tracts were significantly correlated with impaired motor function (ALSFRS-R; p-values <0.001). Increased disease duration was selectively associated with reduced FD of the CST (p-values<0.05).

CONCLUSIONS

While ALS disability reliably correlates with cortical motor and CST integrity, widespread extra-motor neurodegeneration represents an increasingly recognised feature of ALS, that presents significant challenges for reconciling with clinical progression and translation as a clinical biomarker. Current findings present a clinically feasible state-of-the-art approach to localise precise areas of altered intraaxonal volume fraction specific to the core MRI signature of microstructural WM abnormality in ALS. This presents a promising step forward to implementing quantitative clinical MRI metrics for ALS.

Basic Science
OPB001

ASSESSMENT OF THE RASCH-BUILT OVERALL AMYOTROPHIC LATERAL SCLEROSIS DISABILITY SCALE (ROADS) AS A PROGNOSTIC PREDICTOR OF AMYOTROPHIC LATERAL SCLEROSIS

Can Sun[1,2], Christina N. Fournier[3], Nan Zhang[1,2], Nan Li[4,], Dongsheng Fan[1,2,5,*]*
Department of Neurology, Peking University Third Hospital, Beijing, China
Beijing Municipal Key Laboratory of Biomarker and Translational Research in Neurodegenerative diseases, Beijing, China
Department of Neurology, Emory University, Atlanta, America
Research Center of Clinical Epidemiology, Peking University Third Hospital, Beijing, China
Key Laboratory for Neuroscience, National Health Commission/ Ministry of Education, Peking University, Beijing, China

OBJECTIVE
To explore a more responsive and reliable outcome measure for assessing amyotrophic lateral sclerosis (ALS) progression and prognosis.

METHODS
A total of 165 ALS participants who were able to provide informed consent were included in this study. Clinical characteristics and survival duration of each patient were recorded. The ROADS and the ALSFRS-R questionnaires were collected at baseline (February, 2020), and participants were followed longitudinally for 18 months to assess time to tracheostomy and survival. Prognostic risk models of these two scales were constructed using multivariate Cox regression analyses and stratified Cox regression models. And decision curve analysis (DCA), receiver operating characteristic curve (ROC) and restricted cubic splines (NCS) were used to evaluate the predictive performances of the ROADS and the ALSFRS-R.

RESULTS
Of these 165 patients, 54 (32.7%) died over a total 18-month follow-up period. The ROADS is a highly significant predictor for ALS survival (HR =0.95, 95% CI 0.94 to 0.96 , Pï¼œ0.001,). Especially, in the subgroup with ALSFRS-R ≥27, the ROC and DCA demonstrated the ROADS was superior to the ALSFRS-R in terms of prognostic ability. In the cohort with ALSFRS-Rï¼œ27, the ROADS had nearly comparable predictive performance to the ALSFRS-R.

CONCLUSIONS
The ROADS as a quantitative measure of ALS progression, could be more sensitive for patients at the initial phase of the disease course with higher ALSFRS-R scores. Therefore, the ROADS may serve as a promising valuable outcome measure for use in ALS trials and in clinic compared with ALSFRS-R.

Basic Science
OPB002

LONG-TERM LONGITUDINAL PROGRESSION PATTERN OF AMYOTROPHIC LATERAL SCLEROSIS: A TRAJECTORY ANALYSIS OF A 16-YEAR COHORT IN CHINA

Lu Chen MD[a,#], Lu Xu MD[b,#], Lu Tang MSc[a], Shengfeng Wang MD PhD[c,], Siyan Zhan MD PhD[b,c,d,*], Dongsheng Fan MD PhD[a,e,f,*]*
[a]Department of Neurology, Peking University Third Hospital, 49 North Garden Road, Haidian District, Beijing100191, China
[b]Research Center of Clinical Epidemiology, Peking University Third Hospital, 49 North Garden Road, Haidian District, Beijing 100191, China
[c]Department of Epidemiology and Biostatistics, School of Public Health, Peking University, 38 Xueyuan Road, Haidian District, Beijing 100191, China
[d]Center for Intelligent Public Health, Institute for Artificial Intelligence, Peking University, 38 Xueyuan Road, Haidian District, Beijing 100191, China
[e]Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, 38 Xueyuan Road, Haidian District, Beijing 100191, China
[f]Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing 100191, China
#Lu Chen and Lu Xu contributed equally.
**Shengfeng Wang, Siyan Zhan and Dongsheng Fan contributed equally.*

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with a poor but heterogeneous prognosis. Although it has been most commonly used in the disease assessment of ALS, the decreases in the ALS Functional Rating Scale (ALSFRS) do not follow a unitary linear trend.
Group-based trajectory modeling (GBTM) is a method that can take the heterogeneity of declines in ALSFRS into consideration. We analyzed the 16-year trajectory of ALSFRS of patients using the GBTM method, and explored possible reasons for differences.

METHODS

3,257 patients with sporadic ALS from January 2005 to May 2021 were recruited. ALSFRS were the dependent variable in the GBTM. ALSFRS scores were the dependent variable in the groupbased trajectory modeling (GBTM). The baseline characteristics and laboratory indicators in different trajectory groups were compared. A Cox proportional hazards model was used to examine the association between primary outcomes and trajectory groups.

RESULTS

A model with four groups (rapid, moderate, slow, and very slow progression) was adopted. The four groups differed in sex (P=0.002), age at onset (P<0.001), diagnostic delay (P<0.001), phenotype (P<0.001), riluzole use (P=0.001), onset site (P<0.001), cerebrospinal fluid (CSF) protein levels (P=0.044), and neutrophil-to-lymphocyte ratio (NLR; P=0.011). Compared with the moderate progression group, the rapid progression group displayed an increased risk of progression to respiratory insufficiency or death (hazard ratio [HR] 1.66, 95% confidence interval [CI] 1.41 to 1.97), but the very slow progression group (HR 0.06, 95% CI 0.02 to 0.26) had a decreased risk.

CONCLUSIONS

This study provides a novel prognosis prediction method using the ALSFRS trajectory. Notably, the higher NLR and higher protein in CSF of the trajectory groups with faster progression suggested that neuroinflammation may play a crucial role in ALS.

Basic Science
OPB003

VARIANTS IN THE SPTLC1 AND SPTLC2 GENE IN JUVENILE AMYOTROPHIC LATERAL SCLEROSIS

Xunzhe Yang[1], Dongchao Shen[1], Nan Hu [1], Lei Zhang[1], Jing Fan[1], Qing Liu[1], Mingsheng Liu[1], Liying Cui1, 2
[1]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences [2]Center of Neuroscience, Chinese Academy of Medical Sciences

INTRODUCTION

Juvenile amyotrophic lateral sclerosis (ALS) is a rare form of ALS defined by age of symptom onset less than 25 years. Two studies revealed the association of de novo variants in the SPTLC1 with patients diagnosed with juvenile ALS and failure to thrive. Particularly, variants in the SPTLC1 and SPTLC2 gene have been previously shown to be associated with autosomal-dominant hereditary sensory autonomic neuropathy, type 1A, by disrupting an essential enzyme complex in the sphingolipid synthesis pathway.

METHODS

The juvenile ALS patients and their family members were enrolled at Peking Union Medical College Hospital between March 1, 2013 and December 13, 2022. Trio whole-exome sequencing was performed to identify the disease-associated genes in juvenile ALS patients and their family members.
A total of 35 patients with juvenile ALS and 2255 adult patients with ALS participated in the study. Variants in SPTLC1 and SPTLC2 in all of these patients while clinical information was collected.

RESULTS

35 patients with juvenile ALS and 2255 adult patients with ALS were subsequently screened for variants in the SPTLC1 and SPTLC2 gene. De novo variants in SPTLC1 (p.Ala20Ser in one 9year-old child) and SPTLC2 (p.Glu232Lys in one 7-year-old child) were identified separately.

CONCLUSION

Our study broadened the ALS phenotype associated with SPTLC1 and SPTLC2, and suggested that monogenic direct metabolic disturbance may be causally linked to ALS. Further studies waere warranted in identifying the true role of variants in the SPTLC1 and SPTLC2 gene in the pathogenesis of ALS.

Basic Science
OPB004

YOUNG-ONSET AND RAPID PROGRESSIVE AMYOTROPHIC LATERAL SCLEROSIS BY A NOVEL FRAMESHIFT TRUNCATING MUTATION IN TBK1 GENE

Shih-Yu FANG[1], Kang-Yang JIH[1, 2, 3], Pei-Chien TSAI[4], Yi-Chu LIAO[1, 2, 5], Yi-Chung LEE[1, 2, 5]
Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan
Department of Neurology, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan
Department of Physiology, National Yang Ming Chiao Tung University, Taipei, Taiwan
Rong Hsing Research Center for Translational Medicine, National Chung Hsing University, Taichung, Taiwan
Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan

INTRODUCTION

Mutations in TBK1 gene have been associated with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) spectrum disorder. The aim of this study is to clinically characterize a novel truncating frameshift TBK1 mutation in a patient with young-onset and rapidly progressive ALS.

REPORT

We described a 40-year-old male patienting with right hand-onset ALS and rapidly progressive disease course since age of 39 years. He had no family history of ALS or dementia. Neurological examination revealed four limbs weakness and atrophy with more severe upper limbs involvement, generalized hyperreflexia, and a positive bilateral Hoffmann sign. Rapidly progressive disease course was noticed with ALS Functional Rating Scale-revised (ALSFRS-R) scores declining from 38 to 15 within 12 months. The patient had normal cognitive function; however, single photon emission tomography (SPECT) showed hypoperfusion of bilateral superior and middle frontal cortices. Genetic analysis revealed a heterozygous truncating frameshift mutation in *TBK1*, c.456_457delGT (p.Y153Qfs*9), which had never been reported before. The mutation led to a truncated TANK-binding kinase 1 (TBK1) protein product, low protein expression, and loss of TBK1 kinase function and interaction with optineurin.

CONCLUSION

TBK1 c.456_457delGT is a novel pathogenic variant for ALS. We proposed that analysis of *TBK1* gene shall be considered in patients with young-onset and rapidly progressive ALS. Though initial evaluation of cognitive function may be insignificant, brain SPECT may be a potential predictor for diagnosing presymptomatic FTD in carriers of *TBK1* mutations.

Basic Science
OPB005

PHOSPHORYLATED CRMP1, AXON GUIDANCE PROTEIN, IS A COMPONENT OF SPHEROIDS AND IS INVOLVED IN AXONAL PATHOLOGY IN AMYOTROPHIC LATERAL SCLEROSIS

Yuko Kawamoto[1], Mikiko Tada[1], Tetsuya Asano[1], Haruko Nakamura[1], Shun Kubota[1], Shunta Hashiguchi[1], Misako Kunii[1], Hideyuki Takeuchi[1], Hiroshi Doi[1], Fumiaki Tanaka[1]
[1]Department of Neurology and Stroke Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan

INTRODUCTION

In amyotrophic lateral sclerosis (ALS), neurodegeneration is characterized by distal axonopathy that begins at the distal axons, including the neuromuscular junctions, and progresses proximally in a "dying back" manner prior to the degeneration of cell bodies. However, the molecular mechanism for distal axonopathy in ALS has not been fully addressed. Semaphorin 3A (Sema3A), a repulsive axon guidance molecule that phosphorylates collapsin response mediator proteins (CRMPs), is known to be highly expressed in Schwann cells near distal axons in a mouse model of ALS.

METHODS

To clarify the involvement of Sema3A-CRMP signaling in the axonal pathogenesis of ALS, we investigated the expression of phosphorylated CRMP1 (pCRMP1) in the spinal cords of 35 patients with sporadic ALS and seven disease controls.

RESULTS

In ALS patients, we found that pCRMP1 accumulated in the proximal axons and co-localized with phosphorylated neurofilaments (pNFs), which are a major protein constituent of spheroids. Interestingly, the pCRMP1:pNF ratio of the fluorescence signal in spheroid immunostaining was inversely correlated with disease duration in 18 evaluable ALS patients, indicating that the accumulation of pCRMP1 may precede that of pNFs in spheroids or promote ALS progression. In addition, overexpression of a phospho-mimicking CRMP1 mutant inhibited axonal outgrowth in Neuro2A cells.

CONCLUSION

Taken together, these results indicate that pCRMP1 may be involved in the pathogenesis of axonopathy in ALS, leading to spheroid formation through the proximal progression of axonopathy.

Basic Science
OPB006

HYPOXIA, URIC ACID AND METABOLISM IN ALS

Ji He[1], *Wen Cao*[1]
Neurology department, Peking University Third Hospital, Beijing, China

INTRODUCTION

Uric acid is the end product of purine metabolism in the human body and it mainly affects the occurrence and progression of amyotrophic lateral sclerosis (ALS) by affecting energy metabolism, oxidative stress, inflammatory response and other pathways. However, the role of uric acid in ALS is still controversial.

METHOD

Clinical data (121sALS and 104 healthy controls) were collected in detail, with the systematic blood examination (including uric acid), lung function and blood gas examination. The resting metabolism level and exercise capacity were determined by systematic tests (including cardiopulmonary function evaluation technology).

RESULT

After quality controls, the average serum uric acid level in the case group was higher than that in the control group (343.84 ± 86.51 vs 322.78 ± 85.35, $p<0.05$), and was inversely proportional to lung function (FVC%: 81.45 ± 17.39, $p<0.05$). Uric acid levels in women are higher than those in men. Serum uric acid levels were positively correlated with BMI ($p<0.05$). Uric acid level in ALS patients is inversely proportional to KCSS stage (mean: KCSS1: 359.84 μmol/L,KCSS2:332.39 μ mol/L,KCSS3:312.02 μ mol/L)ã€,After controlling BMI, serum uric acid levels in ALS patients were still positively correlated with exercise VO2 peak ($r^2=0.39$, $p=0.031$). Uric acid levels were not significantly correlated with resting metabolic levels.

CONCLUSION

Our research elucidated clearly that uric acid is a protective molecular marker for ALS, and further explored the corresponding clinical mechanisms. In combination with other studies, this result suggested that hypoxia is one of important reasons for the increase in uric acid in ALS, while the compensation decreases as the disease progresses. This indicated the important role of uric acid in clinical staging, as well as an important pathway for purine metabolism to maintain function in ALS. Our study provided important implications for future treatment.

Basic Science
OPB007

MUTANT GGGGCC RNA STIMULATES WNT/B-CATENIN PATHWAY IN C9ALS/FTD

CHEN, Zhefan Stephen[1,2], OU, Mingxi1, TALBOT, Kevin[2] and CHAN, Ho Yin Edwin[1]
School of Life Sciences, The Chinese University of Hong Kong, Shatin N.T., Hong Kong, China[1],
Department of Clinical Neurosciences, University of Oxford, UK[2]

INTRODUCTION

A GGGGCC hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 (C9orf72) gene is a major cause of amyotrophic lateral sclerosis and frontotemporal dementia (C9ALS/FTD).

METHODS

We used SK-N-MC cell line and C9ALS/FTD-induced pluripotent stem cell-derived spinal motor neurons as our cell models and transgenic C9 *Drosophila* as our animal model. Cellbased assays include immunocytochemistry, protein-RNA interaction, chromatin immunoprecipitation, dual-luciferase and lactate dehydrogenase cytotoxicity. *Drosophila* assays performed include adult climbing and survival assays.

RESULTS

We showed that GGGGCC RNA sequesters a transcriptional regulator to RNA foci. This mutant RNA/protein interaction leads to activation of the canonical Wnt/β-catenin pathway and induces synaptic deficits in C9ALS/FTD neurons.

CONCLUSION

Our findings describes a C9ALS/FTD pathogenic mechanism which involves dysregulation of planar polarity gene transcription and Wnt/β-catenin signalling perturbation. This novel pathogenic cascade also provides a potential new target for disease

Clinical
OPC001

THE DIAGNOSTIC UTILITY OF QUANTITATIVE MUSCLE ULTRASOUND IN AMYOTROPHIC LATERAL SCLEROSIS.

Andrew Hannaford[1], Nathan Pavey[1], Mehdi van den Bos[1], Parvathi Menon[1], Matthew Kiean[2], Neil Simon[3] and Steve Vucic[1]
[1]Brain and Nerve Research Centre, Concord Clinical School, University of Sydney, Sydney, Australia;
[2]Brain and Mind Center, University of Sydney, Sydney, Australia; [3]Northe Beaches Clinical School, Macquarie University, Sydney, Australia.

OBJECTIVES
We prospectively assessed the diagnostic utility of quantitative muscle ultrasound to distinguish ALS patients from neuromuscular mimics. Additionally, we explored the association between ultrasound parameters and clinical markers of disease severity.

METHODS
46 patients suspected of ALS were studied using ultrasound of 17 different muscle groups. Muscle fasciculations and quantitative muscle echo-intensity were recorded. Muscle specific echointensity reference values were generated from 39 healthy controls, with hyperechoic muscles defined as Z score >1.5 SD. The diagnostic utility of these metrics and their association with disease severity was determined.

RESULTS
34 patients met the diagnosis of ALS over the follow up period. 12 patients were diagnosed with other neuromuscular disorders. Longer ALS disease duration was associated with more hyperechoic muscles ($r=0.44$ $p=0.003$) and less fasciculating muscles ($r=0.35$ $p<0.001$). ALS subjects had significantly more fasciculating muscles when compared to mimic subjects (mean 7.9±3.9 vs 1.9±2.8 $p<0.01$). By contrast, the number of hyperechoic muscles was not significantly different between groups (mean 2.0±0.3 vs 3.1±0.9 $p=0.167$). In the diagnosis of ALS ≥ 5 fasciculating muscles was 82% sensitive and 87.5% specific (AUC 0.88) while a total fasciculation count of ≥7 was 82% sensitive and 75% specific (AUC = 0.86). The ratio of fasciculating muscles to hyperechoic muscles was calculated. A ratio of ≥ 1.5 was 87% sensitive and 89% specific (AUC 0.94) for ALS.

CONCLUSIONS
The ratio of fasciculating muscles to hyperechoic muscles on ultrasound is highly accurate for the diagnosis of ALS.

Clinical
OPC002

CURRENT PRACTICE AND PERSPECTIVES ON DELIVERING A DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS: AN INTERNATIONAL SURVEY IN ASIAN AND OCEANIAN COUNTRIES.

Miki Yoshitake[1.], Kazumoto Shibuya[1.], Matthew Kiernan[2.], Nortina Shahrizaila[2.], Seung Hyun Kim[2.], Gen Sobue[2.], Naoki Atsuta[3.], Atsushi Takeda[4]., Kimihito Arai[4]., Kongkiat Kulkantrakorn[2.], Jong Seok Bae[2.], Liu Jia[5.], Sheila Agustini[2.], Mario Prado Jr[6.], Tien-tzu Laing[7.], Jiaqi Wang[1.], Masahisa Katsuno[8.], Takayoshi Shimohata8.,Ikuko Iwata[8.], Ritsuko Hanajima[8.],Yasumasa Kokubo[8.],Mieko Ogino[2.], Yuki Hatanaka[2.], Osamu Onodera[2.], Makoto Urusitani[2.], Takanori Yokota[2.], Ryuji Kaji[2.], Mitsusya Morita[8.], Yuishin Izumi[8.], Kengo Nagashima[9.],Masaru Yoshitake[10],Yuichi Noto[8.],Win Min Thit[2.], Atchayaram Nalini[2.], Tuan Tu Quoc Le[2.], Richard Roxburgh[2.], Ang Kexin[2.], Sonoko Misawa[1.], Satoshi Kuwabara[1].
[1]Department of Neurology,Graduate school of Medicine, Chiba university, Chiba, Japan
[2]PACTALS Study group
[3]Japanese Consortium for Amyotrophic Lateral Sclerosis Research, Japan
[4]National Hospital Organization,Japan
[5]Beijing University of Chinese Medicine Institute for Brain Disorders,Beijing,China
[6]Department of Neurosciences,Section of Adult Neurology,University of the Philippines,Manila,Philippines
[7]Institute of Innovative Research,Tokyo Institute of Technology,Tokyo,Japan
[8]The Research Committee of CNS Degenerative Diseases,Japan
[9]Clinical and Translational Research Center,Keio University Hospital,Tokyo,Japan
[10]Faculty of Science,Kanagawa university,Kanagawa,Japan

INTRODUCTION

Delivering the diagnosis of amyotrophic lateral sclerosis (ALS) poses a challenge for clinicians. Despite the inherent complexities, few studies have focused on this perspective, and there are no inteational studies or guidelines. The aim of the current study was to present an overview of current practice and the perceived difficulties of delivering the diagnosis of ALS, utilizing the Pan-Asian Consortium for Treatment and Research in ALS (PACTALS) network.

METHODS

An inteational online survey for doctors about ALS diagnosis was developed and distributed to 14 Asian and Oceanian countries of PACTALS. The questions were grouped in 5 categories: demographics (including nationality and religion), ALS treatment, delivery of ALS diagnosis, difficulties encountered when delivering a diagnosis and training needs.

RESULTS

In total, 304 doctors (Japan=148;Thailand=65; South Korea=24; China=23; Indonesia=5; Myanmar=1 responded to the survey, 59% were male, and the median length of practice was 14.8 years(SD=11.2). From this cohort, 85% of doctors reported “delivering ALS diagnosis is somewhat to very difficult” and 88.8% of doctors reported “always to sometimes feeling stress when delivering an ALS diagnosis”. Nevertheless, only 10.9% doctors reported having received training for delivering the diagnosis.

CONCLUSIONS

The results suggest that while most doctors across the PACTALS ALS network experienced difficulties and stress when delivering an ALS diagnosis, they have not received training. Development of a dedicated training module and implementation of consensus guidelines through collaborative inteational consortiums such as PACTALS, is advocated.

Clinical
OPC003

NECK WEAKNESS IN MND/ALS: AN INVESTIGATION OF PREVALENCE AND PHYSIOTHERAPY MANAGEMENT - A RETROSPECTIVE DESCRIPTIVE STUDY

Timothy Sheehy[1], Trinh Nguyen[1], Stephanie Zhao[1], Sally Mathieson[1], Rosanne Gibb[1], Anna Smith[2], Dr Christine Wools[3], Prof Prue Morgan[4]
[1]Physiotherapy Department, Statewide Progressive Neurological Disease Services, Calvary Health Care Bethlehem, Melboue, Australia
Statewide Progressive Neurological Disease Services, Calvary Health Care Bethlehem, Melboue, Australia
Department of Neurology, Statewide Progressive Neurological Disease Services, Calvary Health Care Bethlehem, Melboue, Australia
Head of Physiotherapy School of Primary and Allied Health Care, Monash University, Australia
Research is conducted in collaboration with Motor Neuron Disease Association Victoria.

INTRODUCTION

Neck weakness occurs in MND resulting in head dropping forward or to the side and can cause issues with breathing, swallowing and communication, and lead to social embarrassment (Gourie-Devi et al, 2003). The current literature appears to under report its prevalence with 1-3% of people with MND experiencing neck weakness (Gourie-Devi et al 2003, Uemura et al 2013). Very little is known about the progression and management of neck weakness in people with MND. Neck weakness is not mentioned in the most recent NICE guidelines (2016) and neck collars and headrests were only briefly mentioned amongst other adaptive technologies that a person with MND may need.

THE FOLLOWING OBJECTIVES FOR THIS STUDY WERE:

Explore the prevalence of neck weakness in MND
Explore the types of head support strategies used by people with MND and how it changes as their disease progresses
Explore the changes of mobility in people with MND and its relationship with neck weakness

METHODS

Data was extracted from existing electronic medical records of people with MND who attended specialist multi-disciplinary progressive neurological service in Melboue, Australia. All patients with a diagnosis of MND were screened according to selection criterion and data extracted in reverse chronological order until our target sample size of 360 was achieved.

RESULTS

Prevalence of neck weakness in our cohort was 39% (141/360). Median onset for neck weakness was 24 months however it can start as early as the initial symptom. 79% of the cohort used two or more head support strategies. Those with neck weakness were twice as likely to require assistance to walk and three times more likely to become wheelchair reliant.

CONCLUSION

Neck weakness prevalence is far higher than previously reported in literature. Neck weakness has a significant impact on independence and mobility in people with MND.

Clinical
OPC004

A POSSIBLE DISTINCT GENETIC SPECTRUM OF LATE-ONSET AMYOTROPHIC LATERAL SCLEROSIS IN CHINA

Lu Tang[1,2], Lu Chen[1,2], Xiaolu Liu[1,2], Xiangyi Liu[1,2], Dongsheng Fan[1,2,3]
Department of Neurology, Peking University Third Hospital, Beijing, China
Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Peking University Third Hospital, Beijing 100191, China
Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing 100191, China

INTRODUCTION

Genetic contributions have been widely proven in the pathogenesis of amyotrophic lateral sclerosis (ALS). However, little is known about patients with late-onset ALS (LoALS) , whose numbers are increasing due to the aging of the global population.

METHODS

The cut-off of 65 years for LoALS was applied in the current study according to a previous ALS epidemiology study covering 0.43 billion Chinese residents. We performed whole-exome sequencing and GGGGCC expansion repeat detection of C9orf72 in our cohort of patients with LoALS. Thirty-four ALS-related genes were analysed. The clinical features of patients with identified mutations/variants were collected and analyzed. Additionally, a systematic review of Chinese patients with LoALS and identified mutations was conducted adhering to PRISMA guidelines.

RESULTS

Five patients (55.6%) with familial ALS and 4 (33.3%) with sporadic ALS carried definitive mutations or damage-supporting variants. We analyzed them in combination with 48 cases from the systematic review, finding that the most frequently causative genes were SOD1, NEK1, ANXA11, and TBK1 in LoALS patients, which were not the same distribution with adult-onset patients (usually between 45-64 years in China). Nearly one-third of LoALS patients with available data had bulbar onset. The median (IQR) survival was 32 (25.2-78.1) months.

CONCLUSION

Our results highlight the high genetic identification (42.9%) in LoALS patients, and the possible distinct genetic distribution in LoALS patients compared with the adult-onset ALS patients. Our findings support the use of sequencing in ALS patients at diagnosis, irrespective of family history and age at onset, who could be candidates for gene-based therapy.

Clinical
OPC005

CORTICAL HYPEREXCITABILITY IN AMYOTROPHIC LATERAL SCLEROSIS IS MEDIATED BY DISTINCT NEURONAL POPULATIONS

Pavey, Nathan[1], Menon, Parvathi[1], Hannaford, Andrew[1], Van Den Bos, Mehdi[1], Matthew C. Kiernan[2], Vucic, Steve[1].
Brain and Nerve Research Centre, NSW Australia; University of Sydney, New South Wales, Australia.
Brain and Mind Centre, University of Sydney, Sydney, New South Wales, Australia

INTRODUCTION

Threshold tracking transcranial magnetic stimulation (TMS) is an established technique to identify cortical dysfunction in ALS. Short interval cortical inhibition (SICI) is an important neurophysiological biomarker of upper motor neurone dysfunction in ALS that is reliably demonstrated with TMS. Physiological processes differentially sensitive to current direction are thought to mediate cortical excitability, however the mechanisms are not fully understood in diseases such as ALS.
Consequently, the aim of the present study was to delineate the directional processes that mediate cortical inhibition and facilitation in ALS.

METHODS

Threshold tracking TMS, utilising the paired pulse technique with a figure-of-eight coil, was undertaken in 29 subjects with the coil oriented in posterior-anterior (PA), anterior-posterior (AP) and latero-medial (LM) directions were performed in all participants. The mean SICI and short interval cortical facilitation (SICF) were analysed.

RESULTS

Twelve ALS and 17 healthy control participants were recruited. The median age of ALS patients was 70 (IQR:64-76) while the median age of healthy controls was 57 (IQR: 50-61). The mean SICI (ISI 17ms) was significantly lower in ALS compared to healthy control participants in the PA (-0.5±12.3 vs 10.0±10.4, P= 0.019) and LM (-8.1±10.4 vs 6.1±5.1, P<0.001) stimulation directions. In contrast SICI with AP stimulation was similar between ALS (9.5±6.1) and controls (13.4±6.6, P=0.172). The mean SICF (ISI 1-5ms) in ALS was significantly reduced with LM directed stimulus (-28.4±7.5) compared to healthy controls (-14.0±7.2, P<0.01).

CONCLUSION

The present study has established that PA and LM oriented inteeuronal populations are dysfunctional in ALS, contributing to cortical hyperexcitability. Treatment aimed at modulating the PA and LM oriented neuronal populations may prove to be of therapeutic benefit.

Clinical
OPC006

DESIGNING A MIXED REALITY SETUP TO REDUCE THE COMMUNICATION BARRIER BETWEEN ALS PATIENTS AND THEIR FAMILY/CARETAKERS

Mandar RANE[1], Ajay PARGE[2], Purba JOSHI[3]
[1,3] IDC School of Design, IIT Bombay, Mumbai, India [2] Digital Art VRe, Pune, India

Due to neural degeneration, ALS patients with speech problems find it difficult to communicate with people in their surroundings. Our observation and interaction with the stakeholders (patients, families, doctors, caregivers) confirmed that establishing communication concerning the patient's daily needs is tedious and frustrating. We envisaged a communication system with need-based icons to resolve this barrier.

Research with the stakeholders was conducted to identify patients' needs. Realising that the list of requirements is endless, it was narrowed down to the patient's core needs of food, movement, hygiene and sanitation. A professional graphic designer created icons for every need, which were tested using ISO standardised tests.

The first prototype to implement these icons was built using a laptop with Eyetribe (eye-tracking device) and its Software Development Toolkit (SDK). The user's stare activated the letters on the screen keyboard. The setup failed as it was tedious for the user to type using her eyes, and the device required calibration every time the laptop restarted.

Meta Quest Pro was chosen for the next-generation prototype because it had Passthrough and eye tracking. Unity software was used to develop the eye-tracking application. A 3-second stare by the user activated the essential icons like water and toilet. An online mobile messaging service was integrated to send an sms to the desired number when the icon was activated.

This mixed-reality system allows users to observe their surroundings while accessing the need-based icons. For example, a user can now watch TV with family members with the icons floating in the real world, and when needed, the user can stare at the icons and ask for food, water and other urgent needs. The idea opens up tremendous opportunities to think of an ecosystem to bridge the communication gap between ALS patients with speech problems and their families/caregivers.

Clinical
OPC007

EFFICACY OF A NEED BASED PSYCHOSOCIAL INTERVENTION IN ALS

Priya Treesa Thomas[1], *Manjusha Warrier G.*[2], *Seena Vengalil*[3], *Atchayaram Nalini* [3]
Department of Psychiatric Social Work, National Institute of Mental Health and Neuro Sciences, Bangalore
Department of Psychology, Christ (Deemed to be University), Bangalore
Department of Neurology, National Institute of Mental Health and Neuro Sciences, Bangalore

INTRODUCTION

Amyotrphic Lateral Sclerosis has a relentless deteriorating course that requires that psychological and social care is provided parallel to the spiralling of loss. We aimed to understand the efficay of an individualised psychosocial intervention to address the role of psychosocial variables in adaptation of persons with ALS(PwALS) and their families to the diagnosis of ALS.

METHOD

A quasi experimental research with pre-post test design was condcuted. Functionality (ALSFRS-R scale), psychosocial functioning of (Becks Depression Inventory (BDI), Beck's Anxiety Inventory (BAI), Quality of life (ALSQOL-R), and coping (Brief COPE) were assessed and family caregivers were assessed on coping (Brief COPE) and Burden (Zarit Burden Interview) at the baseline. Intervention was based on Rolland's (1994) psychosocial conceptualization of chronic illness. Post intervention, assessmnts were done at 15 days and 3 months. Psychosocial variables, BDI, BAI, QoL, and ALSFRS scores as well as ZBI scores were subjected to RMAnova across three time points.

RESULTS

Ninety-three PwALS (64 males and 29 females) and their family caregivers took part in the study, between ages 23 to 73 with a mean age of 52.34. Duration of illness varied from three months to 11 years with a mean of 16.93 months. 71 had limbic onset MND. Post intervention, there was significant improvement in the psychosocial variables seen soon after intervention, among the PwALS and the caregivers, but the results from the interventions showed a downward trend at the three month assessment.

CONCLUSION

The results show that despite of the physical difficulties and functional limitations caused by the very nature of illness, psychosocial functioning can be enhanced by structured interventions. As the needs and challenges faced by the patients and the caregivers changes across the illness trajectory. This points towards the need for continuous structured home based psychosocial interventions with community participation.

Basic Science
PB001

ACID SPHINGOMYELINASE AS A BIOMARKER REFLECTING DISEASE ACTIVITY OF ALS

Jinseok Park1, Min Yeop Nahm1 ,Min Young Noh 1, Hee Kyung Jin 2,3, Jae-sung Bae 2,4, Kyoung Jin Shin5, Seung Hyun Kim 1
Department of Neurology, College of Medicine, Hanyang University, Seoul, Korea
KNU Alzheimer's disease Research Institute, Kyungpook National University, Daegu 41566, South Korea
3Department of Laboratory Animal Medicine, College of Veterinary Medicine, Kyungpook National University, Daegu, Korea.
4Department of Physiology, Cell and Matrix Research Institute, School of Medicine, Kyungpook National University, Daegu, Korea.
5Department of Neurology, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea

Acid sphingomyelinase (ASM) which is one of the significant sphingolipid-metabolizing enzymes has been found in various neurodegenerative diseases such as Alzheimer's disease(AD) or Parkinson's disease(PD). Similar to other neurodegenerative diseases, in Amyotrophic lateral sclerosis (ALS) abnormality in sphingolipid and cholesterol metabolism had been reported. We found a difference in CSF-ASM activity in ALS patients from a normal population. This finding was also observed in other previous studies which conducted on other neurodegenerative diseases like AD or PD. And assuming that the progression of the disease is not constant, we divided ALS patients into three groups according to disease status (ALSFRS-R score) at the time of CSF sampling. The ASM activity showed relatively elevated in certain ALS patient groups. From this result, we tentatively concluded that ASM activity in ALS patients rises and falls from a certain stage of the disease. And we would look forward to the possibility of ASM as a disease activity biomarker of ALS.

Basic Science
PB002

RIPK1 ACTIVATION CONTRIBUTES TO DISEASE PATHOPHYSIOLOGY IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND DRIVES A PRO-INFLAMMATORY GENE SIGNATURE IN A HUMAN iPSC-DERIVED TRI-CULTURE SYSTEM

Matija ZELIC[1], Anna BLAZIER[1], Fabrizio PONTARELLI[1], Michael LAMORTE[1], Ozge E. TASDEMIR-YILMAZ[1], Tracie TRELEAVEN[1], Emma McGUIRK[2], Yi REN[1], Jim DODGE[1], Nellwyn HAGAN[1], Nazem ATASSI[1], Joseph GANS[1], Giorgio GAGLIA[1], Timothy R. HAMMOND[1], Dimitry OFENGEIM[1]
[1]Sanofi, Cambridge, MA, USA
[2]Brandeis University, Waltham, MA, USA

INTRODUCTION

RIPK1, a critical regulator of inflammatory signaling and cell death, is implicated in pathogenic cellular pathways of ALS. Utilizing ALS SOD1^{G93A} mouse model, we previously showed an increase in RIPK1 activation and expression in spinal cord, with delayed symptom onset and motor impairment upon RIPK1 inhibition. Further, RIPK1 activation and expression were elevated in postmortem spinal cord samples from sporadic ALS patients. While these data suggest RIPK1 activation in CNS may mediate ALS disease progression, we interrogate RIPK1-induced gene expression changes in an *in vitro* tri-culture system and elucidate RIPK1 activity role in ALS patients by correlating gene changes with RIPK1 expression using single nucleus RNA-sequencing.

METHODS

We established human induced pluripotent stem cell (iPSC)-derived tri-culture system comprising motor neurons, microglia, and astrocytes to derive a human RIPK1-dependent gene signature. Human ALS post-mortem spinal cord samples were obtained from NIH NeuroBioBank. RIPK1 activation and expression levels in samples were assessed by Meso Scale Discovery (MSD) assay. *In vitro* and *in vivo* RIPK1-dependent gene and pathway regulation were assessed using single cell and single nucleus RNA-sequencing, respectively.

RESULTS

We identified an immune and neuro-inflammatory gene signature driven by microglia and astrocytes upon RIPK1 activation in iPSC-derived tri-culture system. In post-mortem ALS spinal cord samples, we identified disease-associated microglia and astrocyte subpopulations and profiled pathway changes in ALS patients. Increased RIPK1 expression may correlate with gene and pathway modulation and cell population shifts, namely loss of neurons and endothelial cells and increases in astrocytes and microglia, relative to control as assessed via single nucleus RNA-sequencing.

CONCLUSION

Human data sets are being further explored to correlate transcriptomic changes with RIPK1 expression levels and understand pathway changes in ALS associated cell type-specific subpopulations. These data suggest that aberrant RIPK1 activation in various CNS cell types may contribute to motor neuron loss in ALS.

Basic Science
PB003

PLASMA MIRNA-214 IS A PREDICTIVE CANDIDATE BIOMARKER OF PROGRESSION SPEED IN PATIENTS WITH ALS

Min-Young Noh[1], Min-Soo Kwon[2*], Ki-Wook Oh[1], Jinseok Park[1], Hee Kyung Jin[3], Jae-sung Bae[3], Seung Hyun Kim[1]*

[1]Department of Neurology, College of Medicine, Hanyang University, Wangsimniro 222-1, Seoul 04763, Republic of Korea.

[2]Department of Pharmacology, Research Institute of Basic Medical Science, School of Medicine, CHA University, CHA Bio Complex, 335 Pangyo, Gyeonggi-do 13488, Republic of Korea.

[3]Department of Laboratory Animal Medicine, College of Veterinary Medicine, Kyungpook National University, Daegu 41566, Republic of Korea.

This study was designed to develop and validate a reliable biomarker to predict the progression speed reflecting the immune function of amyotrophic lateral sclerosis (ALS). After establishing the induced microglia model (iMGs) derived from peripheral blood monocytes, comparative studies to find factors related to phagocytic differences between iMGs of patients with rapidly progressive ALS [ALS(R)iMGs, n = 15] and those of patients with slowly progressive ALS [ALS(S)-iMGs, n = 14] were conducted in the discovery cohort. To validate discovered candidate and whether it could be used as a reliable biomarker predicting the progression speed of ALS, we recruited 132 patients with ALS and 30 age-matched healthy controls as the validation cohort. ALS(R)-iMGs showed impaired phagocytic function. Transcriptomic analysis revealed that the perturbed phagocytosis in ALS(R)-iMGs was related to the decreased expression of NCKAP1 (NCK-associated protein 1) and NCKAP1 overexpression rescued the impaired phagocytic function. miRNA-214-3p targeting NCKAP1 in ALSiMGs was correlated with progression speed in the discovery cohort. The validation cohort revealed that plasma miRNA-214-3p levels were significantly increased in ALS patients ($p < 0.0001$, AUC = 0.839), correlated with disease progression speed ($p = 0.0005$), and distinguished the rapidly progressive subgroup (Q1) from the slowly progressive (Q4, $p = 0.029$), respectively. Plasma miRNA214-3p can predict the progression speed in ALS. Plasma miRNA-214-3p could be used as a simple and easily accessible biomarker for predicting the future progression speed related to phagocytic dysfunction in ALS patients.

Basic Science
PB004

PLASMA AND SALIVARY ACETYLCHOLINESTERASE ACTIVITY IN ALS

Aydar N. KHABIBRAKHMANOV[1,2], Irina V. ZUEVA[3], Konstantin A. PETROV[3], Enver I. BOGDANOV[2], Marat A. MUKHAMEDYAROV[1]
Department of Normal Physiology, Kazan State Medical University, Kazan, Russia
Department of Neurology and Rehabilitation, Kazan State Medical University, Kazan, Russia
Laboratory of chemical-biological research, Arbuzov Institute of Organic and Physical Chemistry, Federal Research Center "Kazan Scientific Center of the Russian Academy of Sciences", Kazan, Russia

INTRODUCTION

Acetylcholinesterase (AChE) activity has been shown to change in blood plasma in ALS (Rasool et al., 1983; Niebrój-Dobosz and Mickielewicz 1999). It is now assumed that plasma AChE can be a potential biomarker for ALS (Campanari et al., 2016; Verma et al., 2022). Thus, we decided to measure plasma and salivary AChE activity in ALS patients and evaluate its diagnostic capability for the first time after the implementation of mode ALS diagnostic criteria.

METHODS

17 patients with ALS were examined (31 to 71 y.o.), including 6 patients with bulbar onset and 11 patients with spinal onset of ALS. 9 patients with ALS mimics served as disease controls (33 to 61 y.o). 15 healthy persons served as normal controls (36 to 72 y.o.). Samples of venous blood and unstimulated saliva were collected, AChE activity was measured by using the Ellman calorimetric method. The Mann-Whitney U-test was used to evaluate statistical significance.

RESULTS

There was no significant difference in plasma AChE activity between the ALS group and the control groups. Also, no correlation between plasma AChE activity and disease severity, stage, duration, progression rate was found. However, the significant increase of salivary AChE activity was found in ALS patients compared to the normal control (p=0,031). Next, the ALS group was divided into bulbar and spinal onset ALS subgroups. Bulbar onset ALS patients showed significantly increased salivary AChE activity compared to the spinal onset ALS patients (p=0,022) and the normal control (p=0,035).

CONCLUSION

We suppose that plasma AChE activity cannot be considered as a diagnostic biomarker for ALS. At the same time salivary AChE activity is increased in ALS patients with bulbar onset compared to spinal onset ALS patients and normal control. However, it does not allow to separate ALS patients from ALS mimics.

Basic Science
PB005

THE LEVEL OF PLASMA GELSOLIN AS A BIOMARKER IN PATIENTS WITH ALS

Sugyeong Ahn[1], Min-Young Noh[1], Minyeop Nahm[2], and Seung Hyun Kim[1]*
1 Department of Neurology, College of Medicine, Hanyang University, Seoul, Republic of Korea 2 Dementia Research Group, Korea Brain Research Istitute, Daegu, Republic of Korea

Amyotrophic lateral sclerosis (ALS) is the most common incurable motor neuron disease with no effective treatment or biomarker. Plasma gelsolin (pGSN) is an actin-binding protein that is secreted into the extracellular fluid, with the skeletal muscle being its major source. The level of pGSN has been shown to be related to inflammation, protein aggregation, and clinical conditions in various diseases. Here, we evaluated pGSN levels as a potential biomarker in patients with ALS and compared them with the plasma Neurofilament light chain (pNfL) level.

Blood and CSF samples of ALS patients (n = 125) and age-matched HC (n = 70) were collected from the ALS cohort of Hanyang University Hospital, and retrospective analysis was conducted. We stratified ALS into two subgroups based on the disease progression rate (ΔFS) and the median values of pGSN and pNfL. We compared the correlation between pGSN or pNfL levels with clinical parameters, CSF inflammatory cytokines, and between them.

pGSN and pNfL levels were significantly elevated in ALS patients compared to HC, and ROC curve analysis revealed the ability to discriminate between ALS and HC (p =0.0002 in pGSN). In subgroup analysis, the ALS rapidly progressive group had statistically higher pGSN and pNfL levels than HC. In Kaplan-Meier analysis, both high-pGSN and high-pNfL groups showed positive correlations with ΔFS and had worse prognoses. There was a positive correlation between pGSN and pNfL. pGSN levels had no correlation with CSF inflammatory cytokines, but pNfL levels showed a positive correlation with the levels of IL-15, IL-1Ra, IL-6, and MCP-1. Our results suggest that elevated levels of pGSN have discriminating power and prognostic performance. However, the measurement of pGSN did not reach the significance of pNfL in this cross-sectional study. Therefore, we suggest the need for longitudinal studies to evaluate another role of pGSN as an ALS biomarker.

Basic Science
PB006

CHARACTERIZATION OF FAMILIAL AND SPORADIC ALS USING HUMAN MOTOR NEURONS

Sandra DE LA FUENTE[1], Laurent GUILLAUD[1], Marco TERENZIO[1]
[1]Molecular Neuroscience Unit. Okinawa Institute of Science and Technology Graduate University (OIST), Okinawa, Japan

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disorder that has no effective cure. One of the biggest challenges to develop effective treatments for ALS is that, by the time ALS is diagnosed, the degeneration of neurons has already occurred. Thus, there is a need for the discovery of reliable biomarkers for pre-symptomatic, or early stages of the disease, that will facilitate the development of better prognostic criteria, subclinical classification of the disease, and the development of targeted drugs and effective therapeutic interventions. Murine models can recapitulate the most salient features of the genetic forms of human ALS, but are not representative of the sporadic forms ALS, which constitute 95% of the total case numbers. To overcome these limitations, we work with motoneurons (MNs) derived from ALS patient's inducible pluripotent stem cells (iPSCs). Our iPSC lines are derived from both sporadic and familial ALS patients. To advance the understanding of the pathological changes that lead to MNs degeneration, we analyzed key pathological changes to highlight the differences between genetic and familiar forms of ALS. TDP43 is the first pathological hallmark to appear in MNs derived from ALS patients as it already shows differences in its cytoplasmic localization at 10 days *in vitro*. After 20 days *in vitro*, all ALS MNs show higher neurite degeneration compared to healthy control cells. Similarly, mitochondria morphology and distribution in the axon are affected in sporadic and genetics forms of ALS. Our next step will be performing proteomics analysis to uncover the mechanisms underlying ALS pathology in familial and sporadic cases and identify reliable biomarkers for diagnostics and development of effective therapeutic strategies.

Basic Science
PB007

SMALL RNA SEQUENCING OF CIRCULATING SMALL EXTRACELLULAR VESICLES MICRORNAS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Yoonho Hong1, Jin-Ah Kim2, Canaria Park3, Seok-Jin Choi2, Jung-Joon Sung2, Do-Jin Seo4
Deparment of Neurology, Seoul National University College of Medicine, Seoul Boramae Medical Center, South Korea
Department of Neurology, Seoul National University Hospital, South Korea
Department of Neurobiology, Harvard Medical School, Boston, MA, USA
Department of Neurology, Seoul National University College of Medicine

INTRODUCTION
Dysregulation of microRNAs (miRNA) in small extracellular vesicles (sEV) such as exosomes have been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS). Although circulating cell-free miRNA have been extensively investigated in ALS, sEV-derived miRNAs have not been systemically explored yet.

METHODS
Here, we performed small RNA sequencing analysis of circulating sEV miRNA from ALS patients and age- and sex-matched healthy controls. Differentially expressed miRNAs were further evaluated using droplet digital PCR (ddPCR) in an independent cohort. To assess the pathophysiological relevance of validated miRNAs, bioinformatic analysis was performed for the miRNA-target interaction and biological pathways enriched in the target genes.

RESULTS
The sEV was isolated from the serum samples by using a commercial kit (exoEasy, QIAGEN), and characterized by transmission electron microscopy, nanoparticle tracking analysis and weste blot. We identified 5 differentially expressed miRNA in a discovery cohort of 12 patients and 11 age- and sex-matched healthy controls (fold change > 2, $p < 0.05$). Two of them (up- and downregulation of miR-23c and miR192-5p, respectively) were confirmed in a separate validation cohort (18 patients and 15 healthy controls) by droplet digital PCR. Bioinformatic analysis revealed that these two miRNAs interact with distinct sets of target genes and involve biological processes relevant to the pathomechanism of ALS.

CONCLUSIONS
Our results suggest that circulating sEV from ALS patients have distinct miRNA profiles which may be potentially useful as a biomarker of the disease.

Basic Science
PG001

HOTSPOT VARIANTS IN THE LOW-COMPLEXITY DOMAIN OF ANXA11 CAUSE AMYOTROPHIC LATERAL SCLEROSIS-FRONTOTEMPORAL DEMENTIA AND IMPAIRED STRESS GRANULE DYNAMICS.

Wonjae Sung[1], Minyeop Nahm[2], Su Min Lim[1], Min-Young Noh[1], Sanggon Lee[1], Sung-Min Hwang[3], Yong Ho Kim[3], Jinseok Park[1], Ki-Wook Oh[1], Chang-Seok Ki[4], Young-Eun Kim[5], Hee Kyung Jin[6], Jaesung Bae[7], and Seung Hyun Kim[1]
Department of Neurology, College of Medicine, Hanyang University, Seoul, Republic of Korea
Dementia Research Group, Korea Brain Research Institute, Daegu, Republic of Korea
Gachon Pain Center and Department of Physiology, College of Medicine, Gachon University, Incheon, Republic of Korea
GC Genome, Yongin, Republic of Korea
Department of Laboratory Medicine, College of Medicine, Hanyang University, Seoul, Republic of Korea
Department of Laboratory Animal Medicine, College of Veterinary Medicine, Kyungpook National University, Daegu 41566, Republic of Korea
Department of Physiology, Cell and Matrix Research Institute, School of Medicine, Kyungpook National University, Daegu 41944, Republic of Korea

INTRODUCTION

Increasing genetic evidence supports the hypothesis that variants in the annexin A11 gene (*ANXA11*) contribute to amyotrophic lateral sclerosis pathogenesis. Therefore, we studied the clinical aspects of sporadic amyotrophic lateral sclerosis patients carrying *ANXA11* variants. We also implemented functional experiments to verify the pathogenicity of the hotspot variants associated with amyotrophic lateral sclerosis-frontotemporal dementia.

METHODS

Korean patients diagnosed with amyotrophic lateral sclerosis (n = 882) underwent genetic evaluations through next-generation sequencing, which identified 16 *ANXA11* variants in 26 patients. We analyzed their clinical features, such as the age of onset, progression rate, initial symptoms, and cognitive status. To evaluate the functional significance of the *ANXA11* variants in amyotrophic lateral sclerosis-frontotemporal dementia pathology, we additionally utilized patient fibroblasts carrying frontotemporal dementia-linked *ANXA11* variants (p.P36R and p.D40G) to perform a series of in vitro studies, including calcium imaging, stress granule dynamics, and protein translation.

RESULTS

The frequency of the pathogenic or likely pathogenic variants of *ANXA11* was 0.3%, and the frequency of variants classified as variants of unknown significance was 2.6%. The patients with variants in the low-complexity domain presented unique clinical features, including late-onset, a high prevalence of amyotrophic lateral sclerosis-frontotemporal dementia, a fast initial progression rate, and a high tendency for bulbar-onset compared with patients carrying variants in the C-terminal repeated annexin homology domains. In addition, functional studies using amyotrophic lateral sclerosis-frontotemporal dementia patient fibroblasts revealed that the *ANXA11* variants p.P36R and p.D40G impaired intracellular calcium homeostasis, stress granule disassembly, and protein translation.

CONCLUSION

This study suggests that the clinical manifestations of amyotrophic lateral sclerosis and amyotrophic lateral sclerosis-frontotemporal dementia spectrum patients with *ANXA11* variants could be distinctively characterized depending upon the location of the variant.

Basic Science
PG002

AN ANALYSIS OF TARDBP VARIANT IN THE KOREAN POPULATION WITH AMYOTROPHIC LATERAL SCLEROSIS

Wonjae Sung[1], Jin-Ah Kim[2], Yongsung Kim[1], Min-Young Noh[1], Ji Hyun Kim[1], Jinseok Park[1], Ki-Wook Oh[1], Chang-Seok Ki[3], Young-Eun Kim[4], and Seung Hyun Kim[1]
Department of Neurology, College of Medicine, Hanyang University, Seoul, Republic of Korea
Department of Translational Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea
GC Genome, Yongin, Republic of Korea
Department of Laboratory Medicine, College of Medicine, Hanyang University, Seoul, Republic of Korea

BACKGROUND
Amyotrophic lateral sclerosis (ALS) has been linked to variants in the TARDBP gene. However, Korean ALS patients harboring the *TARDBP* variant have been rarely found. Here, we introduce a case series of ALS due variants in the *TARDBP*. Moreover, Clinical characteristics and prognosis were investigated by analyzing previously reported cases carrying *TARDBP* variant p.M337V.

METHOD
From November 2014 to August 2022, all participants in this study were recruited from the ALS clinic at two tertiary hospitals in Seoul, Korea. According to the El Escorial Revised Criteria, all patients met the diagnostic criteria for possible, probable, laboratory-supported, or definite ALS. In addition, their clinical characteristics, such as onset age, progression rate, initial symptoms, and cognitive state, were evaluated. Previous articles demonstrating subjects' characteristics were reviewed.

RESULTS
Four patients with the *TARDBP* variant were detected. All subjects carried the same missense variant (c.1009A>G; p.M337V), previously introduced as a pathogenic variant. Two patients revealed positive family history, whereas the other two subjects were sporadic. The mean age of onset was 56.6. Additionally, familial ALS patients carrying the *TARDBP* variant presented younger onset than the sporadic form of ALS (49 vs. 64). Familial ALS patients had bulbar-onset, and sporadic ALS patients had limb-onset as an initial symptom. None of the patients showed cognitive impairment, such as FTD. Fifty-eight patients carrying TARDBP variant p.M337V from ten studies delineated lower mean age of onset (51.6) and higher frequency of bulbar onset patients (58%) than general ALS patients.

CONCLUSION
This study reveals the presence of pathogenic *TARDBP* variants in Korea as a familial and sporadic form, although its prevalence and type of variant are rare compared to other populations. Nonetheless, genetic screening of *TARDBP* variants should also be conducted in both familial and sporadic patients with ALS in Korea.

Basic Science
PG003

PROGRANULIN HAPLOINSUFFICIENCY MEDIATES TDP43 CYTOPLASMIC AGGREGATION WITH LYSOSOMAL DYSFUNCTION IN THE HUMAN MODEL OF MICROGLIA

Min-Young Noh[1,†], Wonjae Sung[1,†], Mi-Hyeon Kang[1], and Seung Hyun Kim[1] [1]Department of Neurology, College of Medicine, Hanyang University, Wangsimniro 222-1, Seoul 04763, Republic of Korea.

BACKGROUND
Progranulin (PGRN) haploinsufficiency due to *granulin* (*GRN*) variants causes frontotemporal dementia (FTD) with TAR DNA-binding protein 43 (TDP-43) accumulation. Previous models of PGRN haploinsufficiency have demonstrated neuronal TDP43 pathology with microglial dysfunction. However, precise pathomechanisms of microglia, including whether microglial TDP43 pathology is present and what triggers microglial pathology, are not clearly delineated.

METHODS
We developed induced microglia-like cells (iMGs) from FTD-*GRN* patients' monocytes carrying pathogenic or likely pathogenic variants (p.M1? and p.W147*) to design a human microglial model with PGRN haploinsufficiency. *GRN* mRNA levels and microglial markers, pro-inflammatory cytokines, and lysosomal-related gene expression of patients-derived iMGs were analyzed by qRTPCR to evaluate phagocytic function. Patient-derived iMGs performed immunocytochemical analysis to detect microglia TDP-43 pathology and lipid droplets and assessed complements amount by ELISA from patient-derived iMGs.

RESULTS
Each patient's monocytes-derived iMGs revealed reduced *GRN* mRNA and PGRN levels. Moreover, each type of PGRN-deficient iMGs failed to maintain its homeostatic molecular signatures. The human model of microglia showed prominent cytoplasmic TDP-43 pathology and lipid droplets with profound lysosomal dysfunctions and impaired phagocytosis. Additionally, these pathomechanisms were mediated by C1q complement activation and upregulated proinflammatory cytokines.

CONCLUSION
This study demonstrated that *GRN*-LOF variants in the human cell model caused microglial dysfunction with abnormal cytoplasmic TDP-43 aggregation as well as impaired lysosomal function. These pathological and functional characteristics shown in this microglia model would be an important clue for developing a precisional therapeutic strategy for FTD patients with PGRN haploinsufficiency.

Basic Science
PG004

NEK1 MUTATIONS FOUND IN ALS DISRUPT PRIMARY CILIA FUNCTION, TUBULIN STABILITY, MITOCHONDRIAL DISTRIBUTION, AND CELL CYCLE PROGRESSION

Min-Young Noh[1,†], Mi-Hyeon Kang[1], Wonjae Sung[1], Ki-Wook Oh[1], and Seung Hyun Kim[1]
[1]Department of Neurology, College of Medicine, Hanyang University, Wangsimniro 222-1, Seoul 04763, Republic of Korea.

The NIMA-related kinase 1 (*NEK1*) gene has been identified as a risk gene for amyotrophic lateral sclerosis (ALS). *NEK1* is a serine/threonine kinase implicated in mediating various cellular functions, including cell cycle, cilia formation, DNA-damage response, microtubule stability, neuronal morphology, and axonal polarity. Although loss-of-function (LOF) variants and several erroneous variants have been reported, the mechanistic studies on ALS pathogenicity have not yet been precisely established, except for its association with the DNA damage response. Here, we investigate the role of *NEK-1* in ALS pathology. We analyzed the exome sequences of Korean patients with sALS and identified twelve *NEK1* variants in 15 patients, including two novel frameshift variants (p.E853Rfs*9, p.D1112Efs*50), one initiation codon variant (p.M1?), two splicing variants (c.3222+1G>A, c.396G>A), and seven missense variants (p.R643H, p.D87Y, p.R91Q, p.K1017N, p.I149L, p.P287A, p.M303T). We subsequently assessed the pathogenic potential of novel identified *NEK1* variants on functional studies focusing on primary cilia formation, DNA damage response, and microtubule stability using patient-derived fibroblasts and neuronal cells transfected with mutated*NEK1* plasmids. *NEK1* LOF-variant-derived fibroblasts reduced *NEK1* mRNA and protein levels compared to control-derived fibroblasts. ALS-linked *NEK1* variants showed impaired primary cilia formation and cilia dysfunction with alteration of cell cycle progression. Furthermore, *NEK1* LOF affected microtubule stability reduction, mitochondrial alteration, and abnormal DNA damage response. Lastly, we attempted the pharmacological inhibition of histone deacetylase 6 (HDAC6). As a result, that is shown to restore impaired microtubule stability, abnormal mitochondrial distribution, and defective primary cilia formation in *NEK1* LOF patient-derived fibroblasts. Our findings suggest that disease-associated LoF variants of *NEK1* can contribute to ALS pathogenesis through altered primary cilium formation, microtubule instability, mitochondrial abnormality, and DNA damage response. Furthermore, we suggest that HDAC6 inhibition may be an interesting therapeutic target for ALS linked to NEK1-LOF defects.

Basic Science
PG005

GENETIC ANALYSIS IN PATIENTS WITH YOUNG ONSET ALS OF CHINESE ORIGIN

Zhangyu Zou[1], Shuyan Feng[2], Sheng Chen[1], Jialin Chen[1], Yinqian Lu[1], Chunhui Che[1], Changyun Liu[1], Huapin Huang[1]
1Department of Neurology, Fujian Medical University Union Hospital, China
2 Department of Neuroelectrophysiology, Henan Provincial People's Hospital, China

OBJECTIVE
Juvenile ALS refers to ALS patients with onset before the age of 45 years. Genetic factors play a greater role in the pathogenesis of young-onset ALS than later-onset ALS. This study aims to conduct a systematic genetic study on a Chinese young-onset ALS cohort.

METHODS
From 2019.1 to 2022.12, 100 patients with young-onset ALS who were diagnosed before the age of 45 in our hospital, whole exome sequencing was performed to detected mutations in ALS related gene. GGGGCC repeats expansions were determined by Repeated primer polymerase chain reaction.

RESULTS
There were 64 males and 36 females (male to female ratio of 1.78:1); the average age of onset was 36.5 years old, and 25 of them had a family history of ALS. Thirteen proband with SOD1 mutations, seven probands with FUS mutations, two probands with TARDBP mutations, 1 case carrying SIGMAR1 compound mutations, and 1 case carrying SPG11 compound mutations were identified in the FALS indexes. Among the 75 sporadic ALS, five cases carrying SOD1 mutations, three patients with FUS mutations; 1 case with TARDBP mutation, 1 case with OPTN mutation, 1 patient with VCP mutation, 1 patient with ANXA11 mutation, 2 patients with SETX mutations. No C9orf72 mutation was found in any patient. SOD1 mutations accounted for 52% of familial youngonset ALS patients, FUS mutations accounted for 28%, TARDBP mutations accounted for 8%, SPG11, and SIGMAR1 mutations accounted for 4%, respectively; 18.6% of sporadic ALS patients had mutations, with SOD1 mutations accounted for 6.7%, FUS mutation accounted for 4.0%, SETX mutation accounted for 2.7%, TARDBP, OPTN, VCP, ANXA11 mutation each accounted for 1.3%.

CONCLUSIONS
The overall detection rates of gene mutations in familial and sporadic juvenile-onset ALS in this study were 96% and 18.6%, respectively. The most common gene mutations in juvenile ALS are SOD1 mutations and FUS mutations.

Basic Science
PG006

SYSTEMIC GENETIC SCREENING OF KOREAN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Jin-Ah Kim[1], ju-hee Chae[2], Jung-Joon Sung[3], Yoon-Ho Hong[4]
[1]Department of Translational medicine, Seoul National University College of Medicine
[2]Department of neurology, Jeonbuk national univerisity college of medicine
[3]Department of Neurology, Seoul National University Hospital
[4]Department of Neurology, Medical Research Council, Seoul Metropolitan Government-Seoul National
University Boramae Medical Center

BACKGROUND & OBJECTIVES
Genetic variations associated with amyotrophic lateral sclreosis (ALS) have been identified in more than 40 genes. The genetic spectrum of ALS varies widely between ethnic groups. Currently, the burden of rare variants in the causative genes for ALS has also been emphasized due to its clinical relevance. In this study, we report the distribution of pathogenic variants and variants of uncertain significance (VUS) in our cohort to provide the architecture of rare variants and their clinical relevances.

METHODS
We included 154 ALS patients who visited Seoul National University Hospital and Seoul Metropolitan Boramae Medical Center ALS clinic between January 2007 and August 2022. Our ALS multigene panel consisted of 27 ALS associated genes based on the classification of Amyotrophic Lateral Sclerosis online Database (ALSoD). Variants were classified according to the American College of Medical Genetics guideline.

RESULTS
We identified 13 pathogenic and likely pathogenic variants in 14 of 154 patients (9%). SOD1 was the most common pathogenic mutation both in familial and sporadic cases, followed by FUS. A total of 37 VUS were detected in 34 (22%) patients in 15 genes. We revealed that patients with pathogenic variants or VUS developed the disease at a significantly earlier age compared to those without such variants.

CONCLUSIONS
In this study, we revealed the genetic architecture of Korean ALS patients and showed not only pathogenic variants but also VUS could have a clinical implication. Furthermore, with the advent of clinical trials targeting patients with specific genetic variants such as SOD1, FUS, and C9orf72 mutations, routine genetic screening should be considered in all patients with ALS with careful genetic counseling.

Basic Science
PG007

RARE FORMS OF GENETICALLY MEDIATED FAMILIAL AND SPORADIC AMYOTROPHIC LATERAL SCLEROSIS FROM INDIA

M S Keerthipriya[1], Mainak Bardhan[1], Ganaraja V H[1], Seena Vengalil[1], Priya Treesa Thomas[2], Atchayaram Nalini[1]
[1]Department of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru, India
[2] Department of Psychiatric Social Work, National Institute of Mental Health and Neuro Sciences, Bengaluru, India

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a clinically and genetically heterogenous neurodegenerative condition. Various genetic mutations have been identified that cause familial ALS or Sporadic ALS. Here we describe the genetic forms of ALS, their clinical phenotypes and genetic pattes.

METHOD

A retrospective analysis of 29 genetically confirmed ALS cases evaluated between 2016 to 2023, and their family members who underwent Next-generation Sequencing (NGS) to identify the pathogenic mutations.

RESULTS

Out of 29 cases (23 males and 6 females), 18 were familial and 11 were sporadic cases.
SOD1(7/29) was the most common genetic variant found in our cohort, followed by C9orf72 (6/29), TARDBP (3/29), FUS (2/29), CHCHD10 (2/29) and SPG11 (2/29), while mutations in VCP, TBK1, OPTN, ERBB4, FIG4, SETX, CCNF, DHTKD1, ITPR1 genes were found in one case for each gene. Mutations in both OPTN and ERBB4 genes were found in one patient and another patient showed mutations in SPG and STX genes. Consanguinity was reported in 3/29 patients, they all had positive family history. The familial group reported an earlier onset of disease (40.09 ± 14.8 years) as compared to sporadic cases (46.78 ± 13.8 years). However, the mean duration of illness was longer among familial cases (42.1 ± 42.2 months) as compared to sporadic cases (10.63 ± 5.48 months). Patients with SOD1 mutation most commonly present with limb weakness at the onset (5/7). Only one patient who had a mutation in DHTKD1 presented with respiratory distress at the onset.

CONCLUSION

The genetic etiology of ALS is complex due to the significant sharing of major causative genes with FTD and other neurogenerative disorders. Interfamilial and intrafamilial phenotypic variations owing to reduced penetrance, genetic pleiotropy, oligogenic and polygenic inheritance are known in ALS. Understanding the genetic basis of disease helps to explore therapeutic options to target these genetic mechanisms.

PG008

HEREDITARY SPASTIC PARAPLEGIA WITH VISUAL DISTURBANCE: NOVEL MUTATION OF ADULT-ONSET NEURONAL CEROID LIPOFUSCINOSIS 6 DIAGNOSED FROM A SKIN BIOPSY

Sanggon Lee[1], Yong Sung Kim[2], Wonjae Sung[2], Jinseok Park[2], Ki-Wook Oh[2], Seung Hyun Kim[2]

[1]Department of Neurology, Chung-Ang University Gwangmyeong Hospital, Gyeonggi-do, Republic of Korea

[2]Department of Neurology, Hanyang University Hospital, Seoul, Republic of Korea

INTRODUCTION

Neuronal ceroid lipofuscinoses (NCL) are inherited neurodegenerative disorders caused by lipofuscin accumulation in neurons and other tissues. NCLs vary in onset age and gene mutations (CLN 1 to 14). Adult NCL has two phenotypes: type A (epilepsy, dementia, ataxia, and motor signs) and type B (behavioral and cognitive impairment, ataxia, and brainstem signs). We report a case of adult-onset NCL 6 with hereditary spastic paraplegia and visual disturbance confirmed by genetic and pathologic tests.

REPORT

A 46-year-old female with progressive lower limb weakness and visual disturbance had a family history of similar symptoms. Brain MRI showed white matter lesions in optic radiation. She was initially diagnosed with complicated HSP but later developed cognitive decline, cortical atrophy, and polyneuropathy. Whole-exome sequencing revealed two variants in CLN6 gene, one of them novel and rare. Skin biopsy confirmed lipofuscin accumulation in fibroblasts. She was diagnosed with adultonset NCL 6 mimicking HSP. This case illustrates the phenotypic spectrum and diagnostic challenges of NCL 6.

CONCLUSION

NCL is a neurodegenerative disorder that can present in adulthood with two major clinical phenotypes, type A and B. CLN6 gene mutation is typically associated with type A presenting seizure and inherited in an autosomal dominant or recessive manner. Our case showed autosomal dominant inheritance based on the family history. However, the patient lacked epileptic features and exhibited more characteristics of type B than type A. Initially, the patient was diagnosed with complicated HSP. However, white matter lesions of the brain and visual impairment prompted us to revise the diagnosis as leukodystrophy and subsequently confirm NCL 6. This implies a spectrum of neurological conditions ranging from complicated HSP to NCL 6. We recommend that patients with complicated HSP with optic radiation involvement undergo CLN6 mutation screening and skin biopsy for diagnosis.

Basic Science
PG009

HEREDITARY SPASTIC PARAPLEGIA WITH NOVEL- COMPOUND MUTATION OF SPG7 PATHOGENIC VARIANTS

Nakhoon Kim, MD[a], Seong-il Oh[b], MD[b], Young-Eun Kim, MD, PhD[c], and Ki-Wook Oh, MD, PhD[a,d] Seung Hyun Kim, MD[a,d]
[a]Department of Neurology, College of Medicine, Hanyang University, Seoul, Republic of Korea
[b]Department of Neurology, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea [c]Department of Laboratory Medicine, College of Medicine, Hanyang University, Seoul, Republic of Korea·
[d] Cell Therapy Center, Department of Neurology, College of medicine, Hanyang University, Seoul, Republic of Korea

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a group of heterogeneous disorders presenting as progressive spasticity and weakness of the lower limbs. Hereditary spastic paraplegia 7 (SPG7) is one of the subtypes of autosomal recessive hereditary spastic paraplegia.

METHOD AND RESULT

A 20-year-old Korean female patient with no known underlying disease was referred from a local orthopedic clinic. In the clinic, she complained of cramping pains of both posterior thigh and calf muscles after 10-15 minutes of walk and she mentioned that the pain eases off after a break or a stretch. She had difficulty walking up or down the stairs due to her ankle weakness. Additionally, she experienced significant weight loss, losing 10 kg in the last three months.

We performed whole exome sequencing (WES) on the patient, and two variants of the *SPG7* gene were identified; c.[244C>T];[1904C>T] p.[Gln82*];[Ser635Leu]. (fig. E) The novel nonsense variant, c.244C>T (p.Gln82*), was located on exon 2 of 17 exons expecting nonsense-mediated mRNA decay (NMD). It also is infrequent in the general population with an allele frequency of 0.00002 (gnomAD, gnomad.broadinstitute,org; accessed on Dec 18 in 2020). The missense variant, c.1904C>T (p.Ser635Leu), has been reported from two HSP patients. [2, 3] The variant is absent from the population database (gnomAD) and located on the functional domain, peptidase M41, where it has been clustered with pathogenic or likely pathogenic variants. [3] Genetic analysis of proband's parents using Sanger sequencing revealed that each parent inherited these variants. According to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG and AMP) guideline, we classified c.244C>T (p.Gln82*) as a pathogenic variant and c.1904C>T (p.Ser635Leu) as likely pathogenic variant.

CONCLUSION AND DISCUSSION

SPG7 mutation is rare in Asian MND. Patient who is HSP with an SPG7 variant of Korean descent is rare.

Basic Science
PG010

NOVEL GENETIC VARIANTS OF ALS IN AN INDIAN COHORT

[1]Seena Vengalil, [2] Ramya Sukrutha, [2] Gautham Arunachal Udupi,[1] Saraswati Nashi, [1]MS Keerthipriya, [1]Atchayaram Nalini
Department of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru, India
Department of Human Genetics, National Institute of Mental Health and Neurosciences, Bengaluru, India

INTRODUCTION

ALS is a relentlessly progressive neurodegenerative disorder, majority being sporadic. About 5-10% of cases of ALS are familial/genetic. Little is known about the genetics of ALS in Indian population. We conducted this study to report the novel genetic variants identified in an Indian cohort of ALS patients.

METHODS

Retrospective study of patients with ALS seen in a referral neurology center in India. Genetic data of patients with probable or definite ALS as per El Escorial criteria was reviewed. These patients had undergone Next Generation Sequencing and Sanger validation. Novel variants identified are reported.

RESULTS

64 patients underwent NGS, 14 patients with 13 novel genetic variants were identified. Male :female ratio- 9:5.Mean age was 51.1+13.8 years.(range 23-69 years). Majority presented in 5th-7th decade except for 1 patient of SOD1 (23 years) and 1 each of ATXN2(35 YEARS) and FUS (37 years). 2 each had heterozygous missense variants of NEFH, ATXN2 and FIG4 gene. The genetic variants identified were- NEFH(c.463G>C (p.Gly155Arg) and c.2036A>T (p.Lys679Met)),ATXN2 (c.1451C>G (p.Ser484Cys),c.110G>A (p.Arg37His)), FIG4 (c.1750G>A (p.Asp584Asn), c.1042G>T (p.Asp348Tyr)). 1 patient each had heterozygous missense variants of TARDBP (c.845G>T (p.Gly282Val), FUS (c.301G>T (p.Gly101Cys), UBQLN2 (c.1307A>T (p.Gln436Leu), SOD1- 2 patients (c.455T>A (p.Ile152Asn), SETX (c.136G>A (p.Glu46Lys). 1 patient had a heterozygous stop gain change in ANXA11 (:c.1027C>T (p.Gln343Ter) and 1 had a homozygous splice acceptor defect in OPTN (c.1402-1G>T)

CONCLUSION

This study expands the genetic spectrum of ALS seen in Indian population and reports novel genetic variants. Novel variants were identified in NEFH, ATXN2,FIG4, SOD1, OPTN, TARDBP,UBQLN2,SETX and ANXA11. Further studies on larger cohorts in Indian population are needed for further insights into genetics and pathophysiology of ALS in Indian subcontinent,

Basic Science
PG011

MUTATIONAL SCREENING OF NEK1 IN A MULTI-ETHNIC MALAYSIAN ALS COHORT

Nurul Angelyn Zulhairy-Liong[1,2], Suzanna Edgar[1,2], Melina Ellis[3], Georgina Samaha[4], Tracey Chew[4],Nur Adilah Abdul-Aziz[1], Khean-Jin Goh[1], Nortina Shahrizaila[1], Marina L. Kennerson[3,4,5], Azlina Ahmad-Annuar[2]
Department of Medicine, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia.
Department of Biomedical Science, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia.
Northcott Neuroscience Laboratory, ANZAC Research Institute, University of Sydney, Concord, NSW, Australia.
Sydney Informatics Hub, University of Sydney, Sydney, NSW, Australia.
Sydney Medical School, University of Sydney, Sydney, NSW, Australia.
Molecular Medicine Laboratory, Concord Hospital, Concord, NSW, Australia

BACKGROUND
Rare, autosomal dominant mutations in *NEK1* (NIMA-related kinase 1) increase the risk of ALS and are found in approximately 3.1% ALS patients. *NEK1* encodes serine-threonine protein kinase and loss of function (LOF) mutations, commonly associated with *NEK1*, have been shown to lead to accumulation of DNA damage in motor neurons.

OBJECTIVE
Potentially pathogenic candidate variants in *NEK1* were screened in a multi-ethnic Malaysian ALS cohort negative for mutations in the four major ALS-causative genes (*SOD1*, *TARDBP*, *FUS* and *C9orf72*).

METHOD
Forty ALS patients with onset between 31 to 79 years old were recruited from the University Malaya Medical Centre and were diagnosed according to the revised El-Escorial criteria. Short-read whole exome sequencing datasets were screened for single nucleotide variants and indels in the *NEK1*. Variants with minor allele frequency (MAF) less than 0.1%, CADD score more than 20 and classified as pathogenic, likely pathogenic or of uncertain significance according to ACMG were prioritised.

RESULTS
One heterozygous, likely pathogenic, mononucleotide duplication (c.1897dupA; p.Ile633fs) was identified in a male sporadic patient of Chinese-Malay ancestry. This frameshift variant causes a premature stop codon, truncating the wildtype protein from 1286 amino acids to 659, removing parts of the coiled-coil domain and the nuclear exportation signal 1-2. This predicted LOF *NEK1* variant has been reported in a Taiwanese sporadic ALS patient with left-hand weakness onset at 54 years old, while comparatively, the Malaysian patient had bulbar-onset at 67, which then extended to his upper and lower limbs.

CONCLUSION

Our study suggests that *NEK1* mutations in Malaysian ALS patients are rare, with the frequency of 2.5%, similar to the average global frequency. Larger cohorts and further functional validation will help to validate the pathogenicity of the variant.

Basic Science
PG012

DE NOVO SCN10A GENE VARIANT IN A PATIENT WITH FAMILIAL EPISODIC PAIN SYNDROME-2 (FEPS2)

Jihyun Kim, MD[1], Hyunkee Kim, MD[1], Yong Sung Kim, MD[1], Wonjae Sung, MD[1], Jinseok Park, MD,PhD[1], Ki-Wook Oh, MD, PhD[1], Seung Hyun Kim, MD, PhD[1]
[1]Department of Neurology, Hanyang University College of Medicine, Seoul, Republic of Korea

INTRODUCTION

Familial episodic pain syndrome-2 (FEPS) is a rare autosomal dominant peripheral neuropathies characterized by adult-onset episodic burning pain which involve the distal extremities. FEPS2 is caused by heterozygous mutation in the SCN10A gene. The pain often triggered by physical stress or exertion, fatigue, fasting, and cold. Herein, we report a case of FEPS2 to a de novo SCN10A gene variant.

REPORT

A 58-year old male with no previous medial history presented to the outpatient clinic for hyperalgesia on distal extremities that started one year ago. After he experienced weight loss about 12 kilograms due to food poisoning, he had painful paresthesia and leg weakness. While motor symptoms gradually improved as he gains weights, sensory symptoms were not improved. NCS showed the prolongation of F-wave and EMG showed widespread denervation potentials. But after four months follow-up EMG showed decreases in denervation potentials. We concluded his state as the resolution of critical illness neuropathy with remnant small fiber neuropathy. Although there was no familial history, he have conducted whole-exome sequencing for the search of de novo genetic variant. As a result, the gene panel showed heterozygous SCN10A gene missense variant (SCN10A NM_006514.3:c.1649C>T (p.Pro550Leu)).

CONCLUSION

FEPS2 is autosomal dominant disorder caused by mutations in the SCNA10A gene that encodes Nav1.8, which expressed specifically in the dorsal root ganglia. Although the patient had no familial history, prominent neuralgia and similar to the patient carrying the SCN10A gene variant, supports this diagnosis. Normally the mutation mainly caused small fibers neuropathy. However, in our case, the patient showed abnormal large fiber neuron involvement. As he had severe weight loss and was recovering, critical illness neuropathy could have occurred these findings. When the electrophysiological tests and clinical symptoms don’t correlate, we have to focus on clinical symptoms and should keep in mind the possibility of rare diseases.

Basic Science
PG013

VERIFICATION OF GENETIC FACTORS AFFECTING SURVIVAL IN JAPANESE PATIENTS WITH SPORADIC AMYOTROPHIC LATERAL SCLEROSIS

Ryoichi Nakamura[1], Genki Tohnai[1], Masahiro Nakatochi[2], Naoki Atsuta[1], Hirohisa Watanabe[3], Daisuke Ito[2], Masahisa Katsuno[2], Yuishin Izumi[4], Mitsuya Morita[5], Takehisa Hirayama[6], Osamu Kano[6], Kazuaki Kanai[7], Nobutaka Hattori[8], Akira Taniguchi[9], Naoki Suzuki[10], Masashi Aoki[10], Ikuko Iwata[11], Ichiro Yabe[11], Kazumoto Shibuya[12], Satoshi Kuwabara[12], Masaya Oda[13], Rina Hashimoto[14], Ikuko Aiba[14], Tomohiko Ishihara[15], Osamu Onodera[15], Toru Yamashita[16], Koji Abe[16], Kouichi Mizoguchi[17], Kenji Nakashima[18], Ryuji Kaji[4], Jun-ichi Niwa[1], Manabu Doyu[1], Gen Sobue[5,29], the Japanese Consortium for Amyotrophic Lateral Sclerosis research (JaCALS) study group
Aichi Medical Universityã€€
Nagoya University
Fujita Health University
Tokushima University
Jichi Medical University
Toho University
Fukushima Medical University [8] Juntendo University
Mie University
Tohoku University
Hokkaido University
Chiba University
Vihara Hananosato Hospital
National Hospital Organization Higashinagoya National Hospital
Niigata University
Okayama University
National Hospital Organization Shizuoka Medical Center [18] National Hospital Organization, Matsue Medical Center

PURPOSE

Amyotrophic lateral sclerosis (ALS) is a clinically heterogeneous disease, and prognosis in patients with the disease has been reported to vary among different ethnic populations. The aim of the present study was to validate single-nucleotide polymorphisms (SNPs) that have been reported to affect survival in Caucasian ALS cohorts using data from a Japanese ALS cohort.

METHODS

A total of 1076 Japanese patients with sporadic ALS, who were diagnosed with clinically definite, probable, probable laboratory-supported or possible ALS according to the revised El Escorial criteria, were enrolled. Genotyping was performed using the HumanOmniExpressExomeBeadChip to analyze SNPs in *CAMTA1*, *IDE*, and *UNC13A*, which have been reported to affect survival in ALS patients in Caucasian cohorts. Survival curves for each genotype group were estimated based on the Kaplan– Meier method and compared using the log-rank test. Multivariate survival analysis was performed using the Cox proportional hazard model.

RESULTS

Previously reported SNPs in Caucasian populations, such as rs2412208 in *CAMTA1*, rs139550538 in *IDE*, and rs12608932 in *UNC13A*, were not associated with survival in the present study, suggesting that genetic factors affecting the prognosis of patients with ALS may differ between Japanese and Caucasian populations. The SNP in *KIFAP3* (rs1541160) was excluded from analysis because the minor allele frequency is < 0.01 in the Japanese population and the present cohort.

CONCLUSIONS

Previously reported SNPs associated with survival in Caucasian ALS patients were not fully replicated in Japanese ALS patients. This could be explained by the different genetic background of ALS in Asian and Caucasian patients affected by the disease. To clarify the genetic background affecting survival in Japanese ALS patients, a genome-wide association study to search for genetic factors supporting prognosis in a Japanese cohort is warranted.

Basic Science
PG014

WHOLE GENOME SEQUENCING (WGS) IDENTIFIES CANDIDATE GENES IN TWO TRIOS IN A MALAYSIAN ALS COHORT

Suzanna EDGAR[1,2], Melina ELLIS[3], Georgina SAMAHA[4], Tracey CHEW[4], Nur Adilah ABDUL-AZIZ[1], Khean-Jin GOH[1], Nortina SHAHRIZAILA[1], Marina L. KENNERSON[3,5,6], Azlina AHMAD-ANNUAR[2]

[1]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[2]Department of Biomedical Science, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[3]Northcott Neuroscience Laboratory, ANZAC Research Institute, University of Sydney, Concord, NSW, Australia

[4]Sydney Informatics Hub, University of Sydney, Sydney, NSW, Australia

[5]Sydney Medical School, University of Sydney, Sydney, NSW, Australia

[6]Molecular Medicine Laboratory, Concord Hospital, Concord, NSW, Australia

INTRODUCTION

As part of an ongoing genetic study, two sporadic ALS (sALS) patients negative for mutations in *SOD1*, *FUS*, *TARDBP*, *C9orf72* and 43 ALS-associated genes were selected for screening in an expanded ALS gene panel as well as for other potential novel genes using a WGS trio-based approach.

METHODS

Patient 1 (T1) of Chinese, and Patient 2 (T2) of Malay ancestries respectively, both male, with limb onset and early age of disease onset (≤ 45 years), and their unaffected parents underwent short-read WGS and queried for coding variants in an additional 139 genes and genomic loci associated with ALS as listed in ALSod and recent studies. In-house bioinformatics pipelines were established to identify compound heterozygous, homozygous, and *de novo* variants in non-ALS related genes.

RESULTS

Neither patient had pathogenic/likely pathogenic variants in the ALS-associated genomic loci. Therefore, screening was expanded to query compound heterozygous, homozygous, and *de novo* variants in non-ALS related genes. For patient T1, we identified eight compound heterozygous variants in three genes: *OBSCN*, *TFPD*, and *SEMA7A*, and three *de novo* variants in *ODF2L*, *ATP8B2*, and *RAB21*. In patient T2, we identified ten compound heterozygous variants in five genes: *FAT3*, *PPPR1B*, *COL5A3*, *EDEM2*, and *TSHZ2*, seven *de novo* variants in *PRAMEF13*, *MUC22*, *UTRN*, *MUC3A*, *MAPKBP1*, *KIR2DL4*, and *SLC25A5* genes and one homozygous variant in *UHRF1BP1*. Of these genes, those associated with reported ALS disease pathways or other neurodegenerative disease phenotypes include *RAB21*, *SEMA7A*, and *TFAP2D* in patient T1, and *FAT3*, *UTRN*, *SLC25A5*, and *UHRF1BP1* in patient T2.

CONCLUSION

Systematic screening of known ALS genes and loci in two sALS patients did not yield any positive results, thus screening for potentially novel ALS genes identified a number of

possible candidates. These candidate genes will require further validation and replication studies by other groups.

Basic Science
PG015

CLINICOPATHOLOGICAL AND GENETIC CHARACTERISTICS OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS WITH SOD1-GLY93SER MUTATION IN JAPAN

Ryoichi Nakamura[1], Yuichi Riku[1], Masahiro Nakatochi[2], Naoki Atsuta[1], Genki Tohnai[1], Daisuke Ito[2], Yuishin Izumi[3], Rina Hashimoto[4], Ikuko Aiba[4], Kouichi Mizoguchi[5], Kazuaki Kanai[6], Masashi Aoki[7], Yuichi Kawagashira[1], Jun-ichi Niwa[1], Manabu Doyu[1], Yasushi Iwasaki[1], Mari Yoshida[1], Masahisa Katsuno[2], Gen Sobue[1]
Aichi Medical University
Nagoya University
Tokushima University
National Hospital Organization, Higashinagoya National Hospital [5] National Hospital Organization Shizuoka Medical Center
Fukushima Medical University
Tohoku University

INTRODUCTION

In Japan, *SOD1* mutations are the most common cause of familial amyotrophic lateral sclerosis (ALS), and *SOD1*-G93S mutation is one of the most common mutations. Therefore, in this study, we aimed to clarify the clinicogenetic and pathological characteristics of ALS patients with *SOD1*-G93S mutation in Japan.

METHODS

We recruited 34 familial ALS patients from 12 pedigrees and 6 sporadic ALS patients with *SOD1*G93S mutation. We assessed the clinical information, such as the onset age, site, and disease duration. For familial ALS patients, we analyzed age differences at onset in the parent–offspring pairs. In addition, we performed haplotype analysis using 8,778 single nucleotide polymorphisms on chromosome 21 and analyzed the pathological characteristics of 6 autopsied patients.

RESULTS

Of the 40 patients, 93.9% had lower limb onset, with predominantly lower motor neuron signs. Median survival was 9.0 years (95% confidence interval: 6.5–11.5). Onset age (range: 29.0–75.0 years) varied among patients, and the offspring had an onset age of 11.1 years younger than the parent (P = 0.024). We identified a common haplotype across 692k bases, suggesting that the mutation arose from a common ancestor. The pathological study revealed marked degeneration in the lower motor neurons of the lumbar spinal cord, degeneration of the posterior dorsal ganglia of the spinal cord and spinocerebellar tract, and neuronal loss in the inferior olive nucleus, dentate nucleus, and Clark's column.

CONCLUSION

In ALS patients with *SOD1*-G93S mutation, the onset sites were almost identical. However, the ages of onset varied, and the presence of anticipation was suggested in the familial cases. Even in patients with the identical mutation, the reason for this variety remains to be elucidated. The pathological study showed neurodegeneration in the sensory and olive-pontine-cerebellar systems.

Basic Science
PG016

A CASE OF FAMILIAL ALS WITH A NOVEL MUTATION IN THE ANXA11 GENE

Seiichi NAGANO[1,2], Kotaro OGAWA[2], Rei SAKURAI[2], Tatsuhiko OZONO[2], Kensuke IKENAKA[2], Hideki MOCHIZUKI[2]
Department of Neurotherapeutics, Osaka University Graduate School of Medicine
Department of Neurology, Osaka University Graduate School of Medicine

INTRODUCTION

5-10% of amyotrophic lateral sclerosis (ALS) cases are familial, and a number of causative genes have been identified to date. Annexin A11 (ANXA11, ALS23) encodes a member of calcium-dependent phospholipid-binding proteins and was shown to be a causative gene of ALS in 2017. In this study, we report an ALS family with a novel mutation in ANXA11 gene.

REPORT

A 65-year-old woman, at 62 years of age, felt a tangle in both legs, followed by difficulty in swallowing and vocalization. At 63 years of age, she visited a physician and was diagnosed with semantic aphasia. She also began to have difficulty in speaking and fell down easily, so she visited our hospital at the age of 64 and was admitted for a thorough examination. As a family history, her mother also suffered from ALS. Neurologically, the patient had difficulty in speech, bulbar palsy, increased mandibular and limb tendon reflexes, decreased distal limb muscle strength, and muscle atrophy of the bilateral thenars. An MRI of the head showed atrophy of the temporal lobe predominantly on the left, and electromyography showed active denervation in the paraspinal muscle. Exome analysis of the genomic DNA of the patient identified a novel mutation in the long N terminal region of ANXA11 gene, and a diagnosis of familial ALS was made.

CONCLUSION

ALS due to ANXA11 mutations is often associated with early appearance of bulbar palsy, and the reported mutations are mostly located in the long N terminal region, which are features consistent with the present case.

Basic Science
PG017

FREQUENCY AND PATHOGENICITY ANALYSIS OF DNAJC7 GENE VARIANTS IN JAPANESE PATIENTS WITH ALS

Genki Tohnai[1], Ryoichi Nakamura[1], Naoki Atsuta[1], Masahiro Nakatochi[2], Masahisa Katsuno[2], Yuishin Izumi[3], Akira Taniguchi[4], Nobutaka Hattori[5], Mitsuya Morita[6], Osamu Kano[7], Satoshi Kuwabara[8], Masaya Oda[9], Koji Abe[10], Kouichi Mizoguchi[11], Ryuji Kaji[3], Gen Sobue[1], The Japanese Consortium forAmyotrophic Lateral Sclerosis Research: JaCALS
Aichi Medical University (Japan)
Nagoya University (Japan)
Tokushima University (Japan)
Mie University (Japan)
Juntendo University (Japan)
Jichi Medical University (Japan)
Toho University (Japan)
Chiba University (Japan)
Vihara Hananosato Hospital (Japan)
Okayama University (Japan)
National Hospital Organization Shizuoka Medical Center (Japan)

INTRODUCTION

DNAJC7 has recently been identified as an amyotrophic lateral sclerosis (ALS) gene by large-scale exome analysis, however its involvement in ALS remains unknown. In this study, we screened a large cohort of Japanese patients with ALS for variants of the *DNAJC7* gene. In addition, we analyzed the toxicity of these variants and their correlation with the ALS phenotype.

METHODS

Whole exome sequencing was performed on 807 patients with sporadic ALS from the Japanese ALS Registry (JaCALS) using Hiseq 2000/2500. All variants of *DNAJC7* were screened using HGVD, gnomAD, and jMorp. Variants were selected by restricting minor allele frequencies to less than 0.1%. Pathogenicity of detected variants was evaluated using in silico prediction tools including: SIFT, PolyPhen2, and CADD. Protein stability was assessed using DUET.

RESULTS

Seven variants (0.87%) were identified in the *DNAJC7* gene among 807 patients with sporadic ALS. Six patients had heterozygous missense variants (p.Asp21Ala, p.Gly98Val, p.Met165Ile, p.Thr302Met, p.Thr341Pro, or p.Tyr344Cys) and all six of these variants were predicted as damaging, by in silico analysis. In addition, one patient had a novel splice site variant (c.1447+2T>C) in the C-terminal domain of the *DNAJC7* gene. Human Splicing Finder 3.1 predicted that this variant would alter the wild-type donor site and affect splicing. We agreed with this prediction. Four variants (Met165Ile, Thr302Met, Thr341Pro, Tyr344Cys) were analyzed by DUET and three of them were predicted to destabilize the protein.

CONCLUSION

In this study, we detected seven variants in the *DNAJC7* gene which have not been reported in any public database in Japan. Furthermore, the missense variants we identified were located around the tetratricopeptide repeat (TPR) domain, which is important for DNAJC7 function. These results suggest a possible link between *DNAJC7* and ALS in the Japanese population.

Basic Science
PM001

PROTEASOME AND AUTOPHAGY EXPRESSION IN THE CENTRAL NERVOUS SYSTEM -A BIOINFORMATIC STUDY-

Yasuhiro Watanabe, Haruka Takeda, Naoto Honda, Ritsuko Hanajima
Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Japan

INTRODUCTION

The ubiquitin proteasome system (UPS) and autophagy lysosome pathway (ALP) are crucial in the control of protein quality. However, data regarding the relative significance of UPS and ALP in the central nervous system (CNS) are limited. In the present study, using publically available data, we computed the quantitative expression status of UPS- and ALP-related genes and their products in the CNS as compared with that in other tissues and cells.

METHODS

We obtained human and mouse gene expression datasets from the reference expression dataset (RefEx) and Genevestigator (a tool for handling curated transcriptomic data from public repositories) as well as human proteomics data from the proteomics database (ProteomicsDB). The expression levels of genes and proteins in four categories—ubiquitin, proteasome, autophagy, and lysosome—in the cells and tissues were assessed. The average expression value of the respective gene (or protein) across different tissues and cells was set as a reference. Perturbation of the gene expression by drugs was also analyzed for the four categories.

RESULTS

Compared with that for ubiquitin, autophagy, and lysosome, gene expression for proteasome was consistently lower in the CNS of mice but was more pronounced in humans. Neural stem cells and neurons showed low proteasome gene expression as compared with embryonic stem cells. Proteomic analyses, however, did not show trends similar to those observed in the gene expression analyses. Perturbation analyses revealed that azithromycin and vitamin D3 upregulated the expression of both UPS and ALP.

CONCLUSION

Gene and proteomic expression data could offer a fresh perspective on CNS pathophysiology. Our results indicate that disproportional expression of UPS and ALP might affect CNS disorders and that this imbalance might be redressed by several therapeutic candidates.

Basic Science
PM002

CELLULAR ANALYSIS OF SOD1 PROTEIN-AGGREGATION PROPENSITY AND TOXICITY: A CASE OF ALS WITH SLOW PROGRESSION HARBORING HOMOZYGOUS SOD1D92G MUTATION

Masanori Sawamura[1], Keiko Imamura[2,3,4], Rie Hikawa[1], Takako Enami[2,4], Ayako Nagahashi[2,4], HodakaYamakado[1], Hidenori Ichijo[5], Takao Fujisawa[5], Hirofumi Yamashita[6], Sumio Minamiyama[1,7], Misako Kaido[8], Hiromi Wada[9], Makoto Urushitani[7], Haruhisa Inoue[2,3,4], Naohiro Egawa[1,2,3], RyosukeTakahashi[1]
Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto, Japan.
Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan.
iPSCâ€'Based Drugâ€'Discovery Cellular Basis Development Team, RIKEN BioResource Research Center (BRC), Kyoto, Japan.
Medicalâ€'Risk Avoidance Based on iPS Cells Team, RIKEN Center for Advanced Intelligence Project (AIP), Kyoto, Japan.
Laboratory of Cell Signaling, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan.
Department of Neurology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan.
Department of Neurology, Shiga University of Medical Science, Shiga, Japan.
Department of Clinical Genetics, Sakai City Medical Center, Osaka, Japan.
Karasuma Wada Clinic, Kyoto, Japan.

INTRODUCTION

Mutations within Superoxide dismutase 1 (SOD1) cause amyotrophic lateral sclerosis (ALS), accounting for approximately 20% of familial cases. The pathological feature is a loss of motor neurons with enhanced formation of intracellular misfolded SOD1. Homozygous SOD1-D90A in familial ALS has been reported to show slow disease progression. We experienced a rare case of a slowly progressive ALS patient harboring a novel SOD1 homozygous mutation D92G (homD92G). Herein, we reported the clinical findings and the molecular mechanism of ALS harboring homD92G.

METHODS & RESULTS

In silico, multiple protein analysis software revealed that G93A SOD1 was toxic, whereas D92G SOD1 was assumed to be normal to mildly abnormal. Protein structure prediction tool, AlphaFold2, showed no significant conformational changes in these proteins. In vitro, the neuronal cell line overexpressing SOD1-D92G showed a lower ratio of the insoluble/soluble fraction of SOD1, fine aggregates of the misfolded SOD1, and lower cellular toxicity than those overexpressing SOD1-G93A, a mutation that generally causes rapid disease progression. Next, we analyzed spinal motor neurons derived from induced pluripotent stem cells (iPSC) of a healthy control subject and ALS patients carrying SOD1-homD92G or heterozygous SOD1-L144FVX mutation. Lower levels of misfolded SOD1 and cell loss were observed in the motor neurons differentiated from patient-derived iPSCs carrying SOD1-homD92G than in those carrying SOD1-L144FVX. [Conclusion] SOD1-homD92G has a lower propensity to aggregate and induce cellular toxicity than SOD1-G93A or SOD1-L144FVX, and these cellular phenotypes could be associated with the clinical course of slowly progressive ALS. The present report provides the new insight to the mechanism of gain of function in SOD1 mutation.

Basic Science
PM003

ACID SPHINGOMYELINASE INHIBITION IMPROVES MOTOR BEHAVIORAL DEFICITS AND NEURONAL LOSS IN AN AMYOTROPHIC LATERAL SCLEROSIS MOUSE MODEL

Hee Kyung Jin[1,2], Seung Hyun Kim[3]
[1]KNU Alzheimer's Disease Research Institute, Kyungpook National University, Daegu 41566, Korea
[2]Department of Laboratory Animal Medicine, College of Veterinary Medicine, Kyungpook National University, Daegu 41566, Korea
[3]Department of Neurology, Hanyang University College of Medicine, Seoul 04763, Korea

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease characterized by the degeneration of motor neurons in the spinal cord. Main symptoms are manifested as weakness, muscle loss, and muscle atrophy. Some studies have reported that alterations in sphingolipid metabolism may be intimately related to neurodegenerative diseases, including ALS. Acid sphingomyelinase (ASM), a sphingolipid-metabolizing enzyme, is considered an important mediator of neurodegenerative diseases. However, the correlation between altered ASM levels and ALS pathology has not yet been fully characterized.

METHODS

The study used three different mouse lines (C57BL/6 WT, FUS-R521C transgenic, and Smpd1-/-) to investigate the role of acid sphingomyelinase (ASM) in amyotrophic lateral sclerosis (ALS). Plasma and spinal cord samples were collected and analyzed for ASM activity using enzymatic assays. Histological analysis was performed using immunofluorescence staining, and behavioral studies were conducted to assess motor function. The statistical analysis was performed using one-way ANOVA and Tukey's HSD test.

RESULTS

Herein, our study showed an increased ASM activity in the plasma or spinal cord of ALS patients and in a mouse model. Moreover, we found that genetic inhibition of ASM improved motor behavioral dysfunction and motor neuronal loss in the spinal cord of an ALS mouse model.

CONCLUSION

These results suggest the role of ASM as a potentially effective target and ASM inhibition may be a possible therapeutic approach for ALS.

Basic Science
PM004

ALN-SOD RNAI THERAPEUTIC TO KNOCKDOWN SUPEROXIDE DISMUTASE 1: A POTENTIAL THERAPY FOR SOD1-ALS

Lan Dang[1], Jeffrey Kurz[1], Jing Li[1], Diana Cha[1], Justin Darcy[1], Dominique Ameroso[1], Adam Castoreno[1], Matthew Whittaker[1], Aarti Sharma[2], Jinghui Zhang[2], Stephen Godin[2], Oren Levy[2], Priyantha Herath[1], Kirk Brown[1], Susan D. Croll[2]
[1]Alnylam Pharmaceuticals, Cambridge, MA 02142, USA
[2]Regeneron Pharmaceuticals, Inc. Tarrytown, NY 10591, USA

INTRODUCTION

Mutations in the superoxide dismutase 1 (SOD1) gene account for approximately 2-5% of ALS cases (SOD1-ALS). Pathogenic SOD1 variants are thought to cause misfolded, toxic aggregates of SOD1 protein. Decreasing SOD1 levels is a potential therapeutic approach to slow disease progression in patients with SOD1-ALS. RNA interference (RNAi) is a therapeutic modality that utilizes the RNA-induced silencing complex (RISC) pathway, an endogenous cellular mechanism, to regulate gene expression by targeting and degrading messenger RNA (mRNA). SOD1-targeting by RNAi therapeutics is hypothesized to be a potential approach to treat patients with SOD1-ALS, by reducing SOD1 levels.

METHODS

ALN-SOD is an intrathecally (IT) administered RNAi therapeutic targeting SOD1 mRNA.
This study explored the in vivo pharmacokinetics and pharmacodynamics of a single 70 mg IT dose of ALN-SOD (N=9) compared with artificial cerebrospinal fluid (aCSF) control (N=4) in non-human primates (NHP; cynomolgus monkeys).

RESULTS

NHPs receiving a single IT dose of ALN-SOD demonstrated 60-70% peak reduction of SOD1 protein in cerebrospinal fluid (CSF), sustained for at least 85 days post dose. At 85 days after dosing, tissue SOD1 mRNA levels decreased by 75–80% in the spinal cord and prefrontal cortex and approximately 60% in the brainstem. Tissue SOD1 protein levels were reduced by 65% in the spinal cord and 90% in the prefrontal cortex, relative to aCSF controls. A strong direct relationship was observed between ALN-SOD drug levels measured in brain tissue and the degree of SOD1 reduction.

CONCLUSION

A single IT dose of ALN-SOD produces robust, sustained reduction of SOD1 in the brain and spinal cord of NHPs, lasting for at least 85 days after dosing. ALN-SOD may have therapeutic value in the treatment of SOD1-ALS.

Basic Science
PM005

UNVEILING A NOVEL ROLE OF PHOSPHORYLATION OF TDP-43

Yohei Iguchi[1], Yuhei Takahashi[1], Jiayi Li[1], Kunihiko Araki[1], Yoshinobu Amakusa[1], Yu Kawakami[1], Satoshi Yokoi[1], Masahisa Katsuno[1,2]
1: Department of Neurology, Nagoya University Graduate School of Medicine
2: Department of Clinical Research Education, Nagoya University Graduate School of Medicine

BACKGROUND
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the selective loss of motor neurons. While the cause of sporadic ALS has not been discovered, cytoplasmic aggregations of misfolded TDP-43 and its nuclear loss are pathological hallmarks of ALS. To halt TDP-43 aggregation; inhibiting TDP-43 aggregation or promoting its degradation, can be the candidate therapeutic strategy for ALS.

METHODS
Using murine and human cell lines, we performed immunoblotting, immunoprecipitation, quantitative RT-PCR, immunocytochemistry, and proteomic analysis. We also generated a novel phosphorylation-specific TDP-43 antibody and performed immunohistochemistry of postmortem spinal cord from ALS patients with this antibody.

RESULTS
We identified that TDP-43 is one of the substrates of “kinase X” . Kinase X phosphorylated the N-terminus of TDP-43 and promotes TDP-43 degradation. Interestingly, kinase X specifically decreased the aggregation-prone TDP-43 but did not affect wild-type TDP-43 expression. The Nterminal phosphorylation of TDP-43 was detected in a different pattern from the C-terminal phosphorylation in the pathological inclusion of ALS motor neurons. Finally, we found that kinase X significantly reduced the disease-causing TDP-43 mutation that recapitulates the pathological features of aggregation in ALS.

CONCLUSION
With regard to TDP-43 phosphorylation, C-terminal phosphorylation has been intensively studied, but little was known about N-terminal phosphorylation. Phosphorylations at the N-terminus of TDP-43 can be a new therapeutic target for ALS.

Basic Science
PM006

REGULATION OF PATHOLOGICAL TDP-43 BY MICRORNAS TOWARD THE TREATMENT OF ALS

Keiko Imamura[1,2,3], *Haruhisa Inoue*[1,2,3]
Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan
iPSC-based Drug Discovery and Development Team, RIKEN BioResource Research Center (BRC), Kyoto, Japan
Medical-risk Avoidance based on iPS Cells Team, RIKEN Center for Advanced Intelligence Project (AIP), Kyoto, Japan

TDP-43 protein levels are elevated in spinal cord and cerebrospinal fluid of amyotrophic lateral sclerosis (ALS) patients. Although TDP-43 expressions are strictly regulated by autoregulation mechanisms, this system is disrupted in ALS. It may be important to regulate TDP-43 levels to develop therapies for ALS. However, precise adjustment is required to avoid reducing TDP-43 excessively, since TDP-43 is essential for cell survival. Then, we focused on microRNAs, which regulate protein expression in biological systems. MicroRNAs are functional nucleic acids consisting of about 20 bases which bind to the 3'-untranslated region of the target RNA. They have an intrinsic RNA silencing machinery that functions by negatively regulating the expression of RNA.

We focused on microRNA-33 (miR-33), a lipid metabolism network regulator. MiR-33 has two isoforms, miR-33a and miR-33b, which have the same seed sequences. MiR-33a is located in intron 16 of sterol regulatory element-binding factor-2 (SREBF-2; sterol regulatory element-binding protein-2, SREBP-2), and miR-33b in intron 17 of SREBF-1. To investigate whether miR-33 regulates the TDP43 protein levels in motor neurons, we generated miR-33a and miR-33b double knockout human iPSCs using CRISPR-Cas9, and investigated the relation between miR-33 and TDP-43 protein levels using iPSC-derived motor neurons. We found that miR-33 could regulate pathogenic TDP-43 in ALS motor neurons. This suggests that targeting microRNAs may lead to possible therapeutic approaches for ALS.

Basic Science
PM007

THERAPEUTIC EFFECT OF CURCUMIN ON TDP-43-RELATED PATHOGENESIS IN FTLD AND ALS

Chi-Chen Huang Ph.D. Program in Medical Neuroscience, College of Medical Science and Technology, Taipei Medical University, Taiwan

INTRODUCTION

In sporadic and familial FTLD and ALS patients, TDP-43 has been identified as the major component of UBIs inclusions which is abnormally hyperphosphorylated, ubiquitinated, and cleaved into Cterminal fragments to form detergent-insoluble aggregates. So far, the effective drugs for FTLD and ALS neurodegenerative diseases are yet to be developed. Autophagy has been demonstrated as the major metabolism route of the pathological TDP-43 inclusions, hence activation of autophagy is a potential therapeutic strategy for TDP-43 pathogenesis in FTLD and ALS. Curcumin, a traditional herbal medicine, is an inhibitor of mTOR signal and an activator for autophagy. Curcumin has been implicated in several kinds of diseases, including the neuronal-related pathogenesis, such as Parkinson's, Huntington's and Alzheimer's diseases. However, the therapeutic effect of curcumin on ALS pathology has never been investigated.

METHODS

Here we analyzed the insoluble TDP-43 fractions levels in wild-type and TDP-43-A315T Tg mice spinal cord by weste blotting and immunofluorescent assays. In addition, we also compared the life span and evaluate their motor cordination by rotarod assay between male and female TDP-43-A315T Tg mice administrated with or without curcumin.

RESULTS

Here we found that female TDP-43-A315T Tg mice administrated with curcumin have longer survival rates, while this difference are not observed in male TDP-43-A315T Tg mice. In addition, curcumin is able to reverse the processing of insoluble TDP-43 aggregates formation in weste blotting and immunofluorescent assays. These results gave us the notion that curcumin is a potential therapeutic strategy for TDP-43 proteinopathies.

CONCLUSION

We supported an important notion that the traditional herb curcumin is a potential alteative therapy for TDP-43-related neuropathology. Here we demonstrated that curcumin is able to reverse the processing of insoluble TDP-43 aggregates formation and provides a novel candidate for the therapeutic development in FTLD and ALS.

Basic Science
PM008

NUCLEIC ACID BINDING REGULATES TDP-43 SOLUBILITY VIA ITS SPACIAL ARRANGEMENT

Motoki Miura[1,2], Fumika Sakaue[1,2], Hirokazu Matsuno[1,2], Kento Morita[1,2], Rintaro Iwata Hara[1,2], Takanori Yokota[1,2,3]
Department of Neurology and Neurological Science, Tokyo Medical and Dental University, Japan
Center for Brain Integration Research (CBIR), Tokyo Medical and Dental University, Japan
TMDU Nucleotide and Peptide Drug Discovery Center (TIDE), Tokyo Medical and Dental University, Japan

INTRODUCTION

Aggregation of the 43 kDa TAR DNA-binding protein (TDP-43) is a pathological hallmark of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). RNA binding and TDP-43 N-terminal domain dimerization have been suggested to ameliorate TDP-43 aggregation. However, the relationship between RNA binding and spacial arrangement including dimerization is largely unknown. Methods: To evaluate TDP-43 solubilization by oligonucleotide binding, we developed new oligonucleotides which regulate TDP-43 inter-molecular interaction via spatial separation. Using in vitro aggregation model, we evaluated effects of these oligonucleotides on the solubility of wild-type and oligomerization-deficient TDP-43. Results: TDP-43 preferable UG-repeat sequence and new oligonucleotides induced one-to-multiple complexes of oligonucleotide and TDP43. UG-repeat sequence antagonized aggregation of wild-type TDP-43 but could not that of oligomerization-deficient TDP-43. In contrast, new oligonucleotides could ameliorate the aggregation of both wild-type and oligomerization-deficient TDP-43. Conclusions: We uncovered that two distinct mechanisms exist for modulating TDP-43 solubility by RNA binding: one is via N-terminal domain dimerization and the other is via spatial separation of two TDP-43 molecules without N-terminal domain dimerization. This study provides new molecular insights into the regulation of TDP-43 solubility.

Basic Science
PM009

DEVELOPMENT OF THERAPEUTIC DRUGS USING IPS CELL-DERIVED MOTOR NEURONS FROM ALS PATIENTS

Genki Tohnai[1], Ryoichi Nakamura[1], Naoki Atsuta[1], Kazunari Onodera[2], Youhei Okada[2], Gen Sobue[1]
1. Aichi Medical University (Japan)

OBJECTIVES

Currently, no model fully reflects the pathogenesis of sporadic ALS. Therefore, we established an ALS pathological model by establishing induced pluripotent stem cells (iPSCs) derived from patients with sporadic ALS and inducing differentiation into motor neurons (MNs). We analyzed the phenotype of these iPSC-MNs to reproduce the patient's pathology and used these iPSC-MNs to evaluate the efficacy of candidate drugs for treatment.

METHODS

Phenotyping of iPSC-MNs was analyzed by measuring MNs neurite length using an In Cell Analyzer, the presence of TDP-43 granules, and multi-cell survival assays using the LDH assay and cck-8 assay. RNA was extracted from iPSC-MNs and analyzed by RNA-Seq at 5-7 points, including the early, projection elongation, maturation, and regression stages. We also extracted ALS risk gene polymorphisms from genetic analysis of patients with ALS, and validated several candidate therapeutic compounds in iPSC-MNs.

RESULTS

Phenotypic differences in neurite outgrowth and cell viability were observed in iPSC-MNs of patients with sporadic ALS compared to those from healthy controls. We also observed an association between the disease progression of iPSC-MNs from patients with ALS and the rate of progression in each patient's clinical profile. Several drugs improved neurite outgrowth and cell survival.

CONCLUSIONS

These results suggest that ALS-derived iPSC-MNs can recapitulate the pathophysiology of specific cases and are sufficiently useful to elucidate pathophysiology and identify novel drug candidates.

Basic Science
PN001

PERIPHERAL IMMUNITY INVOLVEMENT IN THE COGNITIVE IMPAIRMENT OF SPORADIC AMYOTROPHIC LATERAL SCLEROSIS

Tianmi Yang[1], Qianqian Wei[1], Chunyu Li[1], Ruwei Ou[1], Yanbing Hou[1], Lingyu Zhang[1], Kuncheng Liu[1], Junyu Lin[1], Yangfan Cheng[1], Yi Xiao[1], Huifang Shang[1]
[1]Department of Neurology, Laboratory of Neurodegenerative Disorders, Rare Diseases Center,
National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China

INTRODUCTION

Recent studies have suggested that immune activation plays important roles in amyotrophic lateral sclerosis (ALS). However, the effects of peripheral immunity on cognitive impairment in sporadic ALS remains poorly characterized. Thus, we aim to investigate the association between peripheral immune parameters and cognitive impairment in patients with sporadic ALS.

METHODS

A case-control study of 289 patients with sporadic ALS was conducted. All patients underwent cognitive assessment and blood immune parameters measurements. The Main outcomes were the adjusted odds ratio (OR) in multivariate logistic regression analysis and the adjusted coefficient in multivariate linear regression model. Sensitivity analysis was performed restricting by the King's clinical stage.

RESULTS

Cognitive impairment was detected in 98 (33.9%) patients. Higher counts of leukocyte (OR, 0.53; 95% CI, 0.29 to 0.95; $P = 0.03$), neutrophil (OR, 0.48; 95% CI, 0.26 to 0.88; $P = 0.02$), and monocyte (OR, 0.33; 95% CI, 0.18 to 0.60; $P < 0.001$) were significantly associated with better cognitive preformence in sporadic ALS, specifically in patients who were in King's clinical stage 1 and 2. Whereas higher percentage of CD4+ T cell was found to increase the risk of cognitive impairment (OR, 2.79; 95% CI, 1.52 to 5.09; $P = 0.001$), especially in patients who were in King's clinical stage 3.

DISCUSSION

These findings highlight that peripheral immunity is involved in the cognitive impairment of sporadic ALS and might play dynamic and complex roles — beneficial and damaging — according to the disease stages. Revealing the associations between immunity and ALS provides insights into the pathophysiological mechanisms underlying this fatal neurodegenerative disease, as well as potential avenues for immunotherapies.

Basic Science
PN002

REFOCUSED ABERRANT INFLAMMATORY CASCADE IN CNS & PNS OF ALS

Do-Yeon Lee, MS[1,2], Young Nam Kwon, MD, PhD[1,2,3], Jung-Joon Sung, MD, PhD[1,2,4,5]
[1]Department of Neurology, Seoul National University Hospital; Seoul, Republic of Korea.
[2]Department of Neurology, Seoul National University College of Medicine; Seoul, Republic of Korea.
[3]Biomedical Research Institute, Seoul National University Hospital College of Medicine; Seoul, Republic of Korea.
[4]Neuroscience Research Institute, Seoul National University College of Medicine; Seoul, Republic of Korea.
[5]Wide River Institute of Immunology, Seoul National University; Hongcheon, Gangwon-do, Republic of Korea.

INTRODUCTION
As persistent elevation of transforming growth factor-β (TGF-β) promotes fibrosis of muscles and joints, and accelerates disease progression in amyotrophic lateral sclerosis (ALS), we investigated whether inhibition of TGF-β would be effective against both exacerbations.

METHODS
The effects of TGF-β/Smad2 signaling pathway and its inhibitor on myoblasts and fibroblasts were tested *in vitro* and confirmed *in vivo*, and the dual action of a TGF-β inhibitor in ameliorating the pathogenic role of TGF-β in SOD1 G93A TG mice was identified.

RESULTS
In the peripheral neuromuscular system, fibrosis in the muscles and joint cavities induced by excessive TGF-β causes joint contracture and muscular degeneration, which leads to motor dysfunction. In an SOD1 G93A TG mouse, an increase in TGF-β in the central nervous system (CNS), consistent with astrocyte activity, was associated with microglial activity and pro-inflammatory conditions, as well as with neuronal cell death. Treatment with the TGF-β inhibitor halofuginone could prevent musculoskeletal fibrosis, resulting in the alleviation of joint contracture and delay of motor deterioration in SOD1 G93A TG mice. Halofuginone could also reduce glial cell-induced neuroinflammation and neuronal apoptosis.

CONCLUSION
These dual therapeutic effects on both the neuromuscular system and the CNS were observed from the beginning to the end stages of SOD1 G93A TG mice; as a result, treatment with a TGF-β inhibitor from the early stage of disease delayed the time of symptom exacerbation in ALS mouse model, which led to prolonged survival.

Clinical
PAT001

UTILITY OF ANDROID SMARTPHONE ACCESSIBILITY FEATURES IN ALTERNATIVE AND AUGMENTATIVE COMMUNICATION (AAC)

David Paul Capelle[1]
[1] *Department of Medicine, Faculty of Medicine UM, Kuala Lumpur, Malaysia*

INTRODUCTION

Recently an increasing number of acessibility features have become available on Android smarthphones, based either on simple mechanical USB-connected switches or a so-called camera switch. This feature uses the handphone's front facing camera to detect facial gestures such as looking laterally, blinking of the eyes or raising of the eye brows. These gestures can be configured to control the user interface in an individualized manner, allowing users to link gestures which are convenient to generate with particular functionality of the smart phone.

REPORT

Available open-source applications such as the "AsTeRICS" (https://grid.asterics.eu) web based user interface allow communication either via typed letters, available phrases or pictograms in several European and Asian languages with a short training period.

This setup holds several potential advantages over the use of a dedicated eye tracking device connected to a personal computer. With the ubiquitous use of handphones no investment in an eye tracker device is needed and patients are able to continue using devices and familiar applications. The smaller form-factor and lower weight of smart phones is also favourable as it obviates the need for a mechanism mounting a personal computer which is challenging in wheelchair using patients.

A remaining challenge is to optimally match patient's needs and capabilities with a suitable set up and training patients and carers in their use. In our initialy experience this process involves a leaing period which is potentially burdensome and frustrating for patients.

CONCLUSION

In summary the recent developments in handphone accesibility features may be a useful addition to the available range of high-tech but low-cost methods of AAC for PALs and CALs, especially in resorce constrained settings.

Clinical
PAT002

MODIFIED CAP AND STRAP: AN ALTERNATIVE SOLUTION FOR DROPPED HEAD SYNDROME IN MOTOR NEURON DISEASE

Dinsuhaimi F.A[1], Mei Yin P.[1]
[1]Department of Rehabilitation Medicine, Faculty of Medicine, University of Malaya

INTRODUCTION

About 1-3% of patients with motor neurone disease (MND) presented with dropped head syndrome (DHS), and it is associated with bulbar and upper extremity onset. DHS can cause swallowing and posture problems to patients, including neck pain. It also increases patients disability in activities of daily living including eating and dressing. There are various types of head supports available and choosing the right orthosis is based on individual needs and functions. As MND progresses, their needs will also change and regular modifications need to be done to prevent further discomfort and disability

REPORT

We report a case of 68 years old gentleman with upper limb onset MND, who progresses with DHS and significant shoulder girdle weakness. He had difficulty in ambulation due to inability to extend his neck to look forward. He was initially prescribed with soft neck collar, but later causes discomfort as his dysphagia progresses. A trial of cap and strap orthosis was made by using clavicle brace to support his shoulder girdle with a strap attached to his baseball cap. However it was difficult to be fixed during active neck flexion. Further modification was done by anchoring it to a lumbar corset for better attachment. The strap was adjusted to neutral neck alignment with preservation of some degree of active neck flexion as the material used was semi-elastic neoprene strap. This provides better compliance as it still preserves neck movement including lateral rotation. Patient self-reported to have better neck control especially during sitting and walking.

CONCLUSION

The modified cap and strap orthosis can provide a more cost-effective alternative for ambulant MND patients with DHS.

Clinical
PAT003

NEUROPHYSIOLOGICAL STUDY ON THE EFFECT OF VARIOUS SHORT DURATIONS OF DEEP BREATHING

Poh Foong LEE[1], Kok Suen CHENG[2]
[1]Lee Kong Chien Faculty of Engineering & Science, Universiti Tunku Abdul Rahman (UTAR), Jalan Sungai Long, Malaysia.
[2]School of Engineering, Texas A&M University, Corpus Christi, TX 78412, USA

INTRODUCTION

The study aims to study the effects of short duration deep breathing on the EEG power with topography based on parallel group randomized controlled trial design which was lacking in prior reports.

METHODS

50 participants were split into 4 groups: control (CONT), deep breathing (DB) for 5 (DB5), 7 (DB7), and 9 (DB9) minutes. EEG recordings were obtained during baseline, deep breathing session, after deep breathing, and a follow-up session after 7 days of consecutive practice.
Results: Frontal theta power of DB5 and DB9 was significantly larger than that of CONT after the deep breathing session ($p = 0.027$ and $p = 0.006$, respectively) and the profound finding showed that the theta topography obtained a central-focused distribution for DB7 and DB9.

CONCLUSION

The result obtained was consistent with previous literature, albeit for certain deep breathing durations only, indicating a possible linkage between the deep breathing duration and the neurophysiology of the brain.

Clinical
PAT004

RAISING AWARENESS, IMPROVING LIVES: LESSONS FROM AN ONGOING 2YEAR ALS COMMUNITY ENGAGEMENT IN VIETNAM

Nguyen Tran Minh Duc[1], Vu Ngoc Quang Minh[2], Nguyen Thanh Ho[2], Tran Phuong Nam[3], Le Minh Chau[4], Nguyen Trung Truc[5], Nguyen Hoang Nhan[4]
[1] Department of Neurology, Trieu An Hospital, Ho Chi Minh City, Vietnam [2] Faculty of Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam. [3] Department of Inteal Medicine, People's Hospital 115, Ho Chi Minh City, Vietnam.
[4] Department of Inteal Medicine, Cho Ray Hospital, Ho Chi Minh City, Vietnam [5] Department of Psychiatry, An Giang Central General Hospital, An Giang Province, Vietnam.

BACKGROUND
Community engagement is a vital component of rare disease management, particularly in developing countries where access to resources and information is limited. Hence, we aim to present the findings of a 2-year Vietnamese ALS community engagement initiative and the lessons leaed from implementing the program.

METHOD
In June 2021, a community engagement platform for ALS was launched, comprising a website (https://benhals.com) and a Facebook page (https://www.facebook.com/BenhALS.Vietnam). The platform aimed to provide reliable information, guidelines, and tips for handling the difficulties of ALS. The initial format was article writing with illustrations, followed by more engaging formats such as a podcast series and daily posters.

RESULTS
The platform had 5,571 sessions, with the top acquisition channel being organic search (45%), followed by social media (23.3%) and direct search (22.1%). The average time on the page was 2 minutes and 41 seconds. The Facebook page reached 22,423 users, with 1,196 reactions, likes, comments, and shares.

LESSONS LEAED
The success of community engagement initiatives in rare disease management depends on maintaining consistency and delivering high-quality content. To effectively disseminate information and expand the reach of these initiatives, engaging and accessible, we can use forms of media like podcasts and short videos. It is important to tailor the delivery of content to meet the specific needs and preferences of the target audience. Addressing the financial challenges that come with maintaining these initiatives is also a critical component of community engagement efforts.

CONCLUSION
The Vietnamese ALS community engagement initiative showed the importance of community engagement in rare disease management in developing countries. The lessons leaed from this initiative can inform the development of similar programs in other settings and provide a framework for improving the quality of life of patients with rare diseases.

Clinical
PCM001

CLINICAL PRACTICE OF PEG INSERTION IN KOREAN PATIENTS WITH ALS

Bugyeong SON1, Jisu LEE2*, Yongsoon PARK2, Seung Hyun KIM1.*
Cell Therapy Center, Department of Neurology, Hanyang University Seoul Hospital, Seoul, South Korea
Department of Food and Nutrition, Hanyang University, Seoul, South Korea
**Both authors contributed equally.*

INTRODUCTION

Dysphagia is crucial in patients with amyotrophic lateral sclerosis(ALS). Percutaneous endoscopic gastrostomy (PEG) is the most common type of enteral feeding used in patients with severe dysphagia and malnutrition. This study aims to investigate the clinical practice of PEG insertion in Korean patients with ALS.

METHOD

We conducted a retrospective data analysis on the ALS cohort from the ALS database from Hanyang University Seoul Hospital with patients who had undergone PEG insertion and had serial clinical data.

RESULT

Our results from 188 participants showed that the average duration from symptom onset to PEG insertion was 34.07±20.77 months, shorter in patients with bulbar onset (28.97±16.10 months) compared to limb onset (36.89±22.52 months). The ALSFRS-R score at the time of PEG insertion was 17.35±9.55, and the bulbar score was 4.29±2.15.
Linear regression analysis revealed that patients with bulbar onset, shorter time from symptom onset to diagnosis, lower ALSFRS-R score at diagnosis, and faster progression speed were predictors of earlier PEG insertion. 5.3% of the population experienced aspiration pneumonia, and 14.4% had a tracheostomy inserted before the PEG insertion.
Patients tend to show the fastest progression rate between 10% weight loss or a poor swallowing score and PEG insertion. The group with slower progression with higher ALSFRS-R score had prolonged periods of PEG insertion and better survival.

CONCLUSION

This study suggests that patients with the bulbar onset and higher progression speed tend to have early PEG insertion and poor prognosis. The PEG insertion alone may not significantly modify the course of the disease. The results also indicate that earlier discussion of PEG insertion may be beneficial, particularly before patients experience significant weight loss or severe dysphagia, which may not be compensated after PEG insertion, but further investigation is necessary.

Clinical
PCM002

DEVELOPMENT AND PRELIMINARY EVALUATION OF VIDEO-BASED STRETCHING TRAINING PROGRAM FOR PATIENTS WITH ALS (VITALS)

Bugyeong SON1, Seung Hyun KIM1, Yongsoon SHIN2
Cell Therapy Center, Department of Neurology, Hanyang University Seoul Hospital, Seoul, South Korea
School of Nursing, Hanyang University, Seoul, South Korea

INTRODUCTION

This study aimed to develop a VIdeo-based stretching Training program for patients with Amyotrophic Lateral Sclerosis (VITALS) and evaluate its preliminary results in pain relief. Despite ALS being considered a painless disease, recent research has indicated that patients experience pain, especially musculoskeletal pain related to reduced mobility, muscle stiffness, and spasms. Stretching and range of motion exercises are generally recommended as nonpharmacological treatment strategies to alleviate pain.

METHODS

Program development: The VITALS program was developed based on the ADDIE model and consists of five videos, including three follow-along videos demonstrating exercises while sitting, standing, or lying down, and two follow-along videos demonstrating exercises with the assistance of a caregiver.
Program evaluation: This study utilized a quasi-experimental design with a nonequivalent-group pretest-posttest to evaluate the four-week administration of the VITALS program.

RESULTS

Most pain scores in the experimental group decreased from 6.33±1.95 points to 5.42±1.81 points($Z=-2.22$, $p=.027$), and the average pain score also reduced from 4.13±1.90 points to 3.74±1.41 points($t=-2.35$, $p=.031$), and these changes were statistically significant. However, there were no significant differences in scores between the groups or other elements of pain.
Participants expressed high satisfaction with the program and reported explicit instructions and helpful subjective pain relief. They were willing to continue the program and recommend it to others.

CONCLUSION

The VITALS program has the potential to reduce pain in ALS patients and can be easily followed at home with the assistance of a caregiver. The program was well-tolerated, with a median completion rate of 80.5%. These findings support the importance of regular stretching and range of motion exercises for ALS patients, as highlighted in previous literature. The VITALS program could be an easily accessible and potentially beneficial option for patients with ALS suffering from pain.

Clinical
PCM003

MND BEYEOND BORDERS: EXPANDING A SOUTH-EAST ASIAN NETWORK OF MULTIDISCIPLINARY MND CARE THROUGH ONLINE LEARNING

David Paul Capelle[1], Lim Shu Xian [2], Chan Yeow [2,] Premana W. Premadi, Sheila Agustini[1,] Nortina Shahrizaila[1,] Loh Ee Chin[1]
[1]Department of Medicine, Faculty of Medicine UM, Kuala Lumpur, Malaysia
[2]Ministry of Health, Malaysia
[3]Yayasan ALS Indonesia, Indonesia
[4]Mayapada Hospital, Indonesia

INTRODUCTION

As South-East Asian nations rapidly develop, their demographics are shifting towards a rising average age. This will translate into an increasing prevalence of MND in the near future for which nations are currently ill-equipped. Multidisciplinary care has been recognised as the ideal model for MND care, yet the number of such centres across this region is far too low to meet population needs.

An added challenge arises from the fact that medical care is concentrated in urban areas which severely disadvantages patients and carers living with MND (PALs and CALs) in rural areas across the region.

METHODS

To introduce the model of multidisciplinary care and encourage the building of networks across different specialties we launched the MND Beyond Borders programme in 2021 in collaboration between Yayasan ALS Indonesia, Tan Tock Seng Hospital Home Ventilation and Respiratory Support Service (TTSH HVRSS) and MND Malaysia. The programme consisted of a series of live online education sessions accessible to both healthcare providers (HCP) and PALs and CALs over the course of two years. Sessions were run in the moings, addressing healthcare professionals; and in the afteoons addressing PALS and CALS.

The aim was to cover the whole breadth of MND care involving speakers from specialties such as neurology, chest medicine, rehabilitation medicine, palliative care, gastroenterology, respiratory therapy, occupational therapy, physiotherapy, spiritual care, medical social work, art therapy and others.

RESULTS

Events were run as didactic presentations followed by question and answer sessions. Events were simultaneously streamed on social media when possible.

The MND Beyond Borders project has demonstrated the feasibility of building capacity in MND care through online education and network building.

CONCLUSION

Further research is warranted to investigate the optimum strategy to expand MND care to currently underserved populations across the region and to involve a wider range of relevant specialties.

Clinical
PCM004

DOUBLE TROUBLE: REHABILITATION APPROACH IN MOTOR NEURON DISEASE WITH 'BRITTLE BONE'

Syazana Syimah MOHD HANIFA[1], Nur Hanis JAAFAR[1], Sakinah SABIRIN[1], Tze Yang CHUNG[1]
[1]Department of Rehabilitation Medicine, Faculty of Medicine, Universiti Malaya

INTRODUCTION

Motor neuron diseases (MND) is a rare neurological disorder known to be progressively debilitating leading to variety of disabilities and functional impairments. (1) Here, we report a case of MND patient with a rare inherited disorder of connective tissue disease, pathogenic variant of COL1A1 gene. This case report will highlight the challenges posed in rehabilitation management of these complicated conditions.

REPORT

42- year- old lady first presented to MND clinic with symptoms of progressive bilateral lower limb weakness with muscle spasm and spasticity, dysphagia, dysarthria, and respiratory insufficiency. She also has multiple joint pain with contractures which causes significant pain issue. She was admitted for inpatient rehabilitation for multidisciplinary interventions to address her numerous impairment and disability. Examination revealed blue sclera, impaired hearing, multiple joint contractures with the background of recurrent trivial injury fracture requiring surgical fixation leading to a suspicion of osteogenesis imperfecta. Genetic testing revealed pathogenic variant of COL1A1 gene in this patient. Bone mineral density showed severe osteoporosis with vertebral T score -4.1, and hip T score -3.7. During her inpatient stay, pain was optimised by Gabapentin and Clonazepam. Trial of non-invasive ventilation was initiated by respiratory team, while osteoporosis treatment was commenced by Endocrine team.

CONCLUSION

COL1A1 gene is associated with osteogenesis imperfecta, Ehler- Danlos syndrome and Caffey disease that can lead to skeletal deformities especially over long bone and rib fractures. (2) Whilst MND itself causes progressive significant physical impairments. Handling of patient, positioning, and mobilisation must be done properly with caution to prevent occurrence of fracture during therapy as this can lead to devastating vicious cycle of fracture, deformity, immobility, deconditioning and contractures

REFERENCES

Andiappan et al, (2020). Disability profile and the factors affecting functional outcome in Malaysian motor neurone disease population
Nijhuis et al, (2022). Fractures in Osteogenesis Imperfecta

Clinical
PCM005

LONG-TERM ROBOT SUIT TRAINING USING HYBRID ASSISTIVE LIMB MAINTAINS GAIT IN PATIENTS WITH SPINAL AND BULBAR MUSCULAR ATROPHY

Takehisa Hirayama[1], Harumi Morioka[1], Tatsuki Sugisawa[2], Tatsuhiro Yokoyama[1], Masamichi Hozumi[1], Ryuichi Okamoto[1], Hiromi Konaka[1], Mari Shibukawa[1], Junya Ebina[1], Sayori Hanashiro[1], Junpei Nagasawa[1], Masaru Yanagihashi[1], Masayuki Uchi[2], Ikuko Okuni[2], Satoru Ebihara[3], Osamu Kano[1]
Department of Neurology, Toho University Faculty of Medicine, Japan
Department of Rehabilitation Medicine, Toho University Faculty of Medicine, Japan
Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Japan

OBJECTIVE
Spinal and bulbar muscular atrophy (SBMA) progressively impairs gait function, resulting in the need for patients to use a wheelchair approximately 20 years after the onset. We report on 2 cases in which robot-assisted training using the hybrid assisted limb (HAL) resulted in a good outcome.

METHODS
Six courses of treatment with HAL were performed to 2 males aged 62 (Case 1) and 71 (Case 2) with SBMA. They were receiving leuprorelin therapy. Each course had a four- to fiveweek duration, during which the treatment was performed nine times, with a rest period of at least two months between each course. A 2-minute walk test (2MWT) and a 10-m walk test (10MWT) were performed to examine gait ability, and a blood test to examine serum creatine kinase (CK) levels was performed before and after each course of treatment.

RESULTS
In Case 1, the walking distance of 2MWT increased by 33.2% and the walking speed of 10MWT increased by 31.4% over the 2 years, showing an improvement trend ($p=0.004$, $p=0.0296$). In Case 2, the walking distance of 2MWT increased by 42.8% over the 2 years, showing an improvement trend ($p=0.012$). the walking speed of 10MWT did not show improvement trend, however increased by 4.6%. Although serum CK levels did not show a downward trend, decreased by 53.5% and 30.7% in Case 1 and Case 2 over the 2 years, respectively.

CONCLUSIONS
In combination with leuprorelin therapy, robot-assisted training using the HAL improved the gait ability of two patients with SBMA.

Clinical
PCM006

A CASE OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY MISDIAGNOSED AS AMYOTROPHIC LATERAL SCLEROSIS

Eun Kyoung Lee[1], *Sooyoung Kim*[2], *Eunhee Sohn*[2]
[1] *Department of Neurology, Chungnam National University Sejong Hospital, Sejong, Korea* [2] *Department of Neurology, Chungnam National University Hospital, Daejeon, Korea*

INTRODUCTION

It is not uncommon to misdiagnose chronic inflammatory demyelinating polyneuropathy (CIDP) as other neuromuscular disorders. Early detection of CIDP is important because timely treatment reduces morbidity and disability of patient. Herein we report a case of CIDP who was misdiagnosed as amyotrophic lateral sclerosis (ALS) initially.

REPORT

A 76-year-old woman had a 1–year history of progressive weakness and numbness in her all 4 extremities. In her past medical history, she was diagnosed with diabetes mellitus 7 years ago. Initial needle electromyography (EMG) showed widespread active and chronic neurogenic changes and she was diagnosed with “clinically probable” ALS at the rehabilitation medicine. Following nerve conduction study (NCS) performed at the neurology department showed conduction block with temporal dispersion on the upper extremity. She was treated with intravenous steroid pulse therapy under the diagnosis of CIDP and referred to our hospital.

Initial neurological examination showed predominantly distal bilateral symmetric weakness with hyporeflexia and she could not walk independently. There was neither cranial nerve involvement nor upper motor neuron sign. Cerebrospinal fluid (CSF) examination revealed elevated protein level of 118 mg/dL without pleocytosis. No remarkable abnormalities were seen in the magnetic resonance imaging (MRI) of the brain and cervical spinal cord. Left superficial peroneal nerve biopsy revealed demyelinating neuropathy with axonal degeneration. Her electrophysiological findings conducted at our hospital also revealed conduction block with temporal dispersion which met with the electrophysiological criteria of European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) for CIDP. In the following 2 years with maintenance therapy, muscle strength mildly improved so that she could walk without assistance.

CONCLUSION

Chronic progressive course without prominent sensory symptom in diabetic patient made hard to differentiate CIDP from ALS combined with diabetic polyneuropathy. Clinical suspicion and appropriate diagnostic tests helped to diagnose.

Clinical
PCM007

EFFECT OF ANTI-AGING THERAPIES ALONG WITH CELLULAR THERAPY IN PATIENTS WITH ALS

Dr. Hemangi Sane [1&2], Dr. Alok Sharma [1&2], Dr. Nandini Gokulchandran [1&2], Ms. Amruta Paranjape[2], Ms. Pooja Kulkai[2], Ms. Priyanka Sharma [2], Ms. Zubiya Shaikh[2], Ms.Heena Syed [1], Ms. Snehal Sontate [1], Ms. Pallavi Khubchandani [1]
1.Department of Medical Services and Clinical Research, NeuroGen Brain and Spine Institute, India
2.Department of Research & Development, NeuroGen Brain and Spine Institute,India

INTRODUCTION

One of the pathophysiological mechanisms of ALS is considered to be expedited aging process. Hence, anti-aging treatment might be helpful in ALS. Beneficial effect was seen in aging using mode anti-aging therapeutics. Our published research has shown increased estimated survival in patients with ALS using autologous bone marrow mononuclear cell therapy and standard treatment. Our aim is to examine the effect of the anti-aging therapies, cellular therapy, oral Lithium and standard treatments (Anti-aging therapies) in patients with ALS. Telomere length is the most current biomarker to determine aging. Chronic inflammation and oxidative stress shortens telomere length corresponding to estimated biological age. Thus, we used Telomere length and Biological age as an outcome measure.

METHODS

12 patients with ALS/MND received anti-aging therapies such as Hyperbaric Oxygen therapy (HBOT), Deep Tissue Mobilization (DTM), IV Meyer's cocktail, IV Glutathione, cellular therapy and standard treatment.Telomere length and biological age were used as outcome measure before and after intervention. Difference in biological age and telomere length before and after the intervention was compared using paired sample t-test.

RESULTS

12 patients were included in this study. Pre-intervention telomere length measurement showed a mean increase of 10.9 years in biological age (62.5±9.98 years) compared to chronological age (51.67± 9.14 years). Post intervention there was a significant increase in the telomere length from 6.9 kbp to 7.1 kbp ($p=0.003$) which corresponded to a decrease in biological age from 62.5 years to 59.5 years. There was a decrease of 3 years in biological age which was statistically significant ($p= <0.05$).

CONCLUSION

Anti-aging therapies, cellular therapy and standard treatment reduce the biological age and increase telomere length. Current study shows that anti-aging therapies are safe and beneficial in ALS. Larger studies are required to determine the effect of anti-aging therapies on ALS.

Clinical
PCM008

THE KNOWLEDGE AND ATTITUDES ON PAIN ASSESSMENT AND MANAGEMENT AMONGST DOCTORS IN INTERNAL MEDICINE DEPARTMENT, MALAYSIA, A SINGLE CENTRE STUDY

***Wei Ming Tan*[1], *Sarah Zulaikha Samad*[1], *Yi Lin Lee*[2], *Wan Chia Low*[3], *Chin Wen Yap*[3], *Koon Ket Sia*[3]**

INTRODUCTION

Pain is part and parcel of a patient's clinical assessment. The study was aimed to assess the knowledge and attitudes on pain assessment and management amongst doctors who worked in the Internal Medicine Department in one of the tertiary hospitals to identify the gap in the pain knowledge.

METHODS

This was a cross-sectional study using universal sampling technique. The "Knowledge and Attitudes
Survey Regarding Pain" questionnaire used comprised 41 True/False and multiple-choice questions.
The study population were the doctors who worked in the respective department in December 2022.

RESULTS

84 questionnaires were collected and analysed via R statistical software version 4.1.2. 38 out of 84 of the participants passed the questionnaire. The mean score of the study sample was 58%, slightly below the set passing mark of 60%. The doctors fared poorly in terms of the pharmacokinetics of opioid, such as the duration and the recommended route of administration. They also scored poorly when assessing pain severity based on the patients' behaviour, sleeping patte and vital signs. Besides, the doctors were inclined to prescribe lower doses of opioid despite patients complaining of severe pain. The odds of passing the study questionnaires were much higher in the group who worked as registrars, specialists, or consultant (OR 19.2, 95% CI: 3.5- 360.6, p= 0.006) and in the group who had served for more than 5 years in the hospital (OR 12.4, 95% CI: 3.0- 67.2, p= 0.001). The prior experience of attending any pain course did not confer any extra advantage in passing the questionnaire.

CONCLUSION

This study, albeit with its own study limitation, has demonstrated the gap on certain aspects of pain assessment and management among doctors in the respective department. However, multi-centre studies across the region are imperative as the current study may not represent the target population nationwide.

Clinical
PCM009

DIAGNOSIS CHALLENGE IN A CASE OF SUSPECTED KENNEDY'S DISEASE

Yong Chieh Chan[1], *Naimah Mohd Salleh*[2]
Department of Neurology, Hospital Kuala Lumpur
Department of Inteal medicine, Hospital Sultanah Bahiyah

INTRODUCTION

Kennedy's disease is rare progressive motor neuron degenerative disorder. The below is a case of suspected Kennedy's disease.

REPORT

We described a 63-year-old gentleman with underlying hypertension and gastritis with history of helicobacter pylori infection presented with reduced appetite and chronic dysphagia for 5 months. he also had buing sensation and epigastric pain for the past 5 months with 20kg weight loss. He was cachexic no lymphadenopathy. He was initially treated as gastritis for workout of gastrointestinal malignancy however oesophagogastroduodenoscopy was normal. A few days later, he developed respiration failure and was intubated with ventilation support. Arterial blood gas showed type 2 respiratory failure. In view of chronic dysphagia and type 2 respiratory failure, he was empirically treated as myasthenia crisis and started on intravenous immunoglobulin, intravenous hydrocortisone and pyridostigmine. Further examination noted patient bilateral proximal and distal muscle wasting with fasciculation upper limbs and lower limbs, tongue atrophy and fasciculation, weak gag reflex and flail arm syndrome. Acetylcholine receptor antibody was negative. Electromyography of the lumbar, cervical and cranial segments show acute denervation activity predominantly at the cranial segment. Kennedy's disease was suspected in view subsequent clinical and electrophysiological finding. Unfortunately he developed hospital acquired infection with respiratory complication and subsequently passed away after 1 month of hospitalization. His Kennedy genetic study is still pending.

CONCLUSION

Kennedy's disease is one of the mimicker of motor neuron disease. In view of bulbar predominant symptom it may mimic other common disease as well such as myasthenia gravis and other non neurological condition. Early accurate history and examination finding in combination with electrophysiology and genetic study are crucial in confirming the diagnosis of Kennedy's disease.

Clinical
PCM010

LONG-TERM SURVIVAL BENEFITS OF INTRATHECAL AUTOLOGOUS BONE MARROWDERIVED MESENCHYMAL STEM CELLS (NEURONATA-RÃ‚Â®: LENZUMESTROCEL) TREATMENT IN ALS: PROPENSITY-SCORE MATCHED CONTROL, SURVEILLANCE STUDY

Minhee Kim[1], Jae-Yong Nam[1], Sehwan Chun[1], Tae Yong Lee[1,2], Yunjeong Seo[1], Kwijoo Kim[1], Jinseok Park[3], Wonjae Sung[3], Ki-Wook Oh[3], Sanggon Lee[3,4], Jin-Sung Park[5], Juyeon Oh[6], Kyung Cheon Chung[7], Hyonggin An[8], Hyeon Sik Chu[9], Bugyeong Son[9], Seung Hyun Kim[3,9]*
[1]Central Research Center, CORESTEMCHEMON Inc, Seoul, South Korea
[2]College of Pharmacy, Chungbuk National University, Cheongju, South Korea
[3]Department of Neurology, College of Medicine, Hanyang University, Seoul, South Korea
[4]Department of Neurology, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, South Korea
[5]Department of Neurology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, South Korea
[6]College of Nursing, Dankook University, Cheonan, South Korea
[7]Department of Neurology, Bethesda Gospel Hospital, Yangsan, South Korea
[8]Department of Biostatistics, Korea University College of Medicine, Seoul, South Korea
[9]Cell Therapy Center, Hanyang University Hospital, Seoul, South Korea

INTRODUCTION

Neuronata-R® (lenzumestrocel) is an autologous bone marrow-derived mesenchymal stem cell (BM-MSC) product, which was conditionally approved by the Korean Ministry of Food and Drug Safety (KMFDS, Republic of Korea) in 2013 for the treatment of amyotrophic lateral sclerosis (ALS). In the present study, we aimed to investigate the long-term survival benefits of treatment with intrathecal lenzumestrocel.

METHODS

A total of 157 participants who received lenzumestrocel and whose symptom duration was less than 2 years were included in the analysis (BM-MSC group). The survival data of placebo participants from the Pooled-Resource Open-Access ALS Clinical Trials (PRO-ACT) database were used as the exteal control, and propensity score matching (PSM) was used to reduce confounding biases in baseline characteristics. Adverse events were recorded during the one-year follow-up period after the first treatment.

RESULTS

Survival probability was significantly higher in the BM-MSC group compared to the exteal control group from the PRO-ACT database (log-rank, $p < 0.001$). Multivariate Cox proportional hazard analysis showed a significantly lower hazard ratio for death in the BM-MSC group and indicated that multiple injections were more effective. Additionally, there were no serious adverse drug reactions found during the safety assessment, lasting a year after the first administration.

CONCLUSION

The results of the present study showed that lenzumestrocel treatment had a long-term survival benefit in real-world ALS patients.

Clinical
PCN001

MUSCLE ULTRASONOGRAPHY IN THE DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS

Dr. Jee Kaz Niels B. Paber, Dr. Aubrey Punzalan-Sotelo**
*Jose R Reyes Memorial Medical Center Department of Neurology**

Neuromuscular ultrasonography is supplemental to nerve conduction studies and electromyography. It is useful in the understanding of mononeuropathies, trauma, and demyelinating polyneuropathies. Neuronopathies or motor neuron diseases have already been diagnosed by the usage of nerve conduction studies and electromyography but has little data on the neuromuscular ultrasonography to evaluate these diseases especially on the opinion on amyotrophic lateral sclerosis (ALS) and its diagnosis. This case report supports the use of ultrasonography to detect fasciculations in a newly diagnosed case of ALS. We also detect muscle activity in selected muscle groups to increase yield and support the diagnosis of ALS when it is suspected.

Clinical
PCN002

CORTICAL BASES OF THE "SPLIT LEG" PHENOMENON IN HEALTHY SUBJECTS

Ryota KUROIWA[1,2] ,Kazutomo SHIBUYA[1], Atsushi MURATA[2], Satoshi KUWABARA[1]
[1]Department of Neurology, Graduate School of Medicine, Chiba University, Japan [2]Division of Rehabilitaiton Medicine, Chiba University Hospital, Japan

INTRODUCTION

The "split hand" syndrome is a specific sign of amyotrophic lateral sclerosis (ALS), characterized by preferential wasting of the thenar muscles and relative sparing of the hypothenar muscles. Recently, the "split leg" sign in ALS was introduced, as preferential wasting of the gastrocnemius compared to the tibialis anterior. While cortical and peripheral nerve excitability differences have been proposed as pathophysiological bases of the "split hand" phenomenon, pathophysiological bases of the "split leg" sign remain unknown. The present study aimed to investigate whether differences in cortical functions follow a "split leg" pattern across the lower leg muscles in healthy subjects.

METHODS

Cortical functions were examined, using threshold tracking transcranial magnetic stimulation (TMS) in 11 healthy subjects with responses recorded over the tibialis anterior and gastrocnemius in both legs. Short-interval intracortical inhibition (SICI) was measured over the following interstimulus intervals: 1, 1.5, 2, 2.5, 3, and 3.5 ms. Single pulse TMS technique was applied to determine the motor evoked potential amplitude and cortical silent period duration. Results: SICI and the cortical silent period duration were not significantly different between the tibialis anterior and gastrocnemius in both legs.

DISCUSSION

There were almost no differences in cortical excitability between the tibialis anterior and gastrocnemius muscles in healthy controls. Differences in cortical excitability in healthy subjects may not contribute to the "split leg" phenomenon in ALS. Further studies are needed to examine the pathophysiological bases of the “split leg” sign in ALS patients.

Clinical
PCN003

SPINAL CORD MRI IS PREDICTIVE OF DISEASE PROGRESSION AND SUBTYPES IN MOTOR NEURONE DISEASE

Thomas B Shaw[1,2,3], Frederik Steyn[3,4], Jeryn Chang[4], Warwick Rivlin[3], Sicong Tu[5], Robert Henderson[3,6], Shyuan Ngo[3,6,7], Markus Barth[1,2]
School of Electrical Engineering and Information Technology, The University of Queensland, Australia
Centre for Advanced Imaging, The University of Queensland, Australia [3] Royal Brisbane ad Women's Hospital, Neurology Dept., Brisbane, Australia
School of Biomedical Science, The University of Queensland, Australia
Brain and Mind Centre, The University of Sydney, Australia
Centre for Clinical Research, The University of Queensland, Australia
Australian Institute for Biotechnology and Nanotechnology, The University of Queensland, Australia

INTRODUCTION

Disease evolution across MND clinical subtypes remains poorly characterized, but critical for accurate diagnosis and patient care/planning. Notably, *in-vivo* spinal cord (SC) degeneration remains largely under-investigated. We examined relationships between SC MRI metrics, clinical scores, and clinical subtypes over time to better predict disease prognosis and classify diagnostic features.

METHODS

22 patients were scanned (3T MRI) over six months using a previously reported diffusion and anatomical MRI protocol as part of the Biomarkers for Long Surviving forms of MND (BeLong) study. Clinical data was collected, including the PLS Functional Rating Scale (PLSFRS; which can be converted to ALSFRS-R scores) and UMN/LMN predominance (UMN dominant: 3, LMN dominant: 6, mixed L/UMN: 7, PBP: 3, PLS: 3). Bayesian Linear Mixed Effects (LME) modelling was used to investigate whether clinical scores and/or diagnosis are related and predictive of MRI changes, entering formal diagnosis (El Escorial) and clinical scores (PLSFRS,) as fixed effects, and time as a random effect. Differences in Fractional Anisotropy (FA), Magnetisation Transfer Ratio (MTR), and SC grey matter volume were the primary parameters of interest.

RESULTS

Results indicated clinical diagnosis is significantly related to changes in MRI metrics, but not PLSFRS score. SC metrics were related and predictive of disease diagnosis in LMN dominant, PLS, and mixed MN patients, but not for UMN dominant and PBP patients. The relationship between MRI metrics (FA) and diagnosis was significant over time (posterior M = 6.78, 95% CI = 0.73,11.68). Unique alterations in FA were significantly related to each diagnostic subgroup, independently.

CONCLUSIONS

Our findings demonstrate that clinical subtypes differentially impact spinal cord structural integrity and highlight the clinical application of quantitative MRI metrics. Abnormalities in FA, MTR, and volume of the spinal cord was significantly associated with LMN dominant forms of MND.

Clinical
PCN004

RELATIONSHIP OF CLINICAL AND LABORATORY PARAMETERS WITH GYNECOMASTIA IN SPINAL AND BULBAR MUSCULAR ATROPHY USING COMPUTER TOMOGRAPHY (CT)

Minsung Kang[1], *Seong-il Oh*[2], *Jin-Sung Park*[1]
[1]*Department of Neurology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, South Korea*
[2]*Department of Neurology, Kyunghee university medical center, Seoul, South Korea*

INTRODUCTION

Spinal and bulbar muscular atrophy (SBMA) and amyotrophic lateral sclerosis (ALS) are motor neuron disease spectrum disorders. However differentiating these two diseases clinically in the early clinical stages can be challenging. The aim of our study was to compare the breast glandular tissue via chest CT image and propose a surrogate marker reflecting the functional status of SBMA.

METHOD

We retrieved chest CT images based on KNUCH motor neuron disease registry. 15 CT images from genetically confirmed SBMA, and 31 CT images from ALS were retrospectively collected. We evaluated clinical parameters including including revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) and laboratory parameters including sex hormone and creatine kinase. We measured the diameters of bilateral glandular tissue from the chest CT from both SBMA and ALS. We also evaluated the correlation between glandular tissue diameter and the clinical and laboratory parameters.

RESULTS

The mean age of SBMA and ALS at enrollment were 57.4±9.1 and 57.35±11.4 respectively. The mean baseline ALSFRS-R in SBMA and ALS were 38.86±5.1 and 37.81±8.15, respectively.
Based on the chest CT result, 93% (14/15) of SBMA illustrated radiological gynecomastia, while 22.5% (7/31) of ALS showed gynecomastia. All 14 cases of SBMA manifested bilateral gynecomastia and largest diameter in SBMA and ALS was 36.43mm and 18.51mm ($p<0.001$). The mean glandular tissue diameter in ALS and SBMA was 31.97mm vs 17.24mm ($p<0.001$) respectively. The size of the glandular tissue showed a negative correlation to ALSFRS-R total score ($r =-0.492$, $p =0.063$).

CONCLUSION

The evaluation of breast glandular tissue using Chest CT may be an easily accessible and a non-invasive tool in distinguishing SBMA from ALS in the early stage of the disease. The ALSFRS-R negatively correlated with glandular tissues of gynecomastia and further studies are warranted to establish CT as a potential radiological surrogate marker in SBMA.

Clinical
PCN005

MAN-IN-BARREL SYNDROME-OWL'S EYE SIGN:A RARE NEUROIMAGING FINDING IN FLAIL ARM SYNDROME

Norsyafirah M.SALLEHUDDIN[1] Ting Yoong TEE [1],Yin Yin TAN[1],ERIN Shazrin M.RAMLY[2],Md Hanif MD ARIF[2],Dhayalen KRISHNAN[1],Kartikasalwah ABDUL LATIF[2],Shanthi VISWANATHAN[1]
[1]Department of Neurology,Hospital Kuala Lumpur,Malaysia
[2]Department of Radiology,Hospital Kuala Lumpur,Malaysia

INTRODUCTION

Flail arm syndrome variant of motor neurone disease is described as a progressive muscle weakness and atrophy predominantly involving proximal upper limbs, one of the atypical subtypes of amyotrophic lateral sclerosis (ALS).We report a case of man-in-barrel syndrome as a variant of motor neuron disease (MND) presenting with bilateral flail arm syndrome.

REPORT

A 54 years old male presented with progressive painless weakness of the proximal both arms for four years. It slowly progressed causing clumsiness of his hands. However,patient denied any neck pain, numbness of the upper limbs or weakness of the lower limbs.There were no bulbar or respiratory involvement.He has a strong family history of malignancy but no similar presentation among family members.Clinical examination revealed lower motor neuron weakness of both upper limbs as evidenced by bilateral areflexic paresis described as a man-in-a-barrel-like features. Otherwise,there is absence of lower limb and bulbar weakness or tongue fasciculations.Clinical diagnosis of flail arm variant MND was made and supported by normal nerve conduction study (NCS) and needle electromyographic (EMG) findings which showed denervation and reinnervation changes limited to proximal and distal upper muscles.Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) was 45 points.Tumor markers ,paraneoplastic screening and autoimmune profile were negative.CT thorax abdomen and pelvis (CTTAP) reported no evidence of malignancy.MRI cervical spine showed focal long segment bilateral circular T2W/STIR hyper intense foci within the anterior ho of spinal cord from C2/C3 until C3/C4 level which gives rise to owl-eye sign.

CONCLUSION

Given the temporal course of clinical presentation and aid of electrophysiological studies, the diagnosis of atypical variant of motor neurone disease was made.

Clinical
PCN006

DESIGNING A NEUROPHYSIOLOGICAL MODULE FOR MULTICENTER EARLY PHASE CLINICAL TRIALS IN PEOPLE WITH ALS

Boudewijn T.H.M. Sleutjes[1], *H. Stephan Goedee*[1], *Romy L. Verschoor*[1], *Tommy M. Bunte*[1], *Ruben P.A. van Eijk*[1], *Leonard H. van den Berg*[1]
[1]*Department of Neurology, Brain Centre Utrecht, University Medical Centre Utrecht, Utrecht, The Netherlands*

INTRODUCTION

A frequently observed mechanism in rodent and iPSC-derived models of amyotrophic lateral sclerosis (ALS), as well as in patients living with ALS, is changes in motor neuron excitability. Altered excitability have been suggested to represent early pathophysiological mechanisms associated with motor neuron death, and have been associated with more aggressive disease and shorter survival. Compounds that target membrane excitability may therefore hold disease-modifying potential. State-of-the art neurophysiological techniques, such as motor unit number estimate methods and nerve excitability testing, allow for early identification of motor unit loss and changes in nerve excitability in ALS, and could improve timely detection of relevant therapeutic effects. With preclinical evidence of compounds that modulate motor neuron excitability (e.g. QRL-101), axonal excitability measures have the potential to serve as translational tools to validate target engagement.

METHODS

A neurophysiological module will be designed as part of an early phase multicenter study (QRL-101-02). Within this module, nerve excitability testing will form an integral component.
Excitability recordings will be performed on the median nerve at the wrist and motor responses will be obtained from the abductor pollicis brevis. Consecutive recordings will be performed over time in approximately 24 ALS patients.

RESULTS

Markers of motor axonal excitability will serve as exploratory pharmacodynamic endpoints to detect effects of the studied compound (i.e. QRL-101) on (changes in) ion channel activity and axonal membrane properties. These findings will also be related to disease state in terms of axon loss. Conclusion: The results of the current study will provide highly relevant information on measures of axonal excitability as pharmacodynamical markers. This study will also offer input for further optimization of neurophysiological techniques in a multicenter setting, facilitating widespread adoption for future clinical trials, and ultimately contribute to, and guide, early phase ALS drug development.

Clinical
PCN007

ADAPTIVE CENTRAL NEURODEGENERATION ACCOMPANIES PERIPHERAL SENSORY DYSFUNCTION DISCRIMINATING KENNEDY'S DISEASE FROM ALS

Sicong TU[1], Tiffany LI[1], Antonia S. CARROLL[1], Colin MAHONEY[1], William HUYNH[1], Susanna PARK[1], Robert HENDERSON[2], Steve VUCIC[3], Matthew KIERNAN[1], Cindy (Shin-Yi) LIN[1]

[1]Brain and Mind Centre, The University of Sydney, Sydney, Australia
[2]Royal Brisbane and Women's Hospital, Brisbane, Australia
[3]Brain and Nerve Research Centre, The University of Sydney, Sydney, Australia

INTRODUCTION

Kennedy's disease (KD) is a rare genetically inherited lower-motor-neuron disorder commonly misdiagnosed as ALS in the early stage. Increasingly, peripheral sensory dysfunction in KD patients has been reported as a discriminating feature to ALS. The current study examined the presence of adaptive structural brain changes linked to peripheral sensory dysfunction, focusing on motor and somatosensory cortical processing centres.

METHODS

40 participants (10 KD; 15 ALS; 15 Control) were prospectively assessed at the Forefront MND Clinic and underwent 3T MRI scan. Functional nerve excitability assessments were performed on all KD patients. Whole-brain VBM and TBSS were conducted to examine structural grey and white matter abnormalities. Region of interest (ROI) analyses was performed using FastSurfer and MRtrix3 to assess fine-grained structural change in motor (BA6; BA4) and somatosensory (BA1/2/3) cortices and altered diffusivity along their associated white-matter tracts, respectively.

RESULTS

Peripheral sensory dysfunction was consistently observed across neurological examination and functional nerve excitability assessments in KD patients, compared to ALS and control participant data from the Forefront MND database. A selective reduction in cortical thickness and volume was evident in the left somatosensory cortex (BA3b/BA2), with sparing of motor cortical regions, contrasting to ALS and controls (p-values<0.05). Corresponding reduction in cortical-brainstem white-matter streamlines originating from BA3b/BA2 was evident. A significant positive correlation was evident between peak compound sensory action potentials (right index finger) and fractional anisotropy of the left corticospinal tract (FWE, p<0.01) in KD.

CONCLUSIONS

Atrophy of the somatosensory cortex was a feature in KD and associated with sensory axonal dysfunction. Secondary adaptive processes, in response to peripheral nerve dysfunction, may account for these findings. Neuroimaging may serve as a surrogate diagnostic and prognostic biomarker in KD.

Clinical
PCN008

DEVELOPING QUANTITATIVE MRI MARKERS FOR CAPTURING ALS PROGRESSION: THE AUSTRALIAN MND IMAGING INITIATIVE (AMII)

Sicong TU[1], Thomas SHAW[2], Chenyu WANG[1,3], Markus BARTH[2], Robert HENDERSON[4], Paul TALMAN[5], Matthew KIERNAN[1]
[1]Brain and Mind Centre, The University of Sydney, Sydney, Australia
[2]Centre for Advanced Imaging, School of Electrical Engineering and Information Technology,
University of Queensland, Brisbane, Australia
[3]Sydney Neuroimaging Analysis Centre (SNAC), Sydney, Australia [4]Royal Brisbane and Women's Hospital, Brisbane, Australia
[5]Neuroscience Department, Barwon Health District, Melboue, Australia

INTRODUCTION

The Australian MND Imaging Initiative (AMII) is a newly established network led by 3 core MND imaging centres (Brain and Mind Centre [Sydney]; Centre for Advanced Imaging [Brisbane]; Monash Biomedical Imaging Centre [Melboue]) to establish a national imaging platform and repository to develop quantitative MRI markers for clinical monitoring and therapeutic trials in ALS. We present an overview of the AMII framework, imaging platform and protocols.

METHODS

MRI protocol comprises state-of-the-art structural (T1; MP2RAGE; R2*), ^{1}H-MR spectroscopy, and multi-shell diffusion-weighted sequences, developed directly in collaboration with MRI vendors (SIEMENS; GE) to facilitate multi-site harmonization and data-sharing. The imaging platform incorporates two commercial software solutions (Torana/Coeus; TGA/FDA approved Class 1 Medical Device) for managing secure data transfer, data anonymization and metadata search. Imaging data is archived in accordance with the Brain Imaging Data Structure (BIDS). Imaging data will be linked to the national MND clinical registry (MiNDAUS), genetics repository (SALSA), and clinical trials network (ALLSTAR).

RESULTS

We present 3 streams of preliminary imaging results for planned downstream analyses, as well as validated deep-leaing algorithms to accelerate and enhance MRI data preprocessing (skull stripping; tissue segmentation; connectome augmentation) embedded into the platform's analysis pipelines. 1) Cortical hyperexcitability as an effective stratification criterion for reducing inter-individual variance of structural and metabolite motor MR abnormality. 2) Spinal cord imaging-derived metrics of structural abnormality as a discriminant marker of lower-motor-neuron predominant MND. 3) Multi-site validation of the sensitivity of structural cortical motor alteration as a marker of ALS pathology.

CONCLUSIONS

We present an overview of a scalable collaborative imaging framework that allows for harmonized longitudinal data acquisition that could be used with deep-clinical phenotyping and potentially extended across the Asia-pacific region.

Clinical
PCN009

THE 1H-MRS METABOLITE SIGNATURE OF CORTICAL HYPEREXCITABILITY IN ALS

Sicong TU[1], Olivia HUANG[1], Colin MAHONEY[1], William HUYNH[1], Matthew KIERNAN[1]
[1]Brain and Mind Centre, The University of Sydney, Sydney, Australia

INTRODUCTION

Cortical hyperexcitability is an established clinical feature present in the earliest stages of disease onset in ALS and can be used to detect subclinical upper motor neuron dysfunction. The abnormality is believed to reflect an underlying glutamate-induced excitotoxicity implicated in disease pathogenesis and linked to functional motor impairment. While a large body of TMS and MRS research have independently documented the disease signature of ALS, their association remains to be investigated.

AIMS

Characterize the relationship between cortical motor hyperexcitability and metabolite abnormalities.
Examine asymmetry differences in hemispheric cortical motor integrity.

METHODS

32 non-familial ALS patients and 17 age-education matched healthy controls were recruited. All participants received an MRI scan (3T GE MR750; 32-channel head coil) and single-voxel 1H-MRS (PRESS) data was sequentially acquired from the hand region of the left and right motor cortices. All patients underwent TMS to determine presence of cortical hyperexcitability based on SICI threshold (≥ 5.5).

RESULTS

As a whole, ALS patients demonstrated a consistent reduction in NAA/Cr in the left ($p=0.02$) and right ($p=0.01$) hand region, without evidence of hemispheric imbalance relative to controls. Patients with cortical hyperexcitability, however, demonstrated significantly higher levels of Glu/Cr and NAA/Cr across both hemispheres (p values < 0.05), relative to patients with a normal SICI. Interestingly, patients with a normal SICI demonstrated a significantly higher degree of hemispheric NAA/Cr imbalance ($p=0.04$).

CONCLUSIONS

Cortical excitability is associated with a consistent patte of metabolite abnormality across cortical hemispheres underlying hand motor function in ALS.

Clinical
PCN010

MOTOR UNIT NUMBER ESTIMATION IN THE SPLIT HAND OF AMYOTROPHIC LATERAL SCLEROSIS \

Pavey, Nathan[1], Higashihara, Mana[2], Hannaford, Andrew[1], Van Den Bos, Mehdi[1] Matthew C. Kiernan[2], Menon, Parvathi[1], Vucic, Steve[1].
Brain and Nerve Research Centre, NSW Australia; University of Sydney, New South Wales, Australia.
Department of Neurology, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan.
Brain and Mind Centre, University of Sydney, Sydney, New South Wales, Australia

OBJECTIVE
Differential muscle atrophy as evident with the split hand sign is a salient feature of amyotrophic lateral sclerosis (ALS). The split hand index (SI) of the compound muscle action potential amplitude (CMAP) is an established diagnostic tool in ALS. Motor unit number estimation (MUNE) or motor unit number index (MUNIX) are more sensitive techniques for quantifying motor unit loss and less invasive than needle electromyography. Consequently, the aim of the present study is to compare the utility of MUNE and MUNIX with the established CMAP SI in ALS.

METHODS
Thirty ALS and 14 non-ALS neuromuscular control patients were prospectively recruited. In all patients clinical and neurophysiological measurement of the abductor pollicis brevis, adductor digiti minimi, and first dorsal interosseous muscles were recorded on both sides. CMAP, MUNIX and MUNE were assessed for each muscle and split hand index calculated.

RESULTS
The split hand index (CMAP) was significantly reduced in ALS (4.6 ± 5.6) when compared to non-ALS controls (8.0±4.8, P=0.004). The split hand MUNE was significantly reduced in ALS (41.2±56.4) when compared to non-ALS (94.7±129.7 P=0.008). Additionally, split hand MUNIX was significantly reduced in ALS (75.5±76.4) compared to non-ALS (114.7±68.4, P=0.014).

CONCLUSIONS
The present study has confirmed motor unit number estimation and index has utility in the diagnosis and monitoring of ALS and is a potential biomarker for clinical trials.

Clinical
PCN011

MOTOR NEURONE DISEASE IN BRUNEI DARUSSALAM AND ITS RADIOLOGICAL FEATURES

Hazirah SHAFRI[1]; Sunithi E MANI[2]; Dayangku Siti Nur Ashikin PENGIRAN TENGAH
[1]Department of Neurology, Brunei Neuroscience, Stroke and Rehabilitation Centre, Brunei Darussalam
[2]Department of Diagnostic Imaging, Jerudong Park Medical Centre, Brunei Darussalam

INTRODUCTION

The Brunei Neuroscience, Stroke and Rehabilitation Centre (BNSRC) is the only tertiary neurosciences centre in Brunei Darussalam and from November 2018, sees most neurological disorders for the country providing approximate population data. Motor Neurone Disease (MND) remains a challenging diagnosis at the outset. Neuroimaging has been increasingly employed in the evaluation of patients with MND e.g., cortico-spinal tract (CST) hyperintensity and the motor band sign. We aimed to determine the clinical and radiological features of MND in Brunei Darussalam.

METHODOLOGY

Data from 1st January 2019 to 31st December 2021 were collected from our MND registry. Clinical features and demographic data were retrieved from the electronic patient record.

RESULTS

12 patients were diagnosed with MND in Brunei Darussalam during this time (58% male, 42% female). Mean age at onset was 60.5 years. The most common form of MND at onset was amyotrophic lateral sclerosis in seven patients (58%) and bulbar in five patients (42%). Two out of 12 patients died from aspiration pneumonia and respiratory failure respectively.
Magnetic resonance imaging (MRI) findings were: Five patients with CST hyperintensity, six with the motor band sign with three showing both. In two patients, MRI was unremarkable. Diffusion tensor imaging (DTI) was done in only three patients but all three had low functional anisotropy (FA) values. One patient had cervical myelopathy at C4-5 which was a confounding factor.

CONCLUSION

We present the first case series on MND in Brunei Darussalam. The mean age of onset and clinical presentation were comparable with other Asian cohort studies. MRI findings have provided useful supportive diagnostic information in our series. We suggest that susceptibility weighted imaging (SWI) and DTI could be performed more widely in the work-up of such patients if available.

Clinical
PCN012

COMPARISON OF ELECTROENCEHALOGRAM AND COMPUTERIZED TOMOGRAPHY OF BRAIN IN CLINICAL MANIFESTATION HEMORRHAGIC STROKE PATIENTS

Nona Suci Rahayu[1], Nova Dian Lestari[1], Imran[1], Syahrul[1]
Correspondence: nonasucirahayu@yahoo.com
[1] Department of Neurology Faculty of Medicine Syiah Kuala University/Dr. Zainoel Abidin Public Hospital, Banda Aceh, Indonesia

INTRODUCTION

Electroenchepalogram (EEG) is a recording of brain activity that measures electrical activity in the brain. Electroenchepalogram also useful to assess neural function and predict poststroke recovery. Computerized Tomography of Brain (CT imaging) provides anatomical detail and focal structural lesion in hemorrhagic stroke patients. Therefore, electrophysiology test such as EEG and CT brain imaging simultaneously might be useful in diagnosing brain disorder and other clinical manisfestation in hemorrrhagic stroke patiens.

METHODS

This research reported comparison of electroencephalogram and computerized tomography of brain in clinical manifestation hemorrhagic stroke patients. This study reported a 23year-old woman with seizure and hemiplegia sinistra and facial nerve palsy caused by hemorrhagic stroke. The glasgow coma scale of this patient is twelve (E3M5V4).

RESULTS

The result of brain CT Scan showed bleeding from a blood vessel in temporoparietal lobes of right cerebral hemisphere which estimation volume of bleeding 40 cc and has ICH Score mortality index in 30 days is 26%. The resukt of electroenchepalogram showed spike and sharp wave complexes in right cerebral hemisphere which spread in left cerebral hemisphere.

CONCLUSIONS

In this report showed that location of bleeding, the volume of bleeding can relate to clinical manifestation in stroke patients, and also relate to result of CT brain and electroencephalogram. Electroencephalogram and computed tomography of brain are tools might be useful to diagnosing brain disorder in stroke patients.

Keywords: Electroencephalogram, Computerized Tomography of Brain, Hemorrhagic Stroke

Clinical
PCN013

LONGITUDINAL ANALYSIS OF CORTICAL FUNCTION IN AMYOTROPHIC LATERAL SCLEROSIS

Dhayalen KRISHNAN[1,2], Jasmine F. ASHHURST[1], Susanna B. PARK[1], Steve VUCIC[3], Matthew C. KIERNAN[1,2]
Brain and Mind Centre, University of Sydney, Sydney, New South Wales, Australia.
Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia.
Westmead Clinical School, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive and fatal neurodegenerative disease of the motor neurons. There is mounting evidence that cortical hyperexcitability is closely linked to the disease process. Longitudinal studies among pre-symptomatic carriers of SOD1 mutation revealed that cortical hyperexcitability develops prior to clinical onset of ALS. Transcranial magnetic stimulation (TMS), has allowed non-invasive means of assessment of these cortical circuits. The short interval intracortical inhibition (SICI), produced through the paired pulse paradigm has been proven to be the most robust biomarker of cortical excitability. The present study investigated progressive change in SICI through serial assessments of patients with ALS. Methods: Neurophysiology data of all patients who had undergone TMS study at the Brain and Mind Centre in Sydney, NSW between January 2018 and June 2022 for assessment of cortical function was screened. Patients were included only if they had undergone two or more TMS studies on separate occasions involving the same region in the upper or lower limbs. Average SICI defined as the mean of SICI values obtained at each interstimulus interval from 1ms to 7ms was extracted for each patient from every TMS study they underwent.

RESULTS

All patients had a diagnosis of either definite or probable ALS. The average disease duration from onset of symptoms to the first TMS study was 16.5 ± 13.3 months. All patients in this study had progressive decline in SICI over a period of 12-18 months. An increased proportion of patients achieved a SICI value of less than 5.5 over the study period.

CONCLUSION

The present study highlights that cortical hyperexcitability becomes more prominent with disease progression in ALS. Our findings alluded to the possibility of investigating the rate of change in SICI through serial assessment as a potential diagnostic biomarker in ALS.

Clinical
PCN014

SPLIT FOOT SIGN IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Sawsan Albaazi
Clinical Neurophysiologist MD
Department of Neurophysiology, Middle Euphrates Center Of Neurosciences - Najaf (Iraq)

BACKGROUND
The muscle pattes involved in amyotrophic lateral sclerosis (ALS) remains controversial. split leg and split hand signs were assessed previously. However; foot muscles involvement could be not equal in ALS like in case of split hand sign with preference for lateral hand muscles.

OBJECTIVES
To evaluate the patte of the extensor digitorum brevis (EDB), the abductor hallucis (AH) muscles' involvement in ALS and Abductor digiti minimi (ADM) looking for the possibility of having split foot sign like split hand one.

METHODS
We recruited 11 patients with ALS and 12 healthy controls. Compound Muscle Action Potentials (CMAPs) were recorded over the EDB, ADM and AH muscles in all subjects. EDB/AH and ADM/AH ratios were obtained and compared between patients and controls.

RESULTS
The EDB/AH and ADM/AH CMAP amplitude ratio were significantly reduced in patients with ALS (0.26 +_ 0.16, P = 0.001) and (0.27 +_ 0.10, p = 0.001) respectively. These findings indicate a greater loss of lower motor neurons innervating the EDB and ADM and dysfunction of spinal motor neurons innervating these muscles. The EDB/AH and ADM/AH CMAP ratios reliably differentiated patients from HCs, with AUCs of 0.42 (95% CI 0.00-0.9) and 0.41 (95% CI 0.00–0.95), sensitivities of 78%, and specificities of 100% for both with cut-off ratios of 0.12 and 0.15 recpectively.

CONCLUSIONS
These results suggest preferential EDB and ADM compared to AH involvement in ALS. The EDB/AH and ADM/AH CMAP ratios robustly differentiated patients with ALS from HCs, which might facilitate an earlier identification of ALS patients.

Clinical
PCN015

A CASE OF TUBERCULOUS ARACHNOIDITIS MIMICKING DIFFUSE ANTERIOR HORN CELL DISEASE: A CASE REPORT

Zin Nwe Win1, Ohnmar Ohnmar2, Phyu Phyu Lay3
1 Consultant Neurologist, Department of Neurology, Yangon General Hospital, Yangon, Myanmar.
2Associate Professor, Department of Neurology, University of Medicine 1, Yangon, Myanmar.
3Professor/Head, Department of Neurology, Yangon General Hospital, Yangon, Myanmar.

INTRODUCTION

Diagnosis of MND is supported by electrodiagnostic finding of diffuse lower motor neuron involvement.

REPORT

A 59-year-old lady, with diabetes mellitus, presented with fever for 10-day-duration. She denies respiratory, urinary and bowel symptoms of infection. Physician's work up for systemic infection was negative. She also had paraparesis for 1.5 months, so referred to neurology. Neurological examination at first point showed GCS 15, no signs of meningism, no cranial neuropathy and normal upper limbs. Lower limbs showed proximal 2/5, and distal 5/5 without sensory and sphincter involvement, normal tone, reflexes and bilateral flexor plantar. Drug history includes only hypoglycemics. Her investigations by physician showed normal full blood count, creatinine and liver function, negative infection screening, and normal ECG, chest and thoracolumbar X-ray, ultrasound abdomen and pelvis. Electrolytes were normal except sodium 124 mmol/L. CRP was 13.31 mg/L, and ESR 13mm/1st hour. Since our first clinical impression was myopathy, we proceeded with creatinine kinse, vitamin D, lactate, thyroid function, and all were normal. Nerve conduction study was normal. Electromyogram revealed widespread active denervation and chronic reinnervation in cervical, thoracic and lumbosacral segments. At that point, our differentials were diffuse anterior ho cell disease or polyradiculopathy. Few days later, patient's GCS dropped and neck stiffness appeared. CECT (Head) showed meningitis with hydrocephalus. Upon lumbar puncture, CSF was xanthochromic, pressure 8 cmH2O, protein 1097 mg/dL, cells 174 (10% polymorphs, 90% lymphocytes), glucose 44%, negative gram, AFB and indian ink stains, and negative CSF AFB geneXpert. CSF cytology was compatible with chronic inflammatory condition and negative for malignant cells. She rapidly responded to dexamethasone and antituberculous therapy.

CONCLUSION

Our case demonstrates tuberculous arachnoiditis presenting with polyradiculopathy and the necessity of neuroimaging and CSF study to rule out other possible differential diagnoses of diffuse anterior ho cell disease

Clinical
PCN016

BRAIN IMAGING SIGNATURE AND ITS CORRELATES WITH PERIPHERAL MOTOR DEGENERATION IN ALS

Chi-Chao Chao[1], Sung-Ju Hsueh[1,2], Ta-Fu Chen[1], Ya-Fang Chen[3], Hsueh-Wen Hsueh[1], Wen-Chau Wu[3,4], Sung-Tsang Hsieh[1,5]
Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan.
Department of Neurology, National Taiwan University Hospital Yunlin Branch, Douliu City, Yunlin County, Taiwan.
Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan.
Graduate Institute of Medical Device and Imaging, College of Medicine, National Taiwan University Hospital, Taipei, Taiwan.
Department of Anatomy and Cell Biology, National Taiwan University College of Medicine, Taipei, Taiwan.

INTRODUCTION

This study aimed to explore the clinical significance of brain imaging signatures in the context of neurological deficits and the degree of lower motor neuron degeneration in amyotrophic lateral sclerosis (ALS).

METHODS

We performed brain MRI examinations to quantitatively evaluate (1) gray matter volume and (2) white matter tract fractional anisotropy (FA). Image-derived indices were correlated with (1) global neurological deficits of MRC muscle strength sum score, revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R), and forced vital capacity (FVC), and (2) focal scores of University of Pennsylvania Upper motor neuron score (Penn score) and the summation of compound muscle action potential Z scores (CMAP Z sum score).

RESULTS

There were 39 ALS patients and 32 control subjects matched for age and gender. Compared to controls, ALS patients had a lower gray matter volume in the precentral gyrus of the primary motor cortex, which was correlated with FA of corticofugal tracts. The gray matter volume of the precentral gyrus was correlated with FVC, MRC sum score, and CMAP Z sum score, while the FA of the corticospinal tract was linearly associated with CMAP Z sum score and Penn score on multivariate linear regression model.

CONCLUSION

This study indicated that simple assessment of muscle strength and routine measurements on nerve conduction studies provided surrogate markers of brain imaging signatures for ALS. Furthermore, these findings suggested parallel involvement of both upper and lower motor neurons in ALS

Clinical
PCN017

ALTERED MOTOR NERVE EXCITABILITY IN PRIMARY LATERAL SCLEROSIS

Moeko Okushi, Kazumoto Shibuya, Ryo Otani, Tomoki Suichi, Marie Morooka, Hiroki Kano, Yuya Aotsuka, Sonoko Misawa, Satoshi Kuwabara
Department of Neurology, Chiba University Graduate School of Medicine

INTRODUCTION

Primary lateral sclerosis (PLS) is a rare form of motor neuron disease characterized by the absence of clinical signs of lower motor neuron involvement. Whereas motor neuron hyperexcitability in amyotrophic lateral sclerosis (ALS) has been reported, neuronal excitability in PLS has not been well investigated. Methods: Clinical and neurophysiological findings, including nerve conduction and excitability studies, were investigated in 7 PLS patients and 109 his ALS patients. in axonal excitability studies. Fifty-four healthy subjects served as normal controls (NC).

RESULTS

The mean age of PLS and ALS was 61 and 66 years, the mean disease duration was 38 and 18 months, the proportion of male patients was 42 and 61%, and the proportion of patients with bulbar onset was 57 and 25%, respectively. Amplitude of the compound muscle action potential of the abductor pollicis brevis muscle was lower in PLS and ALS than in NC (mean, PLS, 5.9 mV; ALS, 4.0 mV; mV; NC, 12.9 mV). Nerve excitability testing showed longer intensity-duration constants in his ALS (mean 0.52 ms) than in the PLS (0.45 ms) and HC 0.45 ms) groups, suggesting increased sodium currents in the ALS . PLS and ALS patients have a depolarization threshold showed large threshold changes in electrotonus (PLS, 69.9%; ALS, 70.5%). HS: 66.4%) and higher hyperexcitability (PLS: 27.2%, ALS: 26.5%, HS: 18.9%), compared with HS, suggesting a decrease in potassium currents.

CONCLUSIONS

PLS showed a mild but increased axonal excitability of motor neurons. PLS, like ALS, may share an altered lower motor neuron load, leading to decreased motor neuron death.

Clinical
PCN018

FASCICULATION POTENTIALS ARE RELATED TO THE PROGNOSIS IN AMYOTROPHIC LATERAL SCLEROSIS

Keiko Ohnari1, Kosuke Mafune2, Hiroaki Adachi11 Department of Neurology, School of Medicine,
University of Occupational and Environmental Health, Japan2 Department of Mental Health, Institute of Industrial Ecological Sciences, School of Medicine, University of Occupational and Environmental Health, Japan

INTRODUCTION

The progression of amyotrophic lateral sclerosis (ALS) differs among patients, and the biomarkers for prognosis and treatment effects have been identified. Fasciculation potentials (FPs) in electromyography (EMG) are useful for early diagnosis of ALS, and complex FPs are associated with shorter survival in ALS. In this study, we investigated the relationship between the rate of muscles with FPs and the biochemical markers in relation to the prognosis of ALS.

METHODS

Patients with ALS were classified into three groups (less than one year: fast progression; from one year to less than three years: average progression; three years or more: slow progression) based on the interval from onset to death or tracheostomy. The results of EMG, nerve conduction studies, somatosensory evoked potential (SEP) measurements, and motor evoked potential measurements were statistically analyzed. We also analyzed the rate of muscles with FPs and the fibrillation potentials and positive sharp waves in the examined muscles and examined the biochemical biomarkers evaluated on admission.

RESULTS

ALS patients with fast progression showed a higher rate of FPs and lower uric acid (UA) levels. The survival curves demonstrated a relationship between these factors and the survival time in patients with ALS. Furthermore, UA levels were correlated with the rate of FPs. In the nerve conduction study, the motor conduction velocity (MCV) and sensory conduction velocity (SCV) of the ulnar nerve, the MCV of the tibial nerve, and the SCV of the sural nerve in patients with fast progression were significantly lower than those in the other two groups.

CONCLUSION

Our electrophysiological findings suggest that ALS presents with multisystem neurological manifestations from the peripheral to central nervous systems, and these manifestations differed among the groups classified by prognosis. The rate of FPs in EMG and serum UA levels were especially associated with the prognosis of ALS.

Clinical
PCT001

QRL-201-01 - A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTIPLEASCENDING DOSE STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF QRL201 IN AMYOTROPHIC LATERAL SCLEROSIS

Angela Genge[1], Kristiana Salmon[1], John Polzer[1], Clárida Martínez[1], Bryan Boggs[1], Victoria Eon[1], Rakhee Ganti[1], Sandy Hinckley[1], Kristina Johnson[1], Daniel Elbaum[1]
[1]QurAlis Corporation, 100 Cambridgepark Drive, Cambridge, MA, 02140

INTRODUCTION

A hallmark of amyotrophic lateral sclerosis (ALS) in >90% of patients, is the presence of cytoplasmic TAR DNA Binding Protein 43 (TDP-43) aggregates and loss of nuclear expression. Loss of nuclear TDP-43 leads to Stathmin-2 (STMN2) mis-splicing, resulting in decreased expression in the majority of people living with ALS. STMN2 is important for neural repair, axonal stability, and neuromuscular junction innervation. Our therapeutic approach is to correct STMN2 mis-splicing, thereby restoring protein function. QurAlis has shown that this can be accomplished using a splice switching antisense oligonucleotide (ASO) in non-clinical studies. QRL-201 is an investigational ASO that rescues STMN2 expression and protein function in QurAlis' patient-derived neuronal disease models, even in the continued presence of TDP-43 pathology.

METHODS

QurAlis has designed a phase 1 study evaluating the safety and tolerability of multiple doses of QRL201 in people living with ALS. QRL-201-01 is a double-blind, multiple-ascending dose study in which approximately 64 people living with ALS will receive QRL-201, or matching placebo, in a 6:2 ratio. The study design includes six dose escalation cohorts and two exploratory cohorts. This study will include the collection of data on numerous biomarkers, will employ sentinel participant dosing, and include multiple safety reviews.

RESULTS

The primary endpoint will be incidence of adverse events. The secondary endpoints will be measurements of multiple dose pharmacokinetics (PK). This study will include multiple exploratory endpoints – 1) biomarkers of neuronal loss and STMN2 biology; 2) clinical outcome measures (ALSFRS-R, ROADS, SVC, HHD, electrophysiology testing); and 3) CSF PK profile.

CONCLUSION

QurAlis' mission is to bring breakthrough precision medicine technology to people living with ALS. QRL-201-01 is designed to evaluate the safety and tolerability of multiple doses of QRL-201 in people living with ALS, and explore the hypothesis that restoration of STMN2 is a suitable disease-modifying approach in ALS.

Clinical
PCT002

FIRST-IN-HUMAN STUDY OF SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SAR443820, A CENTRALLY PENETRANT RIPK1 INHIBITOR IN HEALTHY PARTICIPANTS

Amy EASTENSON[1], Agnes HINCELIN-MERY[2], Pascale LEWANCZYK[3], Cathy CANTALLOUBE[2], Xavier NICOLAS[4], Myriam BENAMOR[2], Robert POMPONIO[5], Emmanuel KRUPKA[4], Dimitry OFENGEIM[5], Li XIONG[5], Nazem ATASSI[5]
[1]Nucleus Network Pty Ltd, St Paul, MN, United States
[2]Sanofi, Chilly-Mazarin, France
[3]Ividata Life Sciences, Levallois-Perret, France (contracted by Sanofi)
[4]Sanofi, Montpellier, France
[5]Sanofi, Cambridge, MA, United States

INTRODUCTION

RIPK1, which regulates inflammatory signaling and necroptotic cell death, is implicated in neurodegenerative pathology. SAR443820 (DNL788), a selective, oral, centrally penetrant RIPK1inhibitor, is a promising therapeutic option in amyotrophic lateral sclerosis (ALS). We assessed safety, tolerability, pharmacokinetics, pharmacodynamics of SAR443820 in first-in-human, healthy participant, phase 1 trial comprising of randomized, double-blind, placebo-controlled, single-ascending-dose (SAD; Part-1a) and multiple-ascending-dose (MAD; Part-2) cohorts and a separate open-label singledose Part-1b for assessing SAR443820 levels in cerebrospinal fluid (CSF) to confirm CNSpenetrance.

METHODS

In Part-1a, 4 cohorts (n=8 each; 6 SAR443820, 2 placebo) received SAD of SAR443820 (up-to 4-fold the lowest dose) or placebo in fasted conditions. Part-1b included 2 single-dose cohorts (n=6 each) receiving the lowest and 4-fold the lowest doses of SAR443820 in fed conditions. In Part-2, 4 cohorts (n=10 each; 8 SAR443820, 2 placebo) received 14-day SAR443820 or placebo in MAD as once/twice-daily dosing regimens in fasted conditions.

RESULTS

SAR443820 was well-tolerated in all studies, with no treatment-related serious-AEs or AErelated permanent treatment discontinuation. Most common AEs were dizziness and headache. No clinically meaningful changes were noted in hematology, chemistry, vital-signs, or electrocardiogram parameters. Overall, no major deviations noted from dose proportionality for C_{max} and AUCs over the range of SAR443820 doses. Mean plasma $t_{1/2z}$ ranged from 6-8h and 7-9h, following single and repeated SAR443820 doses, respectively. Mean CSF-to-unbound plasma concentration ratio indicated optimal CNS-penetrance. Concentration-QTcF analyses did not indicate any potential for SAR443820 to cause relevant change in QTcF. Maximum median inhibition of phosphorylatedSer166-RIPK1 levels across all SAR443820 groups in SAD and MAD studies reflected a marked target engagement.

CONCLUSION

First-in-human study demonstrated that single and repeated SAR443820 doses were generally safe and well-tolerated, with favorable pharmacokinetics, high CNS-penetrance, and robust RIPK1-target engagement. These results support further development of SAR443820 in a phase 2 Himalaya trial (NCT05237284) in ALS patients.

Clinical
PCT003

AN EXPLORATORY TRIAL OF EPI-589 IN AMYOTROPHIC LATERAL SCLEROSIS (EPIC-ALS)

Shotaro Haji[1], Koji Fujita[1], Ryosuke Oki[1], Yusuke Osaki[1], Hiroyuki Morino[2], Seiichi Nagano[3], Naoki Atsuta[4], Yuki Kanazawa[5], Yuki Matsumoto[6], Atsuko Arisawa[7], Hisashi Kawai [8], Satoshi Sakaguchi[9], Kenta Yagi[9], Tatsuto Hamatani[10], Masafumi Harada[6], Gen Sobue[11], Yuishin Izumi[1]

Department of Neurology, Tokushima University Graduate School of Biomedical Sciences
Department of Medical Genetics, Tokushima University Graduate School of Biomedical Sciences
Department of Neurotherapeutics, Osaka University Graduate School of Medicine
Department of Neurology, Aichi Medical University School of Medicine
Department of Biomedical Information Sciences, Tokushima University Graduate School of Biomedical Sciences
Department of Radiology, Tokushima University Graduate School of Biomedical Sciences
Department of Diagnostic and Interventional Radiology, Osaka University School of Medicine Graduate School of Medicine
Department of Radiology, Aichi Medical University School of Medicine [9] Clinical Research Center for Developmental Therapeutics, Tokushima University Hospital [10] Sumitomo Pharma Co., Ltd.
[11] Aichi Medical University

BACKGROUND
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by extensive loss of motor neurons. Accumulating evidence suggests that oxidative stress is linked to the pathogenesis of ALS. EPI-589 is a small molecule, novel redox-active agent characterized by catalytic activity on oxidative stress and high blood-brain barrier permeability.

OBJECTIVES
This trial aims to assess the safety and tolerability. Preliminary efficacy including clinical assessments and biomarkers of EPI-589 will be evaluated in patients with ALS.

METHODS
A multicenter, open-label, single-arm, early phase 2 study has been designed. We have recruited 10 patients with a diagnosis of definite, probable, or laboratory-supported probable sporadic ALS in accordance with the revised El Escorial criteria. Other main inclusion criteria are patients whose initial symptom of ALS occurred within 1.5 years before screening and patients with ALS Functional Rating Scale-Revised (ALSFRS-R) score progression of >0.3/month. This study consists of the following three periods: observation period (12 weeks), treatment period (24 weeks), and followâ€Â• up period (4 weeks). During the treatment period, patients will orally receive EPI-589 1,500 mg daily. The efficacy will be assessed by ALSFRS-R, time to death or respiratory insufficiency, slow vital capacity, manual muscle testing, grip strength, modified Norris scale, and ALS assessment questionnaire. Biomarkers including 8-hydroxy-2'-deoxyguanosine, 3-nitrotyrosine, neurofilament light chain, phosphorylated neurofilament heavy chain will be evaluated in the plasma or cerebrospinal fluid. Furthermore, magnetic resonance imaging and spectroscopy

will be conducted to measure fractional anisotropy in the corticospinal tract and N-acetyl-aspartate in the primary motor cortex.

RESULTS

This trial began data collection in September 2021 and database lock is scheduled in March 2023. The trial completion is expected in October 2023.

CONCLUSIONS

This study can provide useful data to understand the characteristics of EPI-589.

Clinical
PCT004

EVALUATING THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF QRL-101 IN TWO PHASE 1 STUDIES: QRL-101-01 IN HEALTHY ADULTS AND QRL-101-02 IN ADULTS WITH ALS

Angela Genge[1], Bryan Boggs[1], Rakhee Ganti[1], Sandy Hinckley[1], Kristina Johnson[1], Hannah Kaneb[1], John Polzer[1], Samantha Rubino[1], Kristiana Salmon[1], and Daniel Elbaum[1]
[1]QurAlis, Cambridge Massachusetts, United States

BACKGROUND
Amyotrophic lateral sclerosis (ALS) is a progressively fatal, neurodegenerative disease resulting in the loss of motor neurons in the motor cortex, brainstem, and spinal cord.[1] In ALS, evidence of increased cellular excitability in peripheral nerves and central motor neurons has been observed through advanced neurophysiological, imaging, pathological and biochemical techniques.[2,3] Clinically, hyperexcitability has been correlated with decreased longevity in people living with ALS.[4] QRL-101 is an investigational product targeting motor neuron hyperexcitability. Preclinical studies in models of ALS have indicated QRL-101, a potent, selective KCNQ2/3 channel positive allosteric modulator, may be effective in reducing motor system hyperexcitability in people living with ALS.

METHODS
The safety, tolerability, and pharmacokinetics (PK) of QRL-101 will be evaluated in two, consecutive, randomized, placebo-controlled, double-blind, phase 1 studies. The first, QRL-101-01, is an ongoing first-in-human, single-ascending dose (SAD) study in approximately 40 healthy participants. The study design includes five dose escalation cohorts of 8 participants each, randomized in a 6:2 ratio of study drug to placebo. Information from QRL-101-01 will be used to determine a safe and tolerable dose range for the subsequent multicenter multiple-ascending dose (MAD) study, QRL-101-02, which will evaluate QRL-101 in approximately 24 adults living with ALS. Both studies will utilize a sentinel dosing strategy, as well as multiple safety reviews.

RESULTS
In both studies, the primary and secondary endpoints will be incidence of adverse events and measurements of the PK of QRL-101 at single or multiple doses, respectively. In QRL-101-02, additional exploratory endpoints will be evaluated to assess the impact of QRL-101 on disease state, quality of life, and electrophysiological markers of motor nerve excitability in people living with ALS.

CONCLUSIONS
The findings from these studies will be used to advance the development of QRL-101, and other next-generation precision medicines for people living with ALS and other neurodegenerative diseases.

Clinical
PCT005

THE POTENTIAL OF STEM CELL THERAPY IN THE MANAGEMENT OF CHRONIC PAIN

Putu Yogi Pramana1, Ida Ayu Sri Wijayanti2, Anak Agung Raka Sudewi3
1Dharma Yadnya General Hospital Denpasar, Bali, Indonesia
Department of Neurology, Faculty of Medicine Udayana University, Udayana General Hospital, Jimbaran, Bali, Indonesia
Department of Neurology, Faculty of Medicine Udayana University, Prof.dr.I Gusti Ngoerah Gede Ngoerah General Hospital, Denpasar, Bali, Indonesia

INTRODUCTION
Stem cell transplantation has previously been used with promising results as a therapeutic modality for neurodegenerative diseases and pain but has recently been introduced as a treatment for chronic pain. This systematic review aims to review the available literature on the role of stem cell therapy as a treatment for chronic pain.

METHODS
A review of clinical study reports using the PRISMA method published in Pubmed, EMBASE, and ScienceDirect were used from 2013 to 2023, and the search function was used to search for ongoing, currently active clinical trials and recruit patients. Search keywords used included “chronic pain,” “disc pain,” “cell therapy,” “neuropathic,” “stem cell,” “musculoskeletal.” The research was then carried out to assess the quality of the study using the Critical Appraisal Skills Program (CASP) questionnaire.

RESULTS
There were around 186 studies related to the keyword, and only about 11 studies that met the inclusion criteria included in this article were obtained. Based on the results of the study, it was found that the role of stem cell therapy in the form of MSC and ADS, which was used, had a significant effect as a chronic pain therapy in patients with a treatment period of around 1 month - 36 months. A decrease in the quality of pain was obtained based on VAS, ODI, and NRS assessments as well as an increase in patient function.

CONCLUSION
Despite the evidence from current research supporting the use of stem cells as a novel treatment approach for discogenic, neuropathic, and musculoskeletal pain, further clinical studies will be required to confirm the value and safety of this modality. **Keywords:** chronic pain, review, stem cells, therapeutics

Clinical
PCT006

THE INTEGRATED STRESS RESPONSE IS MODULATED BY EIF2B AGONIST DNL343: RESULTS FROM PHASE 1 HEALTHY SUBJECT AND PHASE 1B ALS PATIENT STUDIES

Linus D. Sun1, Richard M. Tsai1, Ernie Yulyaningsih1, Melania H. Fanok1, Maurits Vissers2,3, Jules A.A.C. Heuberger2, Brittany N. Flores1, Fen Huang1, Lesley Kane1, Isaac V. Cohen1, Shyeilla V. Dhuria1, Meng Fang1, Anthony A. Estrada1, Maksim Osipov1, Brent Willman-Yoswa1, Romeo Maciuca1, Sarah K. Dobbins1, Roni Chau1, Timothy K. Earr1, Hoang N. Nguyen1, Isabel A. Lopez1, Danna Jennings1, Kimberly Scearce-Levie1, Tommy M. Bunte4, Leonard H. Van Den Berg4, Carole Ho1, Geert Jan Groeneveld2,3, Matthew D. Troyer1

Denali Therapeutics, 161 Oyster Point Blvd, South San Francisco, CA 94080 USA
Centre for Human Drug Research, Zernikedreef 8, 2333 CL, Leiden, The Netherlands
Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, The Netherlands
University Medical Center Utrecht, Heidelberglaan 100, 2584 CX, Utrecht, The Netherlands

OBJECTIVE
DNL343 is being investigated as a potential therapeutic agent for Amyotrophic Lateral Sclerosis (ALS).

BACKGROUND
ALS is a fatal neurodegenerative disease with TDP-43 inclusion pathology in 95% of patients. Chronic activation of the integrated stress response (ISR) may contribute to ALS by blocking translation, altering RNA and endosomal trafficking, and increasing formation of TDP-43-containing stress granules. DNL343 is a small molecule that activates a key ISR regulator, eIF2B, which inhibits ISR stress granule formation in cellular models and promotes neuroprotection in animal models.

METHODS
The safety, pharmacokinetics (PK) and pharmacodynamics (PD) of DNL343 were evaluated in a Phase 1 randomized, placebo-controlled trial (RCT) in healthy volunteers (NCT04268784) and a 28-day Phase 1b RCT in ALS participants (NCT05006352), with an ongoing 18-month open label extension (OLE). ISR inhibition was evaluated by measuring *CHAC1* gene expression and ATF4 protein in stimulated peripheral blood mononuclear cells (PBMCs).

RESULTS
In the Phase 1 study, ninety-five healthy participants were randomized (n=48 SAD, n=47 MAD). DNL343 was generally safe and well-tolerated with no serious adverse events (SAEs) or discontinuations related to study drug. DNL343 plasma concentrations were dose-dependent, with a plasma half-life of 38-46 hours and CSF-to-unbound plasma concentration ratio of 0.66-0.92. DNL343 attenuated two ISR biomarkers across the dosing period and at trough 24-hours after the last dose (*CHAC1* [66-94%] and ATF4 [50-73%]) in all MAD cohorts. Safety, pharmacokinetics and ISR pharmacodynamics from the 28-day Phase 1b study in ALS participants will be presented.

CONCLUSION

DNL343 is generally safe and well-tolerated at doses that demonstrate robust inhibition of ISR through *CHAC1* and ATF4 inhibition. The pharmacokinetic profile supports once daily oral dosing and there is extensive CSF distribution. Data from these early-stage studies in HV and ALS patients support further development of DNL343 as a potential therapeutic for the treatment of ALS

Clinical
PCT007

EFFICACY AND SAFETY OF LENZUMESTROCEL (NEURONATA-RÂ® INJ.) IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALSUMMIT STUDY): STUDY PROTOCOL FOR A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, SHAM PROCEDURE-CONTROLLED, PHASE III TRIAL

Kwijoo Kim[1], Jae-Yong Nam[1], Tae Yong Lee[1,2], Sehwan Chun[1], Min Sung Kim[1,2], Jinâ€˜Hong Shin[3] , Jung-‘Joon Sung[4] , Byoung Joon Kim[5] , Byung-‘Jo Kim[6] , Ki-‘Wook Oh[7] , Kyung Suk Kim[1] and Seung Hyun Kim[7*]*
Central Research Center, CORESTEMCHEMON Inc, Seoul, South Korea
College of Pharmacy, Chungbuk National University, Cheongju, South Korea
Department of Neurology, Pusan National University, Yangsan, South Korea
Department of Neurology, Seoul National University, Seoul, South Korea
Department of Neurology, Samsung Medical Center, Seoul, South Korea
Department of Neurology, Korea University Anam Hospital, Seoul, South Korea
Department of Neurology, Hanyang University Hospital, Seoul, South Korea

INTRODUCTION

A single cycle (two repeated treatments) with intrathecal autologous bone marrowderived mesenchymal stem cells (BM-MSCs, 26-day interval) showed safety and provided therapeutic benefit lasting 6 months in patients with ALS but did not demonstrate long-term efficacy. This phase III clinical trial (ALSUMMIT) protocol was developed to evaluate the long-term efficacy and safety of the combined protocol of single-cycle intrathecal therapy and three additional booster injections of BMMSC (Lenzumestrocel) treatment in patients with ALS.

REPORT

ALSUMMIT is a multicentre, randomized, double-blind, parallel-group, sham procedurecontrolled, phase III trial for ALS. The 115 subjects will be randomized (1:2:2) into three groups: (1) study Group 1 (single-cycle, two repeated injections with 26-day interval), (2) study Group 2 (singlecycle + three additional booster injections at 4, 7, and 10 months), and (3) the control group. Participants who have an intermediate rate of disease progression will be included in this trial to reduce clinical heterogeneity. The primary endpoint will be evaluated by combined assessment of function and survival (CAFS), also known as joint rank scores (JRS), at 6 months (study Group 1 vs. control) and 12 months (study Group 2 vs. control) after the first Lenzumestrocel or placebo administration. Safety assessment will be performed throughout the study period. Additionally, after the 56-week main study, a long-term follow-up observational study will be conducted to evaluate the long-term efficacy and safety up to 36 months.

CONCLUSION

Lenzumestrocel is the orphan cell therapy product for ALS conditionally approved by the South Korea Ministry of Food and Drug Safety (MFDS). This ALSUMMIT protocol was developed for the adoption of enrichment enrolment, add-on design, and consideration of ethical issues for the placebo group.

Clinical
PD001

POSTURAL INSTABILITY AND LOWER EXTREMITY DYSFUNCTION IN UPPER MOTOR NEURON-DOMINANT AMYOTROPHIC LATERAL SCLEROSIS

*Xiangyi Liu[1,2], Lu Chen[1,2], Shan Ye[1,2], Xiaoxuan Liu[1,2], Yingshuang Zhang[1,2], Dongsheng Fan[*1,2,3]*
Department of Neurology, Peking University Third Hospital, Beijing, China
Beijing Municipal Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing, China
Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing, China

INTRODUCTION

Upper motor neuron-dominant ALS (UMND ALS) is recognized to have early disease onset and good prognosis, but some may develop gait instability in the early stage. We investigated the clinical features of UMND ALS and UMND ALS accompanied by postural instability or repeated falls.

METHODS

This study included UMND ALS and divided them into two subgroups based on history of repeated falls or postural instability at the first visit (UMND+ ALS) in a prospective recruitment cohort. The lower extremity functional decline of these patients was compared with 1:2 propensity score matched classic ALS patients.

RESULTS

Among the 2353 ALS patients reviewed, 211 (9.0%) had UMND ALS. UMND ALS had a longer diagnosis delay and restricted symptoms. In contrast, UMND+ ALS has an earlier age of onset and more rapid decline of motor function. Although UMND ALS patients had better lower extremity function than classic ALS patients on first evaluation, there was no difference in the time of needing assistance or not being able to walk after disease onset. In the UMND+ ALS subgroup, lower extremity function was no better than that in the classic ALS. The prognosis of UMND ALS and UMND+ ALS were significantly better than those of overall ALS.

CONCLUSIONS

UMND ALS has restricted symptoms but have rapid decline in lower extremity function in the early disease stage. UMND+ ALS have an earlier disease onset and their motor function decline is as fast as classic ALS, this may suggest that they belong to a different subtype of ALS.

Clinical
PD002

AN AUTOPSY CASE OF BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA WITH AMYOTROPHIC LATERAL SCLEROSIS (BVFTD-ALS)

Aya Kawanami[1], Naohiko Togashi[1], Masanobu Miyashita[1], Yuko Kondo[1], Kotona Tateno[1], Tsuwa Ichikawa[1], Miyako Ishiyama[1], Aya Kumon[1], Midori Sagawa[1], Masato Hasegawa[2], Saburo Yagishita[1], Shigeo Murayama[3,4], Kazuko Hasegawa[1]
[1] Division of Neurology, Sagamihara National Hospital, Kanagawa, 252-0392, Japan.
[2] Department of Brain and Neurosciences, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan.
[3]Department of Neuropathology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan.
[4] Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, University of Osaka, Osaka, Japan.

INTRODUCTION

Confirmation of neuropathological background in FTD requires gene, protein and RNA analysis from autopsy cases. Here we present a bvFTD case with abundant p62-positive neuronal cytoplasmic inclusions.

CASE REPORTS

54 years-old Japanese female who has family histories of juvenile dementia and gambling mania, developed gambling problems. Increasing mistakes at work frequently reported. Confusion forced her to resigned the job. She visited our hospital with complaint of memorial loss and diagnosed of bvFTD at 1.6 year after onset. 3 years after onset, she was impossible to walk independent and repeated falling. She developed aspiration pneumonia after 5 years from onset.
Tracheostomy and NPPV were administered due to type 2 respiratory failure at 8 years from onset.
She died of respiratory deterioration at 62 years old. Autopsy was done.
The brain weight was 735g. Macroscopically, marked atrophy was observed in the frontal, temporal, and parietal lobes. Microscopic findings revealed neuronal loss and gliosis in the cortical layers, and astrocytosis in the white matter of the frontal, and temporal lobes. Betz cells were not identified. Pyramidal tract degeneration was observed from brain stem to spinal cord. Oculomotor and hypoglossal nucleus were intact. Cervical and thoracic anterior ho cells were markedly reduced. Numerous round-shaped p62-positive neuronal cytoplasmic inclusions were found in the cerebral cortices, basal ganglia, oculomotor and hypoglossal nucleus, hippocampal granular cells, and spinal anterior ho cells. Those inclusions showed negative for TDP-43, AT-8, and ubiquitin staining. Glial and neuronal FUS-positive inclusions were observed; however, they were rare and inconsistent with the distribution of p62-positive inclusions. Tentative neuropathologic diagnosis is FTD-ALS-p62.

CONCLUSION

Dissociation between p62 and ubiquitin staining is possibly the cue for the etiology in this case.

Clinical
PD003

CLINICAL CHARACTERISTICS AND DISEASE PROGRESSION OF BULBAR-ONSET AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND ISOLATED BULBAR PALSY (IBP) VARIANT OF ALS

Amirul Ab Ghapar[1], Dhalayen K[1], Shanthi V[1]
Department of Neurology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is an incurable motor neuron disorder characterised by progressive destruction of upper and lower motor neurons involving cortex, brainstem or spinal cords. Bulbar-onset ALS amongst all has the most progressive and distinct course. However, isolated bulbar palsy (IBP) variant of ALS with relative preservation of limb function is far less frequently seen and understood. We presented each case of bulbar-onset ALS and IBP variant of ALS in regard to clinical presentation, associated electrophysiological findings and disease progression.

CASE PRESENTATION

We presented a case of 44-year old female who presented with 6-month history of slurring of speech with progressive dysphagia. The patient had hyperreflexia involving left upper and lower limb with no disceible limb weakness. Diagnosis of bulbar-onset ALS was made after Nerve conduction studies (NCS), Electromyography (EMG) and Magnetic Resonance Imaging (MRI). We also presented another case of 65-year old gentleman with progressive dysphagia and speech disturbance with relatively normal peripheral limb examination. NCS and EMG revealed isolated genioglossus involvement sparing the cervical, thoracic, and lumbosacral regions thus diagnosis of possible IBP was made.

CONCLUSION

ALS is a devastating neurodegenerative disorder, and the involvement of genioglossus muscle at presentation has the worse prognosis and shorter survival. However, it has been reported that the disease progression and survival rate were significantly longer in IBP where the latter showed sign of first limb involvement of at least 20 months from the onset of bulbar signs. Hence, the cases aim to highlight the role of NCS and EMG in early diagnosis and to draw awareness on disease progression and prognosis of bulbar onset ALS as compared to IBP variant of ALS. Despite that, it mandates the input from multidisciplinary team for effective management.

Clinical
PD004

BULBAR-ONSET AMYOTROPHIC LATERAL SCLEROSIS (ALS) MIMICKING MUSCLE-SPECIFIC TYROSINE KINASE MYASTHENIA GRAVIS (MuSK-MG)

Nasheeda Saeed[1], *Chen Fei Ng*[1], *Hui Jan Tan*[1], *Rabani Remli*[1]
[1] *Department of Medicine, University Kebangsaan Malaysia Medical Centre, Malaysia*

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder involving primarily motor neurons in the cerebral cortex, brain stem and spinal cord. While establishing an early diagnosis is fundamental, diagnosing ALS, especially when presenting with bulbar symptoms, may be challenging.

REPORT

We report a case of a 63-year-old man who was initially diagnosed with recurrent stroke and referred to our center for further evaluation. His symptoms started one year prior to presentation with history of progressively worsening dysphagia and sialorrhea. Few months prior to presentation he started to have dysarthria, weakness of facial and neck muscles with significant weight loss. Clinically, he had dysarthria, tongue fasciculations, absent gag reflex, weakness of facial and neck muscles with head drop. His MRI brain showed multifocal infarcts and the MRI of cervical spine was unremarkable. Repetitive nerve stimulation showed significant decremental response in right abductor digiti minimi and trapezius. Single-fiber Electromyography (EMG) of the right orbicularis oculi showed prolonged jitter. He was treated with five cycles of plasmapheresis and oral steroids for possible MUSK related myasthenia gravis. However, he did not improve with treatment. Serum Acetylcholinesterase receptor Antibody and MuSK antibody later retued as negative. Follow up after one month showed clinical progression with emergence of hyperreflexia in upper limbs and brisk jaw jerk. Subsequent EMG revealed acute and chronic neurogenic changes. The diagnosis was revised to bulbar-onset ALS and he was started on tablet Riluzole.

CONCLUSION

It is important to be mindful of the wide spectrum of clinical presentations in ALS. Bulbar impairment has been demonstrated in up to 80% of MuSK-MG patients together with axial muscle weakness involving neck extensor, which may present as head drop. Excluding potentially treatable causes that may have similar presentations and a better prognosis while avoiding delays in establishing the diagnosis of ALS is paramount.

Clinical
PE001

MONOCLONAL GAMMOPATHY MAY NOT INFLUENCE THE CLINICAL COURSE OF MOTOR NEURON DISEASE ; CASE SERIES STUDY

Hyunkee Kim[1], Wonjae Sung[1,2], Yong Sung Kim[1,2], Jinseok Park[1,2], Seung Hyun Kim[1,2]
[1]Department of Neurology, Hanyang University College of Medicine, Seoul, Republic of Korea. [2]Cell Therapy Centre, Hanyang University Hospital, Seoul, Republic of Korea

BACKGROUND AND PURPOSE

Monoclonal gammopathy is known to be more frequently accompanied with motor neuron disease (MND) than normal population. Because of this relatively high presence, many MND patients with monoclonal gammopathy treated with various ways but invalid. We also had experiences of treating MND patients with monoclonal gammopathy who were registered in HYNR MND clinic. In this study, we investigate the possibility of monoclonal gammopathy treatment could change clinical course in MND patients. Herein we would share our experiences and observations.

METHODS

From Feb 2005 to June 2015, MND patients were registered through Hanyang Motor Neuron Disease clinic. Among MND patients who were screened protein electrophoresis test, 14 patients revealed monoclonal gammopathy. MND patients with monoclonal gammopathy underwent immunofixation and bone marrow test and investigated disease status and its progression through the ALS Functional Rating Scale-Revised (ALSFRS-R).

RESULTS

MND patients with monoclonal gammopathy showed male-dominant and elder disease onset age than those who without. Among 14 MND patients with monoclonal gammopathy, eight patients had taken immunotherapy (intravenous immunoglobulin, steroids and immune suppressants). There were no significant difference in disease progression speed between treated and non-treated group.

CONCLUSIONS

Monoclonal gammopathy is frequently detected in MND patients. But it is not affect to disease progression in MND patients regardless of immune treatment.

Clinical
PE002

AGE OF ONSET AND LENGTH OF SURVIVAL OF QUEENSLAND PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: DETAILS OF SUBJECTS WITH EARLY ONSET AND SUBJECTS WITH LONG SURVIVAL.

Robert J Nona [a], Zhouwei Xu[b], Gail A Robinson[c], Robert D Henderson [a,d] and Pamela A McCombe [a,d]

[a] University of Queensland, Centre for Clinical Research, Herston, Queensland, Australia
[b] Department of Neurology Shanghai Jiao Tong University Affiliated Sixth People's Hospital Shanghai, China
[c] Queensland Brain Institute & School of Psychology, University of Queensland, St Lucia, Queensland, Australia
[d] Department of Neurology, Royal Brisbane & Women's Hospital, Herston, Queensland, Australia

INTRODUCTION
To document the characteristics of ALS patients in Queensland, to examine factors influencing age of onset and survival, and to study those with early onset (<45 years) disease and those with long (> 5 years) survival.

METHODS
We studied subjects seen at the ALS Clinic at the Royal Brisbane & Women's Hospital. We recorded sex, age of onset, region of onset, length of survival, presence of family history, type of disease and evidence of cognitive involvement. We analysed the influence of these features on age of onset and on survival. We analysed the features of patients with early onset of disease and patients with long survival.

RESULTS
There were 855 ALS patients (505 males) in the cohort. The age of onset was lower in males than females, in patients with a family history of ALS compared to those without and in patients with spinal onset compared to bulbar onset. Early-onset disease was seen in 10% of patients, and had a greater proportion of males, spinal onset and classical ALS phenotype compared to late onset disease. Survival was shorter in females, in patients with bulbar onset, and in patients with classical ALS. Long survival was seen in 18% of patients. Patients with long survival had younger age of onset, greater proportion of males and of spinal onset and fewer patients with classical ALS.

CONCLUSION
Our study confirms that ALS is more prevalent in males, and that spinal onset is more common than bulbar onset. Males have earlier onset but longer survival. We found that overall, patients with classical ALS have worse survival than ALS variants, but some patients who were considered to have classical ALS had long survival. This study confirms the similarity of ALS in our region to ALS in other geographical regions.

Clinical
PE003

CHARACTERISTIC AND MANAGEMENT OF MOTOR NEURON DISEASE IN THE LARGEST TERTIARY HOSPITAL IN THE PHILIPPINES: A ONE-YEAR PERIOD CROSS SECTIONAL ANALYTIC STUDY

Mario B Prado Jr[1,2,3], Geohanna Hamoy-Jimenez[4], Karen Joy B. Adiao[3]
[1]Department of Physiology, College of Medicine, University of the Philippines Manila
[2]Department of Epidemiology and Biostatistics, College of Public Health, University of the Philippines Manila
[3]Section of Adult Neurology, Department of the Neurosciences, Philippine General Hospital, University of the Philippines- Manila 4Asian Hospital Medical Center

BACKGROUND
Motor neuron disease is largely understudied in developing countries, including the Philippines. The management of MND is generally insufficient, and thus, the quality of life of these patients are compromised.

OBJECTIVES
The aim of this study is to determine the clinical profile and describe the management of MND patients seen in the largest tertiary hospital in the Philippines for one year.

METHODS
This is a prospective cross-sectional study of MND patients diagnosed clinically and via EMG NCS in the Philippine General Hospital from January to December 2022. Clinical characteristics, diagnostics and management information were obtained and summarized.

RESULTS
The incidence of MND in our electrophysiology unit was 4.3%, with ALS being the most common variant (67.9%). Male to Female ratio is 1:1, with the median age of onset 55 years old and mean onset duration to diagnosis of 1.5 years. Limb onset is more prevalent (82.14%) with upper limbs initially involved (79.1%). Split hand syndrome was found in almost half of the patients. The median ALSFRS-R score and MRC were 34 and 42, Only half of the patients were able to undergo MRI and only one had neuromuscular ultrasound. Only one of the 28 patients was able to take riluzole. None were on enteral tube feeding or PEG, and none underwent noninvasive ventilation or early tracheostomy.

CONCLUSION
This study showed that the management of MND in the Philippines is largely inadequate and further improvement in the health care system in handling rare neurologic cases must be implemented to enhance their quality of life.

Clinical
PE004

GENETIC ANALYSIS AND PROGNOSTIC FACTORS OF ALS IN TAIWAN

Kang-Yang JIH[1,2], Yi-Chung LEE[1,3]
Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan
Department of Physiology, National Yang-Ming Chiao-Tung University, Taipei, Taiwan
Department of Neurology, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan

INTRODUCTION

Amyotrophic lateral sclerosis is a fatal neurodegenerative disease. In this study, we reported currently the largest Taiwanese ALS cohort with genetic analysis and clinical characteristics.

METHODS

304 patients diagnosed with probable or definite ALS according to revised El Escorial criteria were recruited between 2017 and 2022. Genetic analysis of common ALS associated genes were performed. Clinical characteristics and biannual ALSFRS-R evaluations were recorded. 65 patients also received analysis of serum fluid biomarkers including Nfl and GFAP.

RESULTS

The male and female ratio is 1.42. 87% of the patients exhibits spinal onset. The most common disease associated genes are *C9ORF72* and *SOD1*, followed by *TARDBP* and *FUS*. The average ALSFRS-R score at diagnosis was 34.2 and dropped to 23.8 one year after diagnosis. The mean survival was 53.7 months since disease onset. ALSFRS-R score below 40 at diagnosis, bulbar onset, BMI < 20 at diagnosis, high serum Nfl level (> 50 percentile in the cohort) are associated with shorter survival ($p < 0.01$).

CONCLUSION

Our study revealed a unique genetic feature of Taiwanese ALS patients and suggested ALSFRS-R score, onset region, BMI, and serum Nfl level are potential prognostic factors for survival.

Clinical
PNM001

EFFICACY, SAFETY AND TOLERABILITY OF HIGH CALORIC DIET IN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS: A SYSTEMATIC REVIEW AND META ANALYSIS

Mario Jr PRADO[1,2,3], Karlo PEDRO[3], Karen Joy ADIAO[3]
[1]Department of Physiology, College of Medicine, University of the Philippines- Manila, Manila, Philippines
[2]Department of Epidemiology and Biostatistics, College of Public Health, University of the Philippines- Manila, Manila, Philippines
[3]Department of Neurosciences, University of the Philippines- Philippine General Hospital, Manila, Philippines

INTRODUCTION
Several randomized clinical trials were done to determine whether supplementation with a high caloric diet, either through carbohydrate or lipid supplementation, is safe, tolerable and improves survival. However, most of these trials are small and the results are conflicting.

METHODS
Randomized prospective trials utilizing high caloric supplementation among ALS patients were searched using the term [("Amyotrophic Lateral Sclerosis" or "Motor Neuron Disease" or "ALS" or "MND") AND ("High calorie" or "High fat" or "high protein" or "high carbohydrate" or "supplementation")] in Medline, Cochrane, Embase, Scopus, Prospero and Herdin by 2 neurologists independently. Joual articles deemed relevant were assessed for eligibility.

RESULTS
There were 57 articles obtained from databases, 49 of which were excluded. Four articles were further excluded since all of them had different interventions. Overall, there were 311 ALS patients included in the study, 176 of them were from the intervention group while 135 were used as controls. Overall, high caloric supplementation in ALS is deemed safe and tolerable, and when adverse events, tolerability and mortality are combined using meta-analysis. Although in most jouals the efficacy of giving high caloric supplementation has been generally beneficial, some of the outcome parameters are not statistically different from controls when studies are combined using metaanalysis.

CONCLUSION
Current evidence suggests that high calorie supplementation is generally safe and tolerable for patients with ALS. However, it has not been shown to be efficacious in improving weight and functional disability.

Clinical
PNM002

IDENTIFYING GASTROSTOMY CARE AND HOME ENTERAL NUTRITION-RELATED EDUCATIONAL CONTENTS FOR PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS AND THEIR FAMILY CAREGIVERS: A DELPHI PANEL WITH PROFESSIONAL STAKEHOLDERS

Hyeon Sik Chu[1,2], Seung Hyun Kim[2,3], Young Ran Tak[1], Hanyi Lee[1]
School of Nursing, Hanyang University, Seoul, Korea
Department of Neurology, Hanyang University Hospital, Seoul, Korea
Department of Neurology, College of Medicine, Hanyang University, Seoul, Korea

Enteral nutrition through a gastrostomy tube is commonly used to provide nutritional support to patients with ALS who have developed severe dysphagia at home. Potential complications can arise from gastrostomy and enteral nutrition when family caregivers at home do not provide adequate and appropriate care. The study aimed to identify key areas of educational content that could improve the care of patients with ALS who require gastrostomy care and home enteral nutrition. We conducted a modified three-round e-Delphi survey with experts in healthcare to gather their perspectives on the educational content needed for gastrostomy care and home enteral nutrition for patients with ALS and their family caregivers. The experts were asked to provide their opinions on specific educational content areas, and their responses were analyzed to identify areas of consensus and divergence. A total of 16 experts participated in rounds 1–3 of this study. including registered nurse(n=6), advanced practice registered nurse(n=3), clinical neurologist(n=3), and dietitian(n=4). In round 3, 5 categories and 39 educational components reached consensus. 5 categories were 'gastrostomy site management', 'enteral nutrition', 'coping with emergency situations, and 'daily living with gastrostomy tube'. The results of this study provide a framework to develop educational nursing interventions in family caregivers of patients with ALS receiving home enteral nutrition using gastrostomy tube and defining the essential elements of educational content for such interventions.

Clinical
PNM003

DEVELOPMENT OF A NURSE-LED NAVIGATION PROGRAM FOR FAMILY CAREGIVERS OF PATIENTS WITH ALS RECEIVING GASTROSTOMY TUBE FEEDING: FOCUSED ON HOSPITAL TO HOME TRANSITION PERIOD

Hyeon Sik Chu[1,2], Seung Hyun Kim[2,3], Young Ran Tak[1]
School of Nursing, Hanyang University, Seoul, Korea.
Department of Neurology, Hanyang University Hospital, Seoul, Korea.
Department of Neurology, College of Medicine, Hanyang University, Seoul, Korea

Many patients with ALS live at home, and most are cared for by family members. It is important to understand the methods and complications of gastrostomy tube feeding. However, ALS patients and their families experience a lack of support and information on gastrostomy tube feeding. This is a methodological study to develop a nurse-led navigation program for family caregivers of patients with ALS receiving gastrostomy tube feeding at home focusing on hospital to home transition period. The theoretical framework of this study was the professional navigation framework and the instructional design model for the development of the nurse-led navigation program was based on the ASSURE model. The content of the nurse-led navigation program was prepared by reviewing the literature, online ALS patient online community analysis, in-depth interviews of family caregivers of patients with ALS, and a Delphi survey of health care professionals. This nurse-led navigation program was designed that provides intervention from hospital admission to the transition to home after discharge. The components of this program include simulation-based education, selfmanagement learning through a chatbot, and online individual nursing counseling with an MND specialist nurse.

As part of the nurse-led navigation program, we utilized a low-fidelity model for a gastrostomy tube, the KakaoTalk chatbot builder for self-management learning chatbot, and a KakaoTalk plus channel for online nursing counseling. Heuristic, performance, and user experience evaluations were conducted for program validation. The program was evaluated by IT experts, healthcare providers, and family caregivers of patients with ALS, and all evaluation results were satisfactory. Therefore we confirmed the final content and structure of the nurse-led navigation program.

We specified that the technology-facilitated nursing interventions are related to gastrostomy care and enteral feeding and aimed at ensuring patient safety and supporting family caregivers during the transition period.

Clinical
PNM004

RELATIONSHIP BETWEEN DIETARY TOTAL ANTIOXIDANT CAPACITY AND THE PROGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS

Jihyun EOM1, Bugyeong SON2, Yongsoon PARK1, Seung Hyun KIM2
Department of Food and Nutrition, Hanyang University, Seoul, South Korea
Cell Therapy Center, Department of Neurology, Hanyang University Seoul Hospital, Seoul, South Korea

INTRODUCTION

The purpose of this study was to evaluate whether the dietary total antioxidant capacity (DTAC) of the major food groups is associated with disease progression rate (ΔFS) and survival time based on the hypothesis that antioxidant intake is related to the prognosis of amyotrophic lateral sclerosis(ALS).

METHODS

A total of 301 sALS participants were enrolled from Mar 2011 to Oct 2021. DTAC was estimated using task automation and an algorithm based on 24-h dietary recall. Death, tracheostomy tube insertion, and percuteneous endoscopic gastrostomy(PEG) tube insertion data were also collected. The demographic parameters, clinical characteristics, and survival time of the individuals were compared based on their DTAC tertile and the DTAC of the three primary dietary groups (fruit, vegetable, legume).

RESULTS

There was a negative correlation between the DTAC for vegetables and legumes and the rate of development, as well as a negative correlation between the DTAC for vegetables and legumes and the risk of events, which is consistent with prior research on the neuroprotective roles of dietary isoflavones and vitamin E supplements. However, no significant correlation with total DTAC or fruit DTAC was discovered. This is likely due to a higher fruit juice consumption and less popularity of citrus fruit.

CONCLUSION

These data suggest that the consumption of antioxidants, particularly those derived from vegetables and legumes, has a potentially beneficial impact on slowing disease progression and extending survival in patients with ALS. Therefore, further investigation is essential, including large prospective cohorts and carefully planned clinical trials.

Clinical
PNM005

ASSOCIATIONS BETWEEN POST-PRANDIAL GHRELIN, LEAP2, AND LEPTIN AND DISEASE PROGRESSION IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Stephanie L. Howe[1], Cory J. Holdom[1,2], Pamela A. McCombe[2,3], Robert D. Henderson[2,3], Jeffrey M. Zigman[4], Shyuan T. Ngo[1,2,3], Frederik J. Steyn[2,3,5]
[1]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane, QLD, Australia
[2]Centre for Clinical Research, The University of Queensland, Brisbane, QLD, Australia
[3]Department of Neurology, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia
[4]Center for Hypothalamic Research, Department of Inteal Medicine, University of Texas Southweste Medical Center, Dallas, TX, USA
[5]School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia

INTRODUCTION
Dysfunction of mechanisms of appetite contributes to weight loss and faster disease progression in patients with Amyotrophic Lateral Sclerosis (ALS). Impairment of appetite control in ALS may include altered production and signalling of appetite regulating-hormones, including orexigenic factors such as ghrelin, and anorexigenic factors such as LEAP2 and leptin.

METHODS
In this prospective natural history study we assessed postprandial levels of ghrelin, LEAP2 and leptin in patients with ALS (Cases; n=46) and controls (Controls; n=43). For Cases, measures were compared to changes in body weight, body composition, and clinical outcomes.

RESULTS
Postprandial ghrelin was decreased by 52% in Cases when compared to Controls (p=0.013). The LEAP2:ghrelin molar ratio was increased by 249% (p=0.009) suggesting greater ghrelin resistance. While correlating with measures of functional capacity at baseline, ghrelin, LEAP2, LEAP2:ghrelin ratios and leptin were generally not predictive of change in functional capacity during follow-up. Patients with high postprandial ghrelin, however, had an increased risk for earlier death (HR: 3.54, p=0.012; first quartile compared to fourth quartile).

CONCLUSIONS
Reduced postprandial ghrelin coupled with an increased LEAP2:ghrelin molar ratio suggests loss of ghrelin action in patients with ALS. Given the actions of ghrelin in modulating appetite, metabolism, and neuroprotection, reduced ghrelin and greater ghrelin resistance could contribute to reduced capacity to tolerate the physiological impact of disease in ALS. More comprehensive studies are needed to fully explain the impact of disease on ghrelin and LEAP2 production relative to ghrelin release, and how this might impact weight loss and disease progression in ALS.

Clinical
PO001

THE UNITED STATES NATIONAL AMYOTROPHIC LATERAL SCLEROSIS (ALS) REGISTRY ADVANCES RESEARCH DOMESTICALLY AND INTERNATIONALLY

Paul Mehta, MD[1], Jaime Raymond, MPH[1], Moon Han, PhD[1], Ted Larson, MS[1], Kevin Horton, DrPH[1]
[1] National ALS Registry, Centers for Disease Control and Prevention/ Agency for Toxic Substances and Disease Registry

OBJECTIVE
Describe how the National ALS Registry supports and advances research in the United States and abroad.

INTRODUCTION
The National Amyotrophic Lateral Sclerosis Registry is the largest database of persons with ALS in the United States. One of the purposes of the Registry, as defined by Congress, “is to facilitate research.” In addition to registering patients with ALS and collecting epidemiological data, a National ALS Biorepository was added in 2015 after the completion of a pilot project. The purpose of the Biorepository is to expand ALS research in areas such as genetics, biomarker identification, environmental exposures, and disease progression.

DESIGN/METHODS
Allows eligible persons with ALS to be informed about clinical trials and research studies, provide specimens to the Biorepository, and self-report epidemiologic data securely. Researchers, both domestic and inteational, can apply to receive data from the Registry and samples from the Biorepository as well as have recruitment emails sent for their studies. The Registry also provides funding for investigator-initiated R01 grants.

RESULTS
To date, over 70 institutions (pharmaceutical companies and academia) have used the Registry to recruit for their clinical trials and studies. These include notable clinical trials for Amylyx Pharmaceuticals, Biogen, Inc. MT Pharma, and others. Over 60,000 specimens (e.g., blood, hair) have been collected nationally from >1,500 persons with ALS and >180 post-mortem autopsies (e.g., tissue, bone) have been collected and are available for dissemination to researchers. Survey data are available for researchers from 18 risk factor modules (demographics, occupational, military history, physical activity, smoking/drinking, ALS Functional Rating Scale, clinical onset, etc). Over 100,000 surveys have been completed, and the Registry has funded 24 research grants to date.

CONCLUSIONS
The National ALS Registry is a multi-faceted research platform that provides researchers access to a large national group of ALS cases and data for their research nationally and inteationally.

Clinical
PO002

THE INTERNATIONAL NETWORK FOR ALS RESEARCH AND CARE (INARC)

Juliette Foucher[1,2], Romy Verschoor[3], Mathias Couillard[4], Vanessa Bertone[4], Tommy Bunte[5]
[1] Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden
[2] Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
[3] TRICALS
[4] Clinical Research Unit, Montreal Neurological Institute and Hospital, Montreal, Canada
[5] Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder left with no cure, making ALS patients rely heavily on ALS clinical trials. There has been an increase of ALS clinical trials from two in 2001 up to 35 trials 2021. This new context triggered a growing need for dedicated research staff and communication between centers conducting ALS clinical trials.

METHODS

The inteational network for ALS research and care (INARC) was created in February 2022 to organize a satellite meeting specifically for clinical research staff, in marge of the European Network to Cure ALS (ENCALS) of June 2022. INARC's goal being to create a network strengthening skills of different ALS teams, our organizing committee prepared four topics of discussion that were debated in smaller groups during the meeting. Participants were randomly assigned to four smaller groups, each group being supervised by one member from the organizing committee before reporting back to the assembly the take home messages from the discussions they had had.

RESULTS

INARC's June 2022 meeting gathered representatives from 11 ALS clinical research centers. Attendees came both from countries the European Union Sweden, Ireland, The Netherlands, Slovenia, Denmark and from United Kingdom, Switzerland and Canada. 90% of the teams offered both ALS care and research. INARC has been since been growing, appointing several meeting committees.

CONCLUSION

INARC's 2022 satellite meeting described here is our first step toward building an inteational ALS clinical research staff network. The discussions that happened during the meeting highlighted the need and room for uniformity when it comes to ALS clinical trials, as well as the need for streamlined communication between ALS clinical trial staff. We will use this in our next step toward creating ALS clinical staff guidelines that would help harmonize clinical research practice in the ALS field.

Clinical
PO003

ACOUSTIC CHARACTERISTICS OF STOP CONSONANTS IN WORDS IN NATIVE KANNADA ALS (AMYOTROPHIC LATERAL SCLEROSIS) SPEAKERS - A WINDOW TO DECISION MAKING IN DYSARTHRIA MANAGEMENT OF ALS

Dipti Baskar[1], Yamini BK[2], Nalini A[1], Shivashankar N[2]
[1]Department of Neurology, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, Kaataka, India
[2]Department of Speech Pathology and Audiology, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, Kaataka, India

INTRODUCTION

Speech production is progressively affected in ALS and can progress to anarthria especially in early bulbar onset ALS. Analysis of speech phonemes gives insight into nature of dysarthria. Aim of the study was to analyse the acoustic characteristics of [t] and [k] which are lingualpalatal and lingual-velar voiceless stop phonemes respectively, in Kannada language, in native speakers with ALS.

METHODS

Twenty-six adults with ALS [spinal onset(n=16) and bulbar onset(n=10)] and 19 languageage-gender matched healthy controls were included. Participants repeated the words with [t] and [k] (ISHA battery) in initial position (IP) and medial position (MP) of word. Three parameters: presence/absence of burst, burst duration and voice onset time (VOT) for each of phonemes were measured using wide-band spectrogram of Speech Science Lab (Voice and Speech Systems, India).

RESULTS

Consonant [t]: Burst was present in 61.54 %(IP) and 57.7%(MP) of ALS (bulbar onset:40%[IP] 20%[MP], spinal onset:75%[IP] 81.3%[MP]) while in 100 % of controls with a statistical significant difference of $p < 0.05$.
Consonant [k]: Burst was present in 61.5%(IP) and 46.2%(MP) of ALS (bulbar onset:40%[IP] 20%[MP], spinal onset:75%[IP] 62.5%[MP]) while in 100 % of controls.
Statistically significant difference for burst (presence/absence) was noted between ALS and control for both consonants, in both positions and between bulbar and spinal onset for [t] and [k] in MP only. Burst duration had a significant difference between the spinal and control groups ($p<0.05$) for IP only , with a longer duration in spinal onset. The VOT was significant between spinal and the control groups in [t] alone.

CONCLUSION

Word level articulation was compromised in ALS, more in bulbar onset than spinal onset. Thus analysis of acoustic characteristics of dysarthria in ALS aids in early detection and institution of appropriate communication-oriented strategies.

Clinical
PO004

SUPPORTIVE CARE NEEDS OF CAREGIVERS OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS RECEIVING HOME ENTERAL NUTRITION: A QUALITATIVE STUDY

Hyun Sik Chu[1,3], Seung Hyun Kim[2,3], Young Ran Tak[1]
School of Nursing, Hanyang University, Seoul, Korea.
Department of Neurology, College of Medicine, Hanyang Univerisity, Seoul, Korea
Department of Neurology, Hanyang University Hospital, Seoul, Korea

The aim of this study was to explore the supportive care needs related to gastrostomy care and home enteral nutrition among family caregivers of patients with amyotrophic lateral sclerosis. A qualitative content analysis study was conducted between February 2021 and October 2022, using in-depth interviews of eight family caregivers of patients with amyotrophic lateral sclerosis in an ALS/MND clinic in Korea. The family caregivers who participated in this study were providing gastrostomy care and enteral nutrition, and the patients with amyotrophic lateral sclerosis were classified as King's stage 4a or 4b. The results of this study were analyzed into a total of five main themes, eleven sub-themes, and two categories that could be integrated. The supportive care needs of family caregivers providing home care for ALS patients receiving enteral nutrition through a gastrostomy tube were identified as 'gastrostomy care related knowledge and skills, 'enteral nutrition-related knowledge and skills, 'affirmation of new roles as a caregiver, 'social support', 'missed nursing care and education, and 'information resources regarding gastrostomy care and enteral nutrition'. These themes could be integrated into the categories of 'care navigation needs' and 'current nursing and patient education issues, and new directions'. Based on the results of this study, the supportive care needs of family caregivers of patients with ALS were found to be multifaceted. There is a need for consistent and ongoing care navigation interventions that support decision-making for gastrostomy and the transition to home care following gastrostomy placement, for ensuring the quality of care at home and relieving the caregiving burden.

Clinical
PO005

A CASE OF ADULT-ONSET KRABBE DISEASE INITIALLY MISDIAGNOSED AS CHARCOT-MARIE-TOOTH DISEASE

Seong-il OH[1], Jin Ho JUNG[2]
[1]Department of Neurology, Kyung Hee University Hospital, Seoul, Korea
[2]Department of Neurology, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea

INTRODUCTION

CMT is diagnosed through genetic testing when the patient develops widespread uniformed polyneuropathy with hand or foot deformity. In recent years, various causative genes and their phenotypes have been found due to the development of NGS. Here we report on a patient with Krabbe disease who presented with diffuse demyelinating polyneuropathy and foot deformity and was initially misdiagnosed as CMT.

REPORT

A 34-year-old woman has been suffering from slowly progressive gait disturbance since a few years ago. Her parents had no definite related history.
A neurological examination of the patient revealed subtle motor weakness on all extremities and distal hand paresthesia. Gait examination showed subtle slowed gait speed and mild disequilibrium, and the Romberg sign was equivocally positive. The patient reported mild word-finding difficulty for a few years. Laboratory studies were all unremarkable.
Nerve conduction studies showed sensory motor demyelinating polyneuropathy.
No deletion or duplication was found in the PMP22 gene test. Whole exome sequencing identified compound heterozygous mutations with a pathogenic variant, c.136G>T (p.Asp46Tyr), and a variant of uncertain significance (VUS) (c.1589T>C (p.Leu530Pro) in GALC gene. The GALC enzymatic activity was evidently decreased compared to an age-matched control.

CONCLUSION

In conclusion, the patient was diagnosed with KD through a decrease in β-Galactosylcerebrosidase activity after a heterozygote GALC mutation was confirmed through NGS in a patient with suspected CMT and normal PMP22 gene. Krabbe disease (KD) is a progressive lysosomal storage disorder characterized by the deficiency of the enzyme galactocerebroside beta-galactosidase (GALC). In leukodystrophy diagnosed through the development of these diagnostic technologies, heterogeneous clinical, electrophysiological, and neuroimaging manifestations have been frequently reported, and in this case, non-KD-specific CMT-like manifestations were confirmed in KD patients.

Clinical
PO006

DEVELOPMENT AND VALIDATION OF THE KOREAN VERSION OF EDINBURGH COGNITIVE AND BEHAVIORAL AMYOTROPHIC LATERAL SCLEROSIS SCREEN (ECAS)

Jeeun Lee[1], Ahwon Kim[2], Seok-Jin Choi[3], Eric Cho[4], Jaeyoung Seo[5], Seong-il Oh[6], Jin Ho Jung[6], Ji-Sun Kim[7], Jung-Joon Sung[2], Sharon Abrahams[8], Yoon-Ho Hong[9]
[1]Myongji Hospital, Hanyang University College of Medicine, Gyeonggi-do, Republic of Korea
[2]Department of Neurology, Seoul National University Hospital, Seoul, Republic of Korea
[3]Department of Neurology, Center for hospital medicine, Seoul National University Hospital, Seoul, Republic of Korea
[4]Peabody College of Education and Human Development, Vanderbilt University, Nashville, United States [5]Doo Neurology Clinic, Cheonan, Korea, â€‹Republic of
[6]Department of Neurology, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea, â€‹Republic of [7]Department of Neurology, Incheon Sejong Hospital, Incheon, Republic of Korea
[8]Euan MacDonald Centre for Motor Neurone Disease Research, Human Cognitive Neuroscience, School of Philosophy, Psychology and Language Science, University of Edinburgh, Edinburgh, United Kingdom
[9]Seoul National University Seoul Metropolitan Boramae Medical Center, Seoul, Republic of Korea

INTRODUCTION

Cognitive and behavioral changes are common in amyotrophic lateral sclerosis (ALS) with about 15% of patients presenting with overt frontotemporal dementia (FTD) and approximately 30-50% of patients showing varying degree of impairments. We aimed to develop and validate the Korean version of Edinburgh Cognitive and Behavioral ALS Screen (ECAS-K), a brief multi-domain assessment tool developed for ALS patients with physical disability.

METHODS

We developed the ECAS-K according to the guidelines for translation, and administered to 38 ALS patients and 26 age- and education-matched healthy controls. We also administered the Montreal Cognitive Assessment (MoCA) and Frontal Assessment Battery (FAB) to investigate convergent validity, and the Center for Neurologic Study-Liability Scale (CNS-LS) to assess the association between pseudobulbar affect and cognitive/behavioral changes.

RESULTS

Internal consistency was found to be high between ECAS-K test items with Cronbach's alpha of 0.87. Significant differences were noted between ALS patients and controls in language, fluency, and memory functions ($p < 0.05$). Abnormal performance was noted in 39.4% of patients on the ECAS total score, and 66.6% of patients showed behavioral changes across at least one domain. Significant correlations were observed between the ECAS-K and other cognitive screens (MoCA and FAB, correlation efficient of 0.69 and 0.55, respectively, $p < 0.01$).

CONCLUSION

We developed and validated the ECAS-K which could be used as an effective tool to screen the cognitive and behavioral impairments in Korean ALS patients.

Clinical
PO007

AN ELUSIVE CAUSE OF MUSCULAR DYSTROPHY-BETHLEM MYOPATHY

Ting Yoong TEE [1],Yin Yin TAN[1],Dhayalen KRISHNAN[1],Lock Hock NGU[2],Shanthi VISWANATHAN[1]
[1]Department of Neurology,Hospital Kuala Lumpur,Malaysia
[2]Department of Genectics,Hospital Kuala Lumpur,Malaysia

INTRODUCTION

Congenital myopathy presenting as adult patients are rare especially when most of patients are being diagnosed since young.We herein report a case of Bethlem Myopathy(BM) presenting as an adult patient.

REPORT

A 22 years old male presented with frequent falls associated with proximal muscle weakness since age of 2.His weakness was progressive causing patient to be wheelchair bound by age of 12.He was initially diagnosed as Becker's Muscular Dystrophy based on muscle biopsy and referred to pulmonology team for Obstructive Sleep Apnea with restrictive lung disease secondary to neuromuscular disease.He was subsequently referred to our centre for continuation of care. Upon further assessment,he was still able to perform routine daily activities despite being wheelchair bound.He denied any symptoms of congestive cardiac failure,recurrent infections or bulbar symptoms which is commonly seen among patients with Becker's muscular dystrophy.Family history revealed the proband is offspring of non-consanguineous matrimony and the youngest among 3 unaffected siblings. Physical examination showed predominantly proximal myopathy of upper and lower limb of MRC grading of 2/5. There were multiple keloids over previous trauma sites and long digits with finger contractures. However,there was no calf pseudohypertophy. Electrodiagnostic studies showed normal nerve conduction studies with non irritative proximal myopathic disorder. Patient was referred to genetics team whereby a comprehensive neuromuscular disorder panel using a hybridization-based protocol, and sequenced using Illumina technology confirmed a pathogenic variant, c.868G>A (p.Gly290Arg), was identified in COL6A1. The COL6A1 gene is associated with autosomal dominant and recessive Bethlem myopathy 1 and Ullrich congenital muscular dystrophy 1, collectively known as type VI collagenopathies.

Conclusion, this case illustrates the importance of clinical phenotyping and genetics studies in diagnosing congenital muscular dystrophy.

Clinical
PO008

HIGH PITCHED STACCATO SPEECH AND PYRAMIDAL TRACT SIGN DOMINANT CLINICAL MANIFESTATIONS IN SCA 34 : DIAGNOSTIC CHALLENGE

Yong Sung Kim, MD[1], Young-Eun Kim, MD, PhD[2]
[1]Department of Neurology, College of Medicine, Hanyang University, Seoul, Korea
[2]Department of Laboratory Medicine, College of Medicine, Hanyang University, Seoul, Korea

INTRODUCTION

Spinocerebellar ataxia is a group of inherited disorders, clinically characterized by variable manifestations of progressive ataxia, dysarthria, and abnormal ocular movement. SCA 34 is a very rare autosomal dominant disease caused by heterozygous mutation in the ELOVL4 gene, clinically characterized by slowly progressive ataxia, nystagmus, ophthalmoplegia, dysarthria, erythrokeratodermia variabilis. Here, we report a high pitched staccato speech and pyramidal tract sign dominant SCA34 patient with novel variant of ELOVL4 gene (c.743A>G(p.His248Arg)).

REPORT

A 57-year-old woman, with hypertension, dyslipidemia, depression past medical history, complained of dysarthria and spastic gait. On neurologic examination, she showed spasticity in upper and lower limbs and no remarkable motor weakness and had high pitched staccato speech. Deep tendon reflexes were increased in upper and lower limbs with Babinski sign and Hoffman sign, ankle clonus. Brain MRI revealed no remarkable finding and also electromyography showed no evidence of suggesting peripheral neuropathy or radiculopathy. After 1 year later, on the outpatient department, we reevaluated her status focusing on her high pitched staccato speech and pyramidal tract sign dominant clinical manifestations. On the 1 year follow up brain MRI, we found cerebellar and pontine atrophy without hot cross bun sign in the pons. But genetic tests of SCA showing cerebellar sign and pyramidal tract sign, which include SCA1, SCA3, SCA6 were negative. So we subsequently conducted the whole exome sequencing to evaluate the other subtypes of SCA, she was finally diagnosed as SCA 34 with novel variant of ELOVL4 gene (c.743A>G(p.His248Arg)).

CONCLUSION

Although patient have only high pitched staccato speech as a cerebellar sign and have pyramidal tract sign dominant clinical manifestation, clinicians should consider spinocerebellar ataxia because cerebellar signs are relatively late and variable. And although SCA 34 is a very rare entity in the SCA subtypes, the possibility of SCA 34 should also be considered.

Clinical
PO009

NOVEL VARIANT OF SYNE2 GENE IN PATIENT WITH EMERY-DREIFUSS MUSCULAR DYSTROPHY 5

Yong Sung Kim, MD[1], Young-Eun Kim, MD, PhD[2], Ji Hyun Kim, MD[1]
[1]Department of Neurology, College of Medicine, Hanyang University, Seoul, Korea
[2]Department of Laboratory Medicine, College of Medicine, Hanyang University, Seoul, Korea

INTRODUCTION

Emery–Dreifuss muscular dystrophy (EDMD) is a heterogeneous late-onset disease, clinically characterized by slowly progressive skeletal muscle wasting and weakness, joint contractures with spine rigidity and cardiomyopathy with risk of sudden death. Emery–Dreifuss muscular dystrophy 5 (EDMD5) is caused by heterozygous variant in the SYNE2 gene on chromosome 14q23, which is encoding nesprin-2. EDMD5 is characterized by slowly progressive muscle weakness without apparent contractures, arrhythmia and dilated cardiomyopathy with heart failure. Few cases of EDMD5 reported in the literature, and their age of onset, severity, and progression of muscle weakness and cardiac involvement were varied. Here, we report a EDMD5 patient with novel variant of SYNE2 gene (c.15095A>G(p.Gln5032Arg)).

REPORT

A 53-year-old woman, with hypothyroidism past medical history, complained of right upper extremity weakness which has progressed over the last 2 years. Since childhood, she sometimes had experienced motor weakness. Especially, when she was 8 years old, she had severe motor weakness so that she lied in bed for 6 months. On neurologic examination, she showed right upper extremity weakness and atrophy with decreased deep tendon reflex. And she showed Gower sign and fasciculation in upper and lower limbs. Her elder sister had passed away at sixth decade with cardiac arrest. Brain MRI and cervical spine MRI revealed no remarkable finding. Electromyography showed widespread denervation pattern but reinnervation pattern was only shown on gastrocnemius muscle, and there is no early recruitment pattern. We evaluated genetic tests of myopathy focusing on her very slow progression and Gower sign and elevated circulating creatine kinase concentration, and she was finally diagnosed as EDMD5 with novel variant of SYNE2 gene (c.15095A>G(p.Gln5032Arg)).

CONCLUSION

Although EMG findings show widespread denervation pattern and no early recruitment pattern, if patient have slowly progressive muscle weakness and Gower sign and elevated circulating creatine kinase concentration, clinicians should also consider myopathy.

Clinical
PO010

GLOBAL FUNDAMENTAL RIGHTS IN ALS/MND SURVEY: A LOOK INTO THE GLOBAL RESULTS.

Cathy CUMMINGS1 , Jessica MABE1
1 The Inteational Alliance of ALS/MND Associations

The Alliance has developed a guiding document on fundamental rights for people living with ALS/MND and caregivers of people living with ALS/MND, that states the aspirational rights of the global community. These rights are reviewed annually and are the basis for the survey we will run in 2023, the second survey held by the Alliance in this topic.
Access to and respect of these Fundamental Rights is inconsistent around the world and is dependent on multifactorial inputs such as economics, healthcare systems and professionals, and culture which leads to inconsistent quality of life for people living with ALS/MND.

Our hypothesis are:
*Respect for the global fundamental rights has not changed since 2021 survey.
*Access to highest quality of care remains globally unbalanced between the Global North and the Global South.
*Access remains the biggest issue for treatments (Clinical Trials, Approved Drugs), Assistive Devices and Genetic counselling. And it is unbalanced between the Global North and the Global South. *The right to information and education is better respected in countries where English is spoken. *Caregivers remain feeling unsupported with little access to counselling, and emotional support programs.

The survey will be done by independent research third party, and it will be launched both through our member organizations and on social media in different languages. The survey will run from 1st May 2023 until 30 June 2023.

The survey addresses a range of important topics in the ALS/MND community which includes an assessment of how PALS rights are respected globally, access to healthcare, treatments, health professionals, services, support and much more.

We would welcome the opportunity to share the results of the survey and how they compared to the information collected in 2021.

Clinical
PO011

END-OF-LIFE CARE IN ALS IN INDIA

[1]Seena Vengalil, [1]M S Keerthipriya, [2]Priya Thomas,[1] Saraswati Nashi, [1]Deepak Menon, [1]Atchayaram Nalini
Department of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru, India
Department of Psychiatric social work, National Institute of Mental Health and Neurosciences, Bengaluru, India

INTRODUCTION

Motor Neuron Disease (MND) is a relentlessly progressive neurodegenerative condition with complex needs throughout the course of illness, requiring palliative care from early stages. We aimed to study the current end-of-life care scenario in ALS in India.

METHOD

A questionnaire on End-of-life issues in ALS was conducted as an online survey and shared with bereaved caregivers, to obtain data about the symptoms and suffering in the last month of life. Results: 23 unique responses were received. The mean length of bereavement was 33.8±22.9 (5-84) months. The mean age at death was 59.95±9.8 years, half were males (13/23). The death occurred at home in 17/23 and at hospital in rest, with mean of 5±3.8 days of hospital stay. Repeated hospital admissions in last 1 month of life were reported in 10/13. The cause of death was respiratory failure in 10/23, cardiac arrest in 3/23 and unknown in 10/23 patients. Distress surrounding death was reported in 19/23 patients, mean score of suffering at death being 8.13±3.07 on a scale of 10. Most common troublesome symptoms were breathlessness (56.5%), pain (52.2%), anxiety or restlessness (47.8%). Treatment for breathlessness was received in 39.1% and for pain in 43.5%. 9 of 23 caregivers reported dissatisfaction with the medical care received at the end stage. 16 of the responders did not know about palliative care. However informal planning in advance about the patient's treatment preferences and place of death was made in 10/23 patients which is encouraging.

CONCLUSION

Specialist Palliative care through multidisciplinary teams is known to improve the quality of life of ALS patients. Given the complex needs and rarity of the condition, there is a need to explore and establish ways to improve awareness among healthcare providers and coordinate the care of the patients which will reduce the suffering of people with MND.

Clinical
PO012

STATUS OF SWALLOW IN BULBAR AND SPINAL ONSET AMYOTROPHIC LATERAL SCLEROSIS (ALS) FROM THE REFLEXES SECTION OF FDA2

Yamini B K, S Y Aishwarya, Dr. Seena Vengalil, Dr M S Keerthipriya*, Dr Nalini A*, Dr Priya Treesa Thomas***
Department of Speech Pathology and Audiology, NIMHANS, Bengaluru-560029
Department of Speech Pathology and Audiology, NIMHANS, Bengaluru-560029
**Department of Neurology, NIMHANS, Bengaluru-560029*
***Department of Psychiatric Social Work, NIMHANS, Bengaluru-560029*

INTRODUCTION

Dysphagia in ALS is commonly documented in the early stages of Bulbar onset (BO) ALS, however, persons with Spinal onset (SO) ALS also have dysphagia (Perry et al., 2021). The aim of the current study was to document the status of swallow from the Reflexes section of Frenchay Dysarthria Assessment 2 (Enderby & Palmer, 2008) in BO and SO ALS. **Method**
33 adults with ALS (El Escorial criteria; 22 SO, 11 BO) were recruited. The three subsections of the Reflexes section of FDA2(administered completely to all ALS) namely Cough, Swallow and Drool, were chosen and analyzed.

RESULTS

The mean duration of overall illness in SO and BO was 18.68(±15.33) and 11.9(±9.31) months respectively. The median duration dysphagia signs in SO and BO were 3 and 6 months respectively. Results revealed that, under Cough subsection, in SO, 27.3%(n=6) had no abnormality and 72.7%(n=16) had abnormality (Mild abnormality:50%,n=11;Obvious abnormality: 22.7%,n=5) while in BO, 100% had abnormality(Mild abnormality:54.5%,n=6;Obvious abnormality: 36.4%,n=4;Poor in task:9.1%,n=1).Under Swallow subsection, in SO, 27.3%,n=6 had no abnormality and 72.7%,n=16 had abnormality(Mild abnormality:54.5%,n=12;Obvious abnormality:9.1%,n=2;Poor in task:9.1%,n=2) while in BO,27.3%,n=3 had no abnormality and 72.8%,n=8(Mild abnormality:45.5%,n=5;Obvious abnormality:18.2%,n=2;Poor in task: 9.1%,n=1) had abnormality. Under Drooling subsection, in SO, 59.1%(n=13) had no abnormality and 40.9%,n=9(Mild abnormality:27.3%,n=6;Obvious abnormality:9.1%,n=2;Poor in task: 4.5%,n=1) had abnormality while in BO, 54.5%(n=6) had no abnormality and 45.5%,n=5(Mild abnormality: 27.3%,n=3;Obvious abnormality:18.2%,n=4) had abnormality.

CONCLUSION

The Cough subsection (related to choking), was best able to detect the bulbar component in BO group. Varied degrees of abnormality of dysphagia was evident in both SO and BO groups. Given that ALS, is a neurodegenerative condition, the progression in dysphagia too is inevitable thus suggesting need for dysphagia palliative care.

Clinical
PO013

GENERATION OF MOTOR NEURON ORGANOIDS BY USING VERTICAL MIXING

Suong Ngoc Anh Dang[1], Keiko Imamura[1,2,3], Haruhisa Inoue[1,2,3]
[1]iPSC-Based Drug Discovery and Development Team, RIKEN BioResource Research Center (BRC), Kyoto, Japan.
[2]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan.
[3]Medical-Risk Avoidance Based On iPS Cells Team, RIKEN Center for Advanced Intelligence Project (AIP), Kyoto, Japan.

Amyotrophic lateral sclerosis (ALS) is a type of motor neuron degeneration disease with unclear pathology. In recent years, cellular therapy has been the new hope for ALS treatment, including the transplantation of stem cell-derived neural progenitors to replace the lost or damaged of motor neurons and promote motor function recovery. However, this technology is still in the early stage of development, several difficulties should be overcome such as the safety and efficacy of transplanted cells. Recently we have succeeded in generating a specific brain organoid that has an inverted morphology with a neuron stem cell-outside, neuron-inside as well as ventral forebrain identity by using the vertical mixing. In this study, we continue to use this system to create organoids with the enrich number of motor neuron progenitors ($ISLET1^+$ and/or $HB9^+$) when compare with spinal cord organoids generated by conventional method. Furthermore, the inverted structure of these organoids with concentrated motor neuron progenitors suggests a good source of cells for transplantation with high purity and large amount of motor neuron progenitors. This suggests an opportunity to develop effective transplantation strategies to increase the survival and differentiation/maturation of motor neurons after transplantation.

Clinical
PO014

LEVEL OF KNOWLEDGE ON AMYOTROPHIC LATERAL SCLEROSIS AMONG NURSING STUDENTS IN SELECTED COLLEGES IN THE PHILIPPINES

***Cherry Ann Durante*[13], *Jeeno Jay Frani*[2], *Rufo Calixtro Jr*[3]**
[1] *Emilio Aguinaldo College Manila, Graduate School Department*
[2]*St. Dominic College of Asia, Nursing Department*
[3]*University of Perpetual Help – Dr Jose G Tamayo Medical University, Research Department*

The level of knowledge about ALS among nursing students would directly impact their ability to provide care and accurate health teaching to patients suffering from the disease. This study utilized a cross-sectional research design that employed an 18-item self-administered questionnaire that were distributed in February to March 2023. 190 nursing students from four colleges were recruited to be part of the study. Most participants were female (62%) and on their 3rd year of study (49%). Results showed that more than half (51.58%) of the students had low knowledge about ALS, while 40% had average level of knowledge. About 68% had poor knowledge about the definition of the disease, while 97.89% failed to identify the risk factors. 35% were not able to recognize manifestations; while 22% were not able to detect possible complications. One out of four lacked knowledge on treatment. Almost 90% were not able to identify how to diagnose the disease. Chi-square test for association were run and it was found out that year level was associated with knowledge level and the association was statistically significant (chi2 = 69.77; p-value<0.0001). Because of the results of this study, the researchers conclude that there is a low level of knowledge about ALS among the nursing students in the 4 participating universities. There is a need to enhance the level of instruction about amyotrophic lateral sclerosis, to equip the student nurses with knowledge and skill to treat future ALS patients.

Clinical
PO015

EFFECTIVENESS OF TELEHEALTH EXERCISE THERAPY WITH SUPERVISION BY PHYSICAL THERAPISTS FOR PATIENTS WITH EARLY-STAGE AMYOTROPHIC LATERAL SCLEROSIS

Fariba Yadolahi[1], *Nayyere Hosseini*[1],
[1] *Department of Physical Therapy, School of Rehabilitation, SBMU, Iran*

OBJECTIVE
To verify the effects of structured telehealth exercise therapy with supervision by a physical therapist in patients with early-stage amyotrophic lateral sclerosis (ALS).

BACKGROUND
Amyotrophic lateral sclerosis (ALS) is the most common, disabling, and fatal motor neuron disease among adults. Muscle weakness is very common in people with ALS. the effects of exercise as well as telehealth feasibility in this population are not well understood. We investigated whether patients with early-stage amyotrophic lateral sclerosis can improve their function and voluntary strength with a telehealth exercise program.

METHODS
12 patients with early amyotrophic lateral sclerosis enrolled in this study. As a control group, 12 patients with ALS who underwent either no exercise or range of motion exercise (without supervision) were extracted from a database of patients with ALS and matched with the experimental group in terms of their clinical features. Four physiotherapists supervised training using A PC-based system and a web-based platform. The structured exercises consisted of stretching exercises and strength training for the upper limbs, lower limbs, and trunk muscles; functional training exercises for activities of daily living such as tuing over and standing from a chair. The primary outcome was the score on the ALS Functional Rating ScaleeRevised (ALSFRS-R), the strength of muscles as measured with MMT. We investigated muscle strength and (ALSFRS-R) scores at the start and end of the therapy.

RESULTS
A telehealth exercise program improved the total score on the ALSFRS-R ($P<.05$) and the strength of the lower limb muscle, deltoid, and quadriceps muscles as measured with MMT. No adverse events were reported.

CONCLUSIONS
Our findings revealed that telehealth exercise therapy with supervision is safe and feasible for patients with early-stage ALS and can be easily adapted to family support. Exercise, when prescribed appropriately may be an important component of an overall management plan.

Clinical
PR001

SURVEY OF RESPIRATORY CARE IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS IN DIFFERENT LIVING ENVIRONMENTS

Keisuke Yorimoto[1], Akkiko Hanai[2,] Taiyo Kawaguchi[1]Ã£â‚¬Â• Yuta Miyazaki[1], Takatoshi Hara[1]
[1]Rehabilitation department, National Center of Neurology and Psychiatry,Japan
2Home Support Office, National Center of Neurology and Psychiatry,Japan

OBJECTIVE
This study aims to investigate the utilization of respiratory care interventions, including Noninvasive Ventilation (NIV), Mechanical Insufflation-Exsufflation (MI-E), Lung Volume Recruitment (LVR), and tracheostomy in ALS patients, and how care environment impacts their use.

METHODS
A retrospective analysis of medical records was conducted on 135 patients receiving care at home and 21 patients receiving care in the hospital.

RESULTS
The results showed that LVR and MI-E were used more frequently in the home group, with 71 and 67 patients utilizing LVR and MI-E, respectively, compared to 9 and 0 patients in the hospital group. NIV was used in 69 patients in the home group and 4 patients in the hospital group, while tracheostomy was used in 18 and 12 patients in the home and hospital groups, respectively. Statistical analysis showed significant differences in respiratory physiotherapy for MI-E ($p<0.001$, ES=0.34) and significant differences in patient characteristics for NIV ($p=0.006$, ES=0.22) and tracheostomy ($p<0.001$, ES=0.38) between the two groups.

DISCUSSION
Understanding the utilization of respiratory care interventions in different care environments can help healthcare providers develop effective treatment plans for ALS patients.

Clinical
PR002

RELATIONSHIP BETWEEN LUNG VOLUME RECRUITMENT (LVR) AND SURVIVAL IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Taiyo Kawaguchi[1,2], Takatoshi Hara[1,3], Keisuke Yorimoto[1], Takuya Nakamura[1,2], Yuta Miyazaki[1,2], Kazuki Hagiwara[1,2], Michiyuki Kawakami[1], Tetsuya Tsuji[1]
[1]Department of Physical Rehabilitation, National Center Hospital, National Center of Neurology and Psychiatry, Kodaira, Japan
[2]Department of Rehabilitation Medicine, Keio University School of Medicine, Tokyo, Japan
[3]Department of Rehabilitaion Medicine, The Jikei University School of Medicine, Tokyo, Japan

BACKGROUND
Most deaths from amyotrophic lateral sclerosis (ALS) are due to acute respiratory failure and airway infections caused by decreased respiratory function, and respiratory physiotherapy is important to maintain respiratory function.
Lung Volume Recruitment (LVR) is one of the respiratory physiotherapy treatments for ALS. Lung volume recruitment is expected to improve atelectasis and enhance coughing by injecting air above the lung capacity, but there are few studies on the effects of LVR.

OBJECTIVE
The purpose of this study was to examine the effects of LVR on ALS patients and its impact on respiratory function.

SUBJECTS
The subjects were 156 patients out of 3756 total patients admitted to the Neurology Unit of the Center from April 2015 to March 2020.

METHODS
Retrospectively, age at onset diagnosis, delay in diagnosis, respiratory function, whether LVR was performed, and survival were investigated, and survival was estimated using the Kaplan-Meier survival curve and log-rank test. Survival was calculated as the time from onset to death or censoring, and subgroup analysis was performed based on age at onset and delay in diagnosis.

RESULTS
The age at diagnosis was 63.6±11.3 years, and the time from onset to diagnosis was 29.6±35.9 months.
In the LVR group, the age at diagnosis was 59.8 ± 12.0 years, and the time from onset to diagnosis was 29.4 ± 32.6 months; in the group without LVR, the age at diagnosis was 65.1 ± 10.7 years, and time from onset to diagnosis was 31.7 ±49.7 months. Kaplan-Meier survival analysis showed that the survival rate was not significantly lower in the LVR group despite the earlier diagnosis.

DISCUSSION
The fact that survival was not significantly lower in the LVR group than in the non-LVR group, despite the earlier time to diagnosis, may suggest that LVR had an impact on survival.

Clinical
PR003

POINT OF CARE VENOUS MARKERS OF ACID-BASE HOMEOSTASIS AS A MEASURE FOR RESPIRATORY FUNCTION DECLINE IN PATIENTS WITH MND

Jordana SHEAHAN[1,6], Ruben P. A. VAN EIJK[2,3], Cory J. HOLDOM[1], Stephanie L. HOWE[1], Pamela A.MCCOMBE[4,5], Robert D. HENDERSON[4,5], Shyuan T. NGO[1,4,5], Frederik J. STEYN[4,5,6]

Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Australia

Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands

Biostatistics & Research Support, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Centre for Clinical Research, The University of Queensland, Australia

Department of Neurology, Royal Brisbane and Women's Hospital, Australia 6. School of Biomedical Sciences, The University of Queensland, Australia

INTRODUCTION

There is a need to improve quality of life for patients with Motor Neuron Disease (MND). In the absence of lung function testing, the use of venous blood gas markers to inform improved respiratory support may facilitate clinical care. Using the iSTAT Alinity device, we investigated the utility of venous blood gas markers as indicators of respiratory function decline.

METHODS

We conducted point-of-care serial measurements of venous blood gases and acid-base homeostasis in patients with MND (Cases, n=120) and non-neurodegenerative disease Controls (n=85). Measurements from Cases were compared against clinical features of disease progression and change in respiratory function (including ALSFRS-R and forced vital capacity (FVC, % of predicted) as assessed during routine lung function testing).

RESULTS

At baseline, venous blood gas measurements were not significantly different between Cases and Controls. Within Cases, increasing partial pressure of CO2 (PCO2) was inversely correlated with FVC % of predicted (Kendall's tau=-0.17, p=0.01). Longitudinally, change in PCO2, bicarbonate, total CO2, base excess and chloride corresponded to change in ALSFRS-R respiratory subscore (Slope=0.73, -0.36, -0.39, -0.34, 0.24 respectively, all p<0.01). The relative risk of respiratory decline at any given time was related to changes in PCO2, total CO2, bicarbonate and base excess (multivariable HR=1.06, 1.12, 1.13, 1.14 respectively, all p<0.01).

CONCLUSION

Venous testing for gas exchange may be used as a prognostic biomarker for respiratory function decline in patients with MND. Point-of-care testing of venous gas markers merits further study to help inform clinical decisions regarding respiratory decline in MND.

Clinical
PR004

CURRENT STATUS OF DECISION-MAKING FOR TRACHEOSTOMY IN KOREAN ALS PATIENTS

Jong-Su Kim1, Ju-Hee Chae2, Shin Hye Yoo3, Sun Young Lee4, Seok-Jin Choi1 and Jung-Joon Sung1
1Department of Neurology, Seoul National University College of Medicine, Seoul, South Korea;2Department of Neurology, Jeonbuk National University College of Medicine, Jeonju, South
Korea; 3Center for Palliative Care and Clinical Ethics, Seoul National University Hospital, Seoul, South Korea, 4Public Healthcare Center, Seoul National University Hospital, Seoul, South Korea;

Tracheostomy is a common procedure in patients with amyotrophic lateral sclerosis (ALS) who experience respiratory failure, an expected complication of ALS and the leading cause of mortality in patients. The decision to perform a tracheostomy must consider various factors, including the patient's wishes, quality of life, and prognosis. Therefore, we examined the decision-making processes of tracheostomy in Korean ALS patients focusing on the current status and influencing factors for tracheostomy. 80 consecutive participants who did or did not undergo TIV were recruited from the Korean ALS association. The patient questionnaire consisted of Hospital Anxiety and Depression Scale (HADS), Decision Conflict Scale (DCS), and Control Preference Scale (CPS). Also, it included 27 multiple-choice questions of a modified version of the Columbia University TIV study pertained to various demographic characteristics of the disease, preferences, and reasons for choosing tracheostomy. 42 patients who underwent tracheostomy and 38 patients who did not were enrolled. The time from symptom onset was 60.7±53.9, and 71.9±43.4 months, and the most common onset region was spinal onset, with 79% and 74%. ALSFRS-R scores of total respiratory functions were 8.1±3.6 and 0.4±1.4 points. About the time of the first information about tracheostomy, patients who underwent tracheostomy heard at the time of tracheostomy, and most of the patients who did not have tracheostomy had no discussion. As for the source of information, they had heard the information from the physician and ALS organization. DCS was 35.1±17.8 points and 32.8±19.5 points, and HADS was 24.0±9.5 and 24.5±7.4 points, showing no significant difference between the two groups. However, patients with high DCS (DCS>25) showed a significantly higher HADS score (P=0.01, 0.02). Patients who undergo tracheostomy should have access to palliative care services and should be provided with adequate support to make informed decisions about their care.

Clinical
PR005

PROGNOSIS OF ALS PATIENTS USING NON-INVASIVE VENTILATION THERAPY IN JAPAN

Naoki Hayashi[1,2], Naoki Atsuta[1], Ryoichi Nakamura[1], Masahiro Nakatochi[3], Genki Tohnai[4], Daisuke Ito[5], Masahisa Katsuno[5], Yuishin Izumi[6], Mitsuya Morita[7], Osamu Kano[8], Kazumoto Shibuya[9], Satoshi Kuwabara[9], Naoki Suzuki[10], Masashi Aoki[10], Gen Sobue[11]
Department of Neurology, Aichi Medical University, Japan
Department of Neurology, Kariya Toyota General Hospital, Japan
Public Health Informatics Unit, Department of Integrated Health Sciences, Nagoya University, Japan
Division of ALS Research, Aichi Medical University, Japan
Department of Neurology, Nagoya University Graduate School of Medicine, Japan 6
Department of Clinical Neuroscience, Tokushima University, Japan
Division of Neurology, Jichi Medical University, Japan
Division of Neurology, Toho University School of Medicine, Japan
Department of Neurology, Chiba University Graduate School of Medicine, Japan
Department of Neurology, Tohoku University Graduate School of Medicine, Japan
Aichi Medical University, Japan

INTRODUCTION

Although non-invasive ventilation (NIV) therapy has become widely used in the respiratory care for ALS patients, the effect of NIV on the prognosis of ALS patients is unclear. Since it is difficult to conduct randomized controlled trials to validate NIV treatment, we conducted a real-world data analysis using a large ALS patient registry.

METHODS

We conducted a longitudinal observational case-control study using the multicenter ALS registry in Japan. Survival analysis was performed by propensity score matching analysis using known ALS prognostic factors for the patients that received NIV therapy (NIV group) and those that did not receive NIV therapy (non-NIV group). The survival endpoint was defined as death or tracheostomy invasive ventilation (TIV) induction. Prognostic factors for patients receiving NIV were examined.

RESULTS

We included 318 patients in the NIV group and 1025 patients in the non-NIV group enrolled between February 2006 and September 2018 in this analysis. After excluding the slowly progressing group with an ALSFRS-R decline rate of less than 0.33 per month at enrollment, we performed a propensity score matching analysis to compare the prognoses of the NIV and non-NIV groups. The median survival time of the NIV group was significantly greater than that of the non-NIV group (3.42 years vs. 2.83 years; $p = 0.021$). Analysis using the Cox proportional hazard model showed that older age of onset ($p<0.001$) and male sex ($p=0.016$) were independent factors for poor prognosis after using NIV therapy.

CONCLUSION

It was suggested that NIV therapy may have prolonged survival by about 7 months in ALS patients.

PACTALS 2023

Visit our website for more information

https://pactals2023.com/index.php

Organised by:

PACTALS
Pan-Asian Consortium for Treatment and Research in ALS

CNNS
CLINICAL NEUROPHYSIOLOGY NEUROMUSCULAR SECTION

Supported by:

INTERNATIONAL ALLIANCE OF ALS/MND ASSOCIATIONS

MND Malaysia

Malaysia Convention & Exhibition Bureau

Meet in Malaysia

Malaysia Truly Asia

Congress Secretariat
Medical Conference Partners
9, Jalan 9/3, Section 9, 46000, Petaling Jaya,Selangor, Malaysia
Email: info@pactals2023.com