Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: informahealthcare.com/journals/iafd20

Theme 10 Disease stratification and phenotyping of patients

To cite this article: (2019) Theme 10 Disease stratification and phenotyping of patients, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 20:sup1, 289-300, DOI: 10.1080/21678421.2019.1646998

To link to this article: https://doi.org/10.1080/21678421.2019.1646998

Published online: 08 Nov 2019.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2019; 20(Suppl. S1): 289–300

Theme 10 Disease stratification and phenotyping of patients

DSP-01 Barriers to the diagnosis of motor neuron disease – a South Australian study

Dale F. Sharrad[1,2], David W. Schultz[2,3]

[1]Department of Medicine, Flinders Medical Centre, Bedford Park, Australia, [2]Centre for Neuroscience, Flinders University, Bedford Park, Australia, [3]Department of Neurology, Flinders Medical Centre, Bedford Park, Australia

Email address for correspondence:
dale.sharrad89@gmail.com

Keywords: diagnosis, education

Background: MND is a progressive neurodegenerative disease characterised by death of upper and lower motor neurons, leading to progressive weakness of the bulbar, limb, thoracic and abdominal muscles. MND has a fairly stereotypical course, with death from respiratory failure occurring 2-4 years after symptom onset in most cases (1). Making the diagnosis of MND can be straightforward when key clinical criteria are met; however, at first presentation, rarely do patients meet these criteria, neurological changes may be subtle and disease progression slow. Thus, diagnosis poses a significant challenge, particularly in general practice, where patients are most likely to first present. Not surprisingly, there is usually a delay of 10-18 months between symptom onset and MND diagnosis (2). Importantly, early assessment by a neurologist is associated with a shorter time to MND diagnosis (3), which has significant implications for access to healthcare, including Riluzole and multidisciplinary clinics, which improve survival (4). Although delay in diagnosis is well documented, there have been no studies that have sought to identify factors associated with time to diagnosis, thereby enabling targeted implementation of a public health intervention.

Objectives: To characterise the clinical factors that influence time to diagnosis of MND.

Methods: 112 patients with MND attending the Southern Adelaide MND Clinic enrolled between January 2016 - 2018 were retrospectively recruited in to a cohort study. Information pertaining to the patient's demographics and their journey to diagnosis collected by a specialist physician and stored in the Australian MND Registry during clinic review were analysed to identify factors associated with time to diagnosis.

Results: Mean time to diagnosis was 13 ± 1 months (range 1 – 38 months) from symptom onset. 41% of patients were classified as having fast disease progression; compared to those with slow disease progression, these patients were diagnosed earlier (8 ± 1 months vs 16 ± 2 months) ($p < 0.0001$, $t = 34.6$, df =220), were less likely to undergo multiple specialist opinions prior to referral to a neurologist (53% vs 73%) ($p < 0.05$, *Chi-squared* = 9.5, df =1), and were more disabled at time of diagnosis (mean ALSFRS-R 33 ± 5 vs ALSFRS-R 41 ± 5) ($p < 0.0001$, $t = 12.4$, df =220).

Discussion and conclusions: Fast disease progression identifies a dichotomy of MND patients diagnosed earlier, although more disabled at diagnosis, likely mediated by a more efficient referral process. A greater awareness of MND is required to shorten time to diagnosis.

References

1. Forsgren L, Almay BG, Holmgren G, et al. Acta Neurol Scand. 1983;68:20–29.
2. Chiò A, Mora G, Calvo A, et al. Neurology. 2009; 72(8):725–31.
3. Mitchell JD, Callagher P, Gardham J, et al. Amyotroph Lateral Scler. 2010;11(6):537–41.
4. Rooney J, Byrne S, Heverin M, et al. J Neurol Neurosurg Psychiatry. 2015;86(5):496–501.

DSP-02 Validation study of clinical diagnosis of amyotrophic lateral sclerosis: The Brain Bank for Aging Research (BBAR) project

Tomoyasu Matsubara[1], Yuishin Izumi[2,3], Ryosuke Miyamoto[2], Masaya Oda[3], Hiroyuki Nodera[2], Mana Higashihara[1,4], Renpei Sengoku[1], Ryosuke Oki[2], Koji Fujita[2], Toshitaka Kawarai[2], Chigusa Watanabe[5], Yuko Saito[1,6], Ryuji Kaji[2], Shigeo Murayama[1]

[1]Department of Neurology and Neuropathology (Brain Bank for Aging Research), Tokyo Metropolitan Geriatric Hospital & Institute of Gerontology, Tokyo, Japan, [2]Department of Clinical Neuroscience, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan, [3]Department of Neurology, Mifukai Vihara Hananosato Hospital, Miyoshi, Japan, [4]Department of Neurology, Westmead Hospital, Westmead, Australia, [5]Department of Neurology, National Hospital Organization Hiroshima-Nishi Medical Center, Otake, Japan, [6]Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Kodaira, Japan

Email address for correspondence:
tomoyasumatsubara@gmail.com

Keywords: neuropathology, upper motor neuron/s, clinicopathological correlation

Background: Diagnosis of amyotrophic lateral sclerosis (ALS) is based upon clinical and electrophysiological examinations demonstrating the presence of involvement both upper motor neuron (UMN) and lower motor neuron (LMN). However, the sensitivity of currently employed diagnostic criteria is unsatisfactory, especially in the early phase of the disease (1). This is a significant problem in registration to clinical trials.

Objectives: The purpose of this study is to verify the current diagnostic systems for ALS in each diagnostic category through postmortem neuropathological confirmation.

Methods: We investigated consecutive postmortem case series of clinically diagnosed ALS from three hospitals in Japan from 2011 to 2018. We prospectively collected the clinical information including onset of age, site of onset, disease duration, and clinical diagnostic categories at first and last visit according to updated Awaji criteria (1) and revised El Escorial criteria. Pathologically, we semi-quantitatively assessed neuronal loss and phosphorylated TDP-43 pathology in each area including primary motor cortex, lower motor neuron nuclei, and each area conforming to Brettschneider stage (2). Furthermore, age-associated pathologies including amyloid b, phosphorylated tau, and a-synuclein were also evaluated.

Results: Forty-seven patients were consecutively enrolled (35 males and 12 females; mean age at death, 70.6 years; range: 45-86 years). The median disease duration from onset to death or artificial ventilation was 36 months (range: 8-246 months). Clinically, 28 cases met confirmed ALS at first visit and 40 cases by last visit. Seven cases lacked UMN signs throughout the clinical course, and accordingly did not fall into any of the ALS grades (ie, not applicable). However, pathological examination revealed degeneration of both UMN and LMN in all cases. The breakdown of Brettschneider stage was stage 1 (n=2), stage 2 (n=12), stage 3 (n=8), stage 4 (n=22), and unclassifiable (n=3). While senile changes were generally slight, argyrophilic grain was relatively frequent (12/47 cases). Parkinsonism was observed in four cases: three cases were pathologically diagnosed with Lewy body Parkinson's disease and one case with progressive supranuclear palsy (PSP). Among patients without parkinsonism, pre-symptomatic Lewy body pathology was observed in nine cases.

Discussion and conclusions: The degeneration of UMN was milder in those cases with slight or no clinical UMN signs than those with evident UMN signs. Thus, approach through biomarker is warranted. Neurophysiological approach to detect involvement of UMN signs should be confirmed by postmortem examinations. Three cases of combined pathology of ALS and Lewy body Parkinson disease and a case with ALS and PSP were from Tokushima, quite unique in Japan and may represent regional genetic or cultural bias.

References

1. Geevasinga N, Loy CT, Menon P, et al. Clin Neurophysiol. 2016;127:2684–91.
2. Brettschneider J, Del Tredici K, Toledo JB, et al. Ann Neurol. 2013;74:20–38.

DSP-03 Investigating hidden gelsolin amyloidosis which mimicking slowly progressed motor neuron disease using genetic test

Jinseok Park[1], Young-Eun Kim[1], Sanggon Lee[1], Ki-Wook Oh[1], Min Yeop Nahm[1], Dae Il Jang[2], Chang-Seok Ki[3], Seung Hyun Kim[1]

[1]Hanyang University Hospital, Seoul, Republic of Korea, [2]Kyung Hee University Hospital, Seoul, Republic of Korea, [3]Green Cross Genome, Seoul, Republic of Korea

Email address for correspondence:
jinseok.park0@gmail.com

Keywords: genetic testing

Background: Hereditary gelsolin amyloidosis (HGA) is systemic amyloidosis with autosomal dominant inheritance. Clinical characteristics of GSN amyloidosis are usually presented as lower cranial neuropathy, corneal lattice dystrophy (CLD), loss of skin turgor (cutis laxa) with family history. But skin or eye problems were tended to be overlooked. Therefore, it is difficult to differentiate from non-progressive, long-lasting motor neuron disease (MND) category, especially in case of negative family history.

Objectives: To investigate GSN amyloidosis in non progressive long lasting MND phenotype patients.

Methods: As a tertiary MND referral hospital, we performed genetic test to suspicious MND patients who visit our clinic. We stratified patients with prehospital progression speed, then reviewed their medical records and result of genetic analysis from Nov 2014 to May 2017.

Results: We detected one familial and one sporadic GSN amyloidosis patients with the c.640G>T (p.D214Y) mutation in *GSN* gene. These patients were regarded as non-progressive, long-lasting MND such as progressive bulbar palsy(PBP) before genetic confirmation.

Discussion and conclusions: Especially for sporadic patient like our study, the diagnostic process would be mystery without attention of doctor. Our study suggest that GSN amyloidosis should be considered in patients with long-lasting MND phenotype and not be ignored even in patients with negative family history. We could diagnose more accurately through the development of genetic analysis and physician's concern.

Acknowledgments: This study was supported by the grants from the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT (NRF-2017M 3C7A1025364).

DSP-04 Improvements in the definition of biomarkers for Spinal Muscular Atrophy (SMA) type III and IV: a multimodal longitudinal study

Giorgia Querin[1,2], Jean-Yves Hogrel[3], Rabab Debs[1,4], Véronique Marchand-Pauvert[2], Tanya Stojkovic[3], Anthony Behin[3], Pascal Laforet[5], François Salachas[1], Peter Bede[2,6], Timothée Lenglet[1,4], Pierre-François Pradat[1,2]

[1]Centre référent SLA, APHP, Département de Neurologie, Hôpital Pitié-Salpêtriere, Paris, France, [2]Sorbonne Université, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale, Paris, France, [3]Institute of Myology, [4]Service d'Explorations Fonctionnelles, - APHP; Hôpital Pitié-Salpêtriere, Paris, France, [5]Service de neurologie, centre de référence de pathologie neuromusculaire Nord/Est/Île-de-France, Hôpital Raymond-Poincaré, AP-HP, Garches, France, [6]Computational Neuroimaging Group, Academic Unit of Neurology, Trinity College Dublin, Dublin, Ireland

Email address for correspondence: *giorgia.querin@gmail.com*

Keywords: SMA, biomarker

Background: Spinal muscular atrophy (SMA) is an autosomal recessive lower motor neuron (LMN) disease. SMA type III and IV are adult slowly progressing forms. Disease status is usually evaluated by clinical assessments, which appears inherently suboptimal to detect subtle changes, limiting the ability to test the efficacy of possibly effective drugs.

Objectives: The objective of this study was the longitudinal description of a cohort of SMA type III and IV patients using different methodological approaches and the identification of possible biomarkers of disease status and progression.

Methods: 15 type III and IV adult SMA patients were enrolled in the study. They underwent quantitative muscle force testing, functional evaluation through the SMAFRS and the MFM scales and MUNIX evaluation in 5 muscles in the upper and lower limbs (APB, ADM, deltoid, tibialis anterior and trapezius). A composite MUNIX index was calculated by adding the individual values of the 5 muscle. Participating subjects also underwent a 3Tesla spinal cord (SC) MRI. Structural measures of grey (GM) and white matter (WM) involvement and diffusion parameters of WM integrity were evaluated at each cervical spinal level. The same evaluation protocol was performed at baseline and after 24-months observation time.

Results: Neuromuscular evaluation: Significant modifications over time were observed for the SMAFRS ($p = 0.011$) and for the MFM3 subscale ($p = 0.04$). No significant modifications were observed in the muscle force, and in the 6MWT. Neuroimaging: No significant difference was observed in GM and WM cross-sectional area (CSA) between the baseline and the follow-up evaluation ($p > 0.05$), even if a clear tendency to GM loss over time was observed. No significant differences were observed for DTI parameters. Neurophysiology: A significant reduction between the two time-points was observed in the MUNIX for the ADM muscle ($p = 0.0005$, –23,9%) for the trapezius muscle ($p = 0.034$, –17,43%) and the TA muscle ($p = 0.028$, -13,9%) as well as in the MUNIX total score ($p = 0.0005$, -13,32%).

Discussion and conclusions: Functional outcomes and MUNIX evaluation can detect disease progression in slow progressive type III and IV adult SMA patients, with MUNIX seeming to be the most sensitive biomarker. The constitution of a composite multimodal score could further increase the ability to predict modification over time also in short-lasting clinical trials.

Acknowledgments: We gratefully acknowledge all the patients for participating in this protocol. This study was supported by the Association Française contre les Myopathies (AFM) and the Institut pour la Recherche sur la Moelle épinière et l'Encéphale (IRME). The research leading to these results has also received funding from the program "Investissements d'avenir"-ANR. Peter Bede is supported by the Health Research, the Irish Institute of Clinical Neuroscience IICN – Novartis Ireland Research Grant, and the Iris O'Brien Foundation Ireland.

DSP-05 On-the-spot assessment of venous creatinine as a marker for change in fat-free mass and disease progression in patients with MND

Shyuan T. Ngo[1,2,3,4,5], Cory J. Holdom[1], Diana Lucia[1,3], Ruben P. A. van Eijk[6,7], Leonard H. van den Berg[6], Pamela A. McCombe[3,4,5], Robert D. Henderson[2,3,4,5], Frederik J. Steyn[3,4,5,8]

[1]Australian Institute for Bioengineering and Nanotechnology, [2]Queensland Brain Institute, [3]Centre for Clinical Reasearch; The University of Queensland, Brisbane, Australia, [4]Department of Neurology, Royal Brisbane and Women's Hospital, Brisbane, Australia, [5]Wesley Medical Research, The Wesley Hospital, Brisbane, Australia, [6]Department of Neurology, Brain Center Rudolf Magnus, [7]Biostatistics & Research Support, Julius Center for Health Sciences and Primary Care; University Medical Center Utrecht, Utrecht, Netherlands, [8]School of Biomedical Sciences, The University of Queensland, Brisbane, Australia

Email address for correspondence:
c.holdom@uq.net.au

Keywords: biomarker, disease progression, plasma

Background: Fat-free mass at diagnosis is a prognostic factor in MND (1), and declines as disease progresses (2). As such, a change in fat-free mass could serve as a biomarker for disease progression in MND (1). However, fat-free mass is not routinely measured, and this is likely to be due to limitations in accurately assessing fat-free mass within a clinical setting. Plasma creatinine is predictive for functional status, muscle strength and mortality risk in MND, and could be an inexpensive and easily accessible biomarker for changes in fat-free mass and disease progression in patients with MND (3).

Objectives: We sought to validate the utility of on the spot assessment of venous creatinine as a marker for fat-free mass and disease progression in MND.

Methods: Sixty-five MND patients and 40 non-neurodegenerative disease (NND) healthy controls were enrolled for baseline comparison of venous creatinine with measures of fat-free mass. Fat-free mass was assessed using air displacement plethysmography (BodPod, Cosmed), as we have done previously (4). To improve the clinical utility of venous creatinine assessment, measures were conducted using the iSTAT Alinity (Abbott) point of care device. On-the-spot analysis of venous chemistries was conducted using a CG4 cartridge (Abbott) on the same day as body composition analysis, and was completed within 5 minutes of blood collection.

Results: In patients with MND, measures of fat-free mass correlated with disease progression, as indicated by lower ALSFRS-R scores ($r = 0.249$, $p = 0.045$) and higher King's staging ($r = -0.272$, $p = 0.029$). Venous creatinine was significantly lower in MND patients when compared to NND controls (69.91 ± 14.67 *vs.* 78.75 ± 17.02, $p < 0.001$). Venous creatinine was also significantly correlated with fat-free mass (MND: $r = 0.503$, $p < 0.001$, NND: $r = 0.486$, $p = 0.001$).

Discussion and conclusions: Point of care assessment of fat-free mass may serve as a rapid and reliable biomarker for monitoring of disease progression in MND. Venous creatinine may serve as a proxy measure for fat-free mass in clinical settings where direct assessment of fat-free mass is not routinely available.

Acknowledgments: We thank all individuals who took part in the study. Funding was provided by MNDRIA, RBWH Foundation, MND and Me Foundation, and UQ. The authors declare no conflicts of interest.

References

1. Kirk SE, et al. Front Neurol. 2019;10:191.
2. Ngo ST, et al. Amyotrophic Lateral Scler Frontotemporal Degener. 2019. Accepted, May 2019; In Press.
3. van Eijk RPA, et al. J Neurol Neurosurg Psychiatry. 2018; 89:156–61.
4. Steyn FJ, et al. J Neurol Neurosurg Psychiatry. 2018; 89:1016–23.

DSP-06 The world according to the D50 model of ALS progression

Julian Grosskreutz[1], Ammar Al-Chalabi[2], Leonard van den Berg[3], Mamede de Carvalho[4], Adriano Chio[5], Philippe Corcia[6], Philippe Couratier[6], Philip van Damme[7], Torsten Grehl[8], Caroline Ingre[9], Matthew Kiernan[10], Blaz Koritnik[11], Magdalena Kuźma-Kozakiewicz[12], Thomas Meyer[13], Christoph Neuwirth[14], Susanne Petri[15], Paul Talman[16], Hilmi Uysal[17], Jan Veldink[3], Markus Weber[14], Paul Wicks[18], Janez Zidar[11]

[1]University Hospital Jena, Jena, Germany, [2]King's College London, London, United Kingdom, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]Hospital de Santa Maria-CHLN, Lisbon, Portugal, [5]University of Torino, Torino, Italy, [6]Université François-Rabelais de Tours, Tours, France, [7]University Hospital Leuven, Leuven, Belgium, [8]Alfred Krupp Krankenhaus Rüttenscheid, Essen, Germany, [9]Karolinska Institutet, Solna, Sweden, [10]Royal Prince Alfred Hospital, Sydney, Australia, [11]University Medical Centre Ljubljana, Ljubljana, Slovenia, [12]Medical University of Warsaw, Warsaw, Poland, [13]Charité – Universitätsmedizin Berlin, Berlin, Germany, [14]Cantonal Hospital St. Gallen, St. Gallen, Switzerland, [15]Hannover Medical School, Hannover, Germany, [16]Barwon Health, Geelong, Australia, [17]Akdeniz University Faculty of Medicine, Antalya, Turkey, [18]PatientsLikeMe, Inc., Cambridge, MA, USA

Email address for correspondence:
julian.grosskreutz@med.uni-jena.de

Keywords: ALSFRS-R, progression, modelling

Background: ALS is a highly heterogenous disease both in terms of spread and speed of progression. The D50 model was developed to address drawbacks associated with the traditional ALSFRS-R-derived "Progression Rate" (PR); PR presupposes that progression is linear and remains temporally fixed and has been modified in variable ways to reflect local progression limiting its use as a general tool.

Objectives: We aimed to test the applicability of the D50 model as a screening, stratification and outcome tool in a global set of large cohorts. We aimed to quantify the behaviours of different model indices in relation to each other and identify additional internal quality control parameters.

Methods: Iterative least-square fitting of all available ALSFRS-R scores was used in a sigmoidal state transition with D50 (time taken for ALSFRS-R score to reach 24), dx (time constant of ALSFRS-R decay), and relative D50 (individual disease time with 0 = disease onset and 0.5 = timepoint of halved functionality) 2 local descriptors (functional

loss cFL, local decay rate & functional state cFS, units identical to ALSFRS-R) can be calculated for any event with known time since onset.

Results: Disease descriptors were calculated for 17,230 patients from 15 centers. D50 and dx correlated linearly in all centers (r^2: 0.91–0.997); D50 distribution differed between individual centers reflecting the respective fractions of very slow progressors (D50 > 200 months). rD50 aligns individual patients in terms of elapsed time to 50% loss of function, thus allowing comparability despite different time scales for disease specific events eg spread to 2nd region; diagnosis; spread to 3rd region; wheelchair; gastrostomy; ventilation and death. This staging scale also provides a useful supplement to conventional staging scales like the King's and MITOS systems. This work is ongoing and the latest state of the analyses will be presented with reference to subtype classifications.

Discussion and conclusions: The D50 model provides meaningful descriptors of overall disease aggressiveness, local disease activity, and a unified linear time scale to describe individual disease progression. It a) offers alternative reference points to survival, b) allows the staging of individual events, c) provides a way to pseudo-longitudinally interpret cross-sectional data and d) efficiently compares cohorts from different geographic regions. The model does not allow precise predictions of disease course early on with a limited number of ALSFRS-R readouts available.

Acknowledgments: This work is supported by the BMBF in the framework of the JPND programme ONWebDUALS, the E-RARE programme PYRAMID, the MNDA and the DGM. The D50 global study group includes above PIs and Nayana Gaur, Benjamin Vlad, Robert Steinbach, Tino Prell, Matthieu Moisse, Umberto Manera, Marta Gromicho, Katarzyna Szacka, and Frauke Fartmann.

References

1. Poesen, et al. Neurology. 2017;88:1–8.
2. Gaur, et al. Amyotroph Lat Scler Frontotemporal Degener. 2017;18.
3. Prell, et al. Front Aging Neurosci. 2019;11:5.

DSP-07 Significant events during ALS progression according to the D50 model in the ONWebDUALS cohort

Julian Grosskreutz[1], Mamede de Carvalho[2], Frauke Fartmann[3], Marta Gromicho[4], Magdalena Kuźma-Kozakiewicz[5], Susanne Petri[3], Beatrice Stubendorff[1], Katarzyna Szacka[5], Hilmi Uysal[6]

[1]University Hospital Jena, Jena, Germany, [2]Hospital de Santa Maria-CHLN, Lisbon, Portugal, [3]Hannover Medical School, Hannover, Germany, [4]Universidade de Lisboa, Lisboa, Portugal, [5]Medical University of Warsaw, Warsaw, Poland, [6]Akdeniz University Faculty of Medicine, Antalya, Turkey

Email address for correspondence:
julian.grosskreutz@med.uni-jena.de

Keywords: disease progression, phenotyping

Background: It is difficult to weigh the impact of disease related events during ALS because of highly heterogenous progression rates. In addition, the interplay between genetic and environmental risk factors remains to be fully understood. By incorporating data sets from different European countries, ONWebDUALS aims to understand ALS related risks and prognostic factors in order to enhance patient characterization but a cohorent framework to quantitatively compare timing and significance of the impact of disease related events has been missing.

Objectives: To analyze randomly collected clinical data from 5 centers in the framework of the novel D50 progression model, which normalizes for differences between time and manner of collection therefore enhancing comparability.

Methods: The model uses iterative least-square fitting of all available ALSFRS-R scores which were not part of the original ONWebDUALS questionnaire. Using a sigmoidal state transition the model yields 2 parameters of overall disease aggressiveness: D50 (time to lose 50% of function), dx (decay time constant), and 2 of local disease activity: functional loss (cFL) and functional state (cFS). Normalizing time to D50 gives relative D50 (rD50), a value describing disease course covered where 0 = onset and 0.5 = time-point of halved functionality. rD50 allows aligning of different disease courses in a normalized framework and categorizing of patients into disease phases.

Results: The D50 model was used to simulate the disease course of 1200 patients from 5 European centers. A significant correlation between D50 and dx was noted (r = 0.97). Further, no significant differences in whole-center D50 values were observed. Forty-one and 44% of all consultations occurred in disease phases I and II, respectively. Crucially, all disease-related events could be relatively staged from disease onset ie rD50: 1st consultation at rD50 = 0.05; spread to 2nd region at rD50 = 0.13; formal diagnosis at rD50 = 0.22; spread to 3rd region at rD50 = 0.26; invasive ventilation at rD50 = 0.69; and death at rD50 = 0.77. Finally, cFS at the time of consultation resulted in 44.0 ± 2.0 for patients in phase I, 35.1 ± 3.3 for patients in Phase II and 18.0 ± 6.3 for Phase III/IV patients. Additionally the cFL for these phases was 0.52 ± 0.6, 1.12 ± 1.2 and 1.34 ± 1.5, respectively

Discussion and conclusions: The D50 model provides meaningful descriptors of overall disease aggressiveness, local disease activity, and a unified timing scale rD50 to describe . It allows the comparison of individual events in extremely different disease trajectories and compare the impact of a disease related events. In order to develop preventive strategies according to ALS risk factors it is most important to use such a tool to identify factors that enable to prolong the time until a specific event occurs and/or to decrease the associated functional loss rates.

Acknowledgments: This research is supported by a BMBF grant OnWebDUALS (01ED15511A) in the framework of the JPND.

DSP-08 Structural and functional implications of cortical dysfunction on clinical disease progression in amyotrophic lateral sclerosis

Thanuja Dharmadasa[1], Chenyu Wang[2], Neil G. Simon[3], James Howells[1], Matthew C. Kiernan[1]

[1]University of Sydney, NSW, Australia, [2]Sydney Neuroimaging Analysis Centre, NSW, Australia, [3]St Vincent's Clinical School, NSW, Australia

Email address for correspondence:
thanuja.dharmadasa@sydney.edu.au

Keywords: imaging, cortical dysfunction

Background: Upper motor neuron (cortical) dysfunction remains difficult to clinically detect *in vivo*. While non-invasive methods have continued to evolve, clinical differences across the ALS motor phenotypes have raised questions regarding the variability of underlying cortical pathology (1,2). In particular, the influence of cortical changes on disease progression and prognosis remains unclarified.

Objectives: To assess cortical dysfunction *in vivo* using a novel combined structural and functional approach across ALS motor phenotypes, relating findings to clinical and prognostic patterns of disease.

Methods: 30 patients with classic ALS patients and 20 healthy controls underwent diffusion tensor imaging (DTI) of the corticospinal tracts measuring from the primary motor cortex to the pontomedullary junction bilaterally, assessing multiple DTI scalars. Threshold tracking transcranial magnetic stimulation (TT-TMS) was conducted from both motor hemispheres concurrently, with motor evoked potentials recorded over the abductor pollicis brevis muscles bilaterally. Clinical and functional measures were additionally collected, including disease progression rate.

Results: Structural involvement of both motor pathways was apparent across the ALS cohort with a reduction in functional anisotropy (FA, $p < 0.0001$) accompanied by an increase in mean and radial diffusivity (MD, $p < 0.0001$; RD, $p = 0.04$). This corresponded with evidence of corticomotoneuronal dysfunction from both motor cortices on TT-TMS studies, with reduction in average short-interval intracortical inhibition (SICI, 1-7 ms, $p < 0.001$) bilaterally. Focal structural changes were found in faster disease progressors (n = 11, 37%), who demonstrated a unilateral reduction in axial diffusivity ($p = 0.03$) corresponding to the 'affected' motor cortex . These patients also demonstrated a significantly greater degree of microstructural change overall (as measured by FA, AD, RD) when compared to the slower progressors. Survival was reduced for patients with lower FA values ($p = 0.03$) and higher MD (>0.49). Functional and structural changes were identified across all ALS phenotypes, but were most marked in the bulbar-onset group.

Discussion and conclusions: Microstructural changes along the motor pathways of ALS patients complement the global pattern of functional abnormalities across the motor cortices in ALS. The degree of axonal damage (as measured by FA and AD) corresponds to the rate of disease progression and is linked to survival, offering a potentially measurable central driver of prognosis. These abnormalities are most significant for the bulbar-onset motor phenotype, which may relate to their poorer prognosis. Overall, this supports the importance of central dysfunction in ALS disease mechanisms, and suggests that heterogeneity of these cortical processes may, at least in part, underly the clinical and prognostic differences observed.

Acknowledgments: We acknowledge all the patients involved in this study. Authors declare no conflicts of interest. Funding was granted by The National Health and Medical Research Council of Australia Program Grant (#1037746).

References

1. Huynh W, Simon NG, Grosskreutz J, et al. Clin Neurophysiol. 2016;127:2643–60.
2. Turner M, Agosta F, Bede P, et al. Biomark Med. 2012;6:319–37.

DSP-09 Rapid reprogramming method differentiates CuATSM responders/ nonresponders from ALS patient population

Cassandra Dennys-Rivers[1], Xiaojin Zhang[1], Rochelle Rodrigo[1], Alvaro Estevez[2], Brian Kaspar[1], Joseph Beckman[2], Maria Clara Franco[2], Kathrin Meyer[1]

[1]Nationwide Children's Hospital, Columbus, OH, USA, [2]Oregon State University, Corvallis, OR, USA

Email address for correspondence:
cassandra.dennys-rivers@nationwidechildrens.org

Keywords: CuATSM, in vitro, human therapeutic screens

Patient diversity and unknown disease cause are major challenges for drug development and clinical trial design for Amyotrophic Lateral Sclerosis (ALS). Moreover, the heterogeneity of the ALS patient population is not reflected in the currently available transgenic animal models. Hence, the direct translation of potential therapeutics tested in such models to the clinic has proven difficult. To address this issue, we utilized a rapid reprogramming method to convert skin biopsies from ALS patients into neuronal progenitor cells (NPC). Using induced astrocytes (iAstrocyte) differentiated from these NPCs in co-culture with mouse

embryonic motor neurons, we have developed an *in vitro* model of ALS to screen potentially therapeutic compounds. Using this assay, we have screened numerous compounds on multiple sporadic (sALS) and familial (fALS) patient lines. Our data indicate a diverse patient response to different therapeutic agents, suggesting shared pathways of interest between patient subgroups. Here we investigated the effects of one such compound, CuATSM, on iAstrocyte mediated motor neuron toxicity in both sporadic and familial (mtSOD1 and C9ORF72 patients) lines. We identified responders and nonresponders in co-culture assay for each patient subpopulations. Next, we performed a detailed analysis of the effects of CuATSM on known ALS disease markers (oxidative stress, mitochondrial dysfunction, elevation of stress response systems). We identified one shared parameter present in all ALS patient CuATSM responders, that was nonexistent in nonresponders. Treatment of iAstrocytes with CuATSM restored this disease marker to levels comparable to healthy controls. Together, these findings suggest that patient iAstrocytes can be used to identify both disease modifiers and pathways dysregulated in a given individual. Furthermore, compound screenings can be utilized to restore disease markers to healthy levels. These results indicate that enhanced understanding of cellular profiles could aid clinicians in determining the best treatment approach for patients in the future.

Acknowledgments: We would like to thank patients for donating skin biopsies. Funding was provided by MDA Young Investigator Development Grant awarded to Kathrin Meyer and the ALS Association.

DSP-10 A personalized medicine approach for ALS/MND

Jeffrey Rosenfeld[1,2], Debendranath Dey[3], Shao Feng Yu[3], Amanda Macieik[3], Suganya Selvarajah[3], Dennis Paulvannan[3], Vishwanath R. Lingappa[3]

[1]Loma Linda University Health, Loma Linda, CA, USA, [2]The Center for Restorative Neurology at Loma Linda University Health, Loma Linda, CA, USA, [3]Prosetta Biosciences, San Fransciso, CA, USA

Email address for correspondence: *jrosenfeld@llu.edu*

Keywords: heterogeneity, disease subtypes

Heterogeneity of both disease presentation and underlying etiology of ALS has confounded discovery of effective therapeutic options. Aberrant intracellular localization of multi-protein complexes is, however, a common theme in neurodegenerative diseases, including ALS. We have recently identified and characterized a novel class of drugs that specifically block the aberrant assembly of pathogenic multi-protein complexes that appears to directly impact a primary pathophysiology of motor neuron disease.

The mechanism(s) of selective targets driving protein aggregation and mislocalization was discovered and validated in virus models that modify normal protein assembly to the detriment of their host.

Following an extensive screen of 150,000 small molecules, 300 compounds were identified with specific activity to block formation and the mislocalization of multi-protein complexes. Of the 300 chemotype compounds that modulate protein assembly, a number of them are especially relevant to human disease. The signature of these chemotype compounds, regulating aberrant protein assembly, provide a relevant biomarker for stratification of the heterogeneous ALS patient population. Specifically, we have identified three chemotypes active in cellular models on both relocalization of TDP-43 to the nucleus and prevention of TDP-43 aggregates in stress granules. This has been validated in familial and sporadic ALS models as well as in worm, fly and mouse animal models of ALS.

Using drug resin affinity chromatography (DRAC) we have been able to select patients who are specifically responsive to particular chemotypes, implicating a distinct underlying mechanism for that patient and a selective treatment advantage.

We will present data showing evidence that this approach can be used to i) stratify patients into subsets, ii) identify protein assembly modulators, optimal for correction of a specific molecular defect occurring in a given patient, and iii) track disease progression based on a peripheral blood mononuclear cell DRAC signature, allowing maximal opportunity for personalized treatment and prevention of disability. A first such compound is currently being advanced toward clinical trial.

DSP-11 The clinical phenotype of motor neuron diseases in Bangladesh

Thomas M. Jenkins[1,2], Oliver Bandmann[1,2], Azharul Hoque[3], Badrul Alam[3], Jahirul Chowdhury[3], Pamela J. Shaw[1,2], Quazi Deen Mohammad[3]

[1]Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, United Kingdom, [2]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [3]National Institute for Neuroscience and Hospital, Dhaka, Bangladesh

Email address for correspondence: *t.m.jenkins@sheffield.ac.uk*

Keywords: epidemiology, phenotyping, Bangladesh

Background: MND clinical phenotypes may vary across the world, and offer insights into underlying pathophysiology. The phenotype of MNDs in Bangladesh has not yet been reported.

Objectives: To describe the clinical features of MND in a pilot cohort from Dhaka, Bangladesh, compared to Sheffield, UK.

Methods: We obtained prospective, standardised clinical data from 28 consecutive outpatients from Dhaka. Detailed history, neurological examination, weight, revised ALS functional rating scale (ALSFRS-R), and electromyographic (EMG) data were compared to 28 consecutive outpatients from Sheffield. Between-group comparisons were analysed with chi-squared, Mann-Whitney and unpaired t-tests.

Results: Eighty-six percent of Bangladeshi and 61% of UK patients were male ($p=0.527$). The following between-group differences were found: Dhaka patients were younger (mean 37 versus 62 years, $p<0.001$), duration of weakness was longer to diagnosis (mean 52 versus 16 months, $p=0.003$) and to current assessment (mean 74 versus 17 months, $p<0.001$), and there were fewer regions with both active and chronic denervation on EMG (median 2/3 in Dhaka and 3/4 in Sheffield, $p<0.001$). In Dhaka, 43% percent had ALS, 11% progressive muscular atrophy (PMA) and 46% monomelic amyotrophy. In the UK, 93% had ALS and 7% PMA. Three Bangladeshi patients (all monomelics, no consanguinity) and 5 UK patients (all ALS) had a positive family history of a MND. There were no differences in ALSFRS-R (38/48 in both centres) or weight.

In the ALS subgroups, the following differences were found: Dhaka patients were younger (mean 43 versus 62 years, $p<0.001$), duration of weakness was longer to current assessment (37 versus 17 months, $p=0.017$) and to diagnosis (mean 36 versus 16 months, $p=0.021$), and ALSFRS-R was lower (30/48 versus 38/48, $p=0.012$). There was no significant difference in affected EMG regions (median 2/4 in Dhaka and 3/4 in Sheffield, $p=0.163$). In Dhaka, 50% were leg-onset, 33% arm-onset and 17% bulbar-onset. In the UK, leg, arm and bulbar-onset each comprised 31%, and mixed-onset and thoracic-onset each 4%.

In monomelic amyotrophy patients, mean age at assessment was 30 years (SD 7), the arm was affected in 85% and the leg in 15%. Thirty-one percent had radiological changes consistent with Hirayama disease on cervical MRI. Mean duration of weakness was 114 months (SD 80), and ALSFRS-R 46/48 (SD 1).

Discussion and conclusions: ALS patients in Dhaka appear to exhibit younger age of onset and longer disease duration. There is a high prevalence of benign monomelic amyotrophy in Bangladesh. These patient populations merit study in a larger cohort, to determine whether environmental or genetic factors can explain the clinical phenotypic differences.

Acknowledgments: We thank the patients. This work was supported by the NIHR Sheffield Biomedical Research Centre for Translational Neuroscience, and charitable funding from the Global Challenges Research Fund.

DSP-12 The demographic and clinical characteristics of amyotrophic lateral sclerosis in Malaysia

Nur Adilah Abdul-Aziz, Ee Chin Loh, Khean-Jin Goh, Lydia Abdul Latif, David Capelle, Nortina Shahrizaila

University of Malaya, Kuala Lumpur, Malaysia

Email address for correspondence:
nortina@um.edu.my

Keywords: phenotyping, disease progression, multi-ethnic cohort

Background: There have been many studies describing the clinical features of Amyotrophic Lateral Sclerosis (ALS) in Western populations but information on ALS in developing Asian countries including Malaysia is limited. There is reportedly lower incidence of ALS in Asia and also in populations where there is genetic admixture (1).

Objectives: To describe the demographic and clinical characteristics of patients with ALS in a multi-ethnic Malaysian cohort.

Methods: Consecutive ALS patients presenting to the multi-disciplinary ALS clinic at University Malaya Medical Centre, Kuala Lumpur between January 2015 and May 2019 were recruited following informed consent. Demographic and clinical details were collected using a standardised data collection form. The diagnosis of ALS was made based on the revised El-Escorial and Awaji-Shima criteria.

Results: A total of 112 patients were included. The mean age of onset was 57.2 ± 11.0 years and 14.3% of patients were young-onset (<45 years). There was a male preponderance (66%) with a male: female ratio of 1.9:1. The majority of patients were of Chinese ethnicity (58%) followed by Malay (25%), Indian (12%) and others (5%). In 29% of patients, the onset was bulbar while the majority (71%) were limb-onset. A positive family history was reported in 5 (4.5%) patients. The time from disease onset to diagnosis was 14.9 ± 12.9 months. Only 20 (18%) patients were prescribed riluzole. Non-invasive ventilation was initiated in 31 (28%) patients whereas percutaneous endoscopic gastrostomy was performed in 26 (23%) patients. The mean ALSFRS-R scores at presentation was 29.3 ± 10.5 and the mean rate of deterioration was 1.1 ± 1.8 points per month. There were 41 deaths, the majority due to respiratory complications. The mean survival from disease onset and from diagnosis were 35 months and 25 months, respectively.

Discussion and conclusions: In comparison to Western cohorts, Malaysian ALS patients had a younger age of onset, male predominance, and greater diagnostic delays. These findings are similar to reports from other Asian cohorts. Disease-modifying therapies including riluzole, ventilatory support, and enteral feeding were considered by less than a third of our patients. The mean survival rates were comparable to those reported in the West.

Acknowledgments: We extend our deep gratitude to all patients who willingly participated in this study. The study is supported by funding from the Malaysian Ministry of Education (FP043-2018A) and ALS Association. The authors declare no conflicts of interest.

Reference

1. Shahrizaila N, Sobue G, Kuwabara S, et al. J Neurol Neurosurg Psychiatry. 2016;87(8):821–30.

DSP-13 The genotype and phenotype spectrum of familial amyotrophic lateral sclerosis in China

Xunzhe Yang, Kang Zhang, Shuangwu Liu, Dongchao Shen, Qing Liu, Mingsheng Liu, Liying Cui

Peking Union Medical College Hospital, Beijing, China

Email address for correspondence:
celine23@163.com

Keywords: FALS, phenotyping, genotype-phenotype

Background: Amyotrophic lateral sclerosis (ALS) is a clinically and genetically heterogeneous neurodegenerative disease, with simultaneous upper motor neuron (UMN) and lower motor neuron (LMN) involvement. Genetic advancements in the 10% of patients with familial ALS have provided valuable insights into disease pathogenesis and therapeutic targets in patients with specific gene mutations.

Objectives: We aimed to provide a comprehensive description of genetic and clinical spectrum of the familial ALS in China.

Methods: The relative contributions of the different mutations related to ALS were estimated by systematically screening a cohort of 44 families enrolled in China using molecular analysis techniques and phenotype-genotype correlations analyses were also performed. Age of disease onset, disease duration and site of onset were used for genotype-phenotype correlations.

Results: We report 67% (30/44) of Chinese ALS families in this cohort harbor a known ALS mutation. Mutations in SOD1 account for 52% (23/44) of families We also report ALS families with mutations in FUS 7% (3/44), UBQLN2 2% (1/44), VAPB 2% (1/44), ANXA11 2% (1/44) and KIF5A 2% (1/44). Hexanucleotide repeat expansions in C9orf72 were not detected in Chinese families. Among SOD1 families, p.A5V positive patients had significantly earlier onset (adjusted p-value =0.0003). No significant difference was found in disease durations and site of disease onset between subgroups carrying different SOD1 gene mutations.

Discussion and conclusions: Our report highlights a unique spectrum of ALS gene frequencies among Chinese patients. Further more, this result also provided valuable insights into pinpointed therapeutic targets in patients with specific gene mutations.

Acknowledgments: Thanks to our ALS patients and their families.

References

de Carvalho M, Swash M. Curr Opin Neurol. 2011;24:497–503.
Dion PA, Daoud H, Rouleau GA. Nat Rev Genet. doi:10.1038/nrg2680
Andersen PM. Curr Neurol Neurosci Rep. 2006;6:37–46.

DSP-14 Tracking bulbar impairment using the Beiwe smartphone app

Kathryn Connaghan[1], Jordan Green[1], Sabrina Paganoni[2,3], James Chan[4], Harli Weber[3], Ella Collins[3], Brian Richburg[1], Marziye Eshghi[1], JP Onnela[5], James Berry[2,3]

[1]MGH Institute of Health Professions, Boston, MA, USA, [2]Harvard School of Medicine, Boston, MA, USA, [3]Department of Neurology, [4]Department of Biostatistics; Massachusetts General Hospital, Boston, MA, USA, [5]T.H. Chan Harvard School of Public Health, Boston, MA, USA

Email address for correspondence:
kconnaghan@mghihp.edu

Keywords: speech, bulbar, technology

Background: Early identification of bulbar dysfunction and accurate monitoring of speech changes in ALS is crucial to appropriate treatment planning and for establishing response to treatment in either clinical or trial settings. Longitudinal speech data collected frequently and conveniently can inform ALS disease prognosis, facilitate timely intervention, and can be leveraged to determine responsiveness to treatment (1). Due to their ubiquity, smartphones can be used to reduce barriers to acquiring speech recordings for quantitative analysis from people with ALS. The Beiwe platform provides a flexible smartphone-based app for Android and iOS devices for acquiring active and passive digital data, including high quality audio recordings.

Objectives: We have established the feasibility of using the Beiwe platform for smartphone-based digital phenotyping in ALS across multiple domains (2). The current study extends that work to investigate the utility of Beiwe for identifying and tracking speech decline in ALS. We explored its feasibility for the frequent collection of speech recordings and self-ratings for the purposes of identifying the onset of bulbar symptoms and monitoring ALS progression (3, 4).

Methods: Twelve people with ALS participated over a multi-week period. Participants completed the Revised ALS Functional Rating Scale (ALSFRS-R) and recorded themselves reading the Bamboo passage weekly. Three speech acoustic measures (ie, speaking rate, articulation rate and percent pause) were automatically extracted offline.

Participants were grouped based on baseline speaking rate into those presenting with (Bulbar) and without (No-Bulbar) bulbar signs. Multiple t-tests were conducted to examine ALSFRS-R (Bulbar, Speech subscores) and acoustic (articulation rate, percent pause) group differences at baseline. Separate linear mixed-effects (LME) models were further conducted on these variables to evaluate group differences in the rate of bulbar decline.

Results: Baseline ALSFRS-R (Bulbar, Speech) scores and articulation rate were significantly lower for Bulbar than No-Bulbar participants ($p < .05$). Further, the Bulbar group demonstrated faster rate of decline of these measures ($p < .01$).

Discussion and conclusions: Successful implementation of the Beiwe platform for collection of speech recordings for quantitative analysis provides a promising new paradigm for diagnostic screening and ALS progression monitoring. The convenience of recording the speech signal for use as a biomarker can reduce barriers, such as travel, and thereby promote adherence to clinical and research protocols.

Acknowledgments: This study was funded with the Winthrop Family Fund for ALS Science at Massachusetts General Hospital, NIH grant DP2-MH103909, and NIH-NIDCD K24DC016312.

References

1. Green JR, Yunusova Y, Kuruvilla MS, et al. Amyotroph Lat Scler Frontotemporal Degener. 2013;14(7–8):494–500.
2. Berry JD, Paganoni S, Carlson K, et al. Ann Clin Translat Neurol. 2019;6(5):873–81.
3. Green JR, Beukelman DR, Ball LJ. J Med Speech-language Pathol. 2004;12(4):149.
4. Allison KM, Yunusova Y, Campbell TF, et al. Amyotroph Lat Scler Frontotemporal Degener. 2017;18(5–6):358–66.

DSP-15 Foreign Accent Syndrome (FAS) and amyotrophic lateral sclerosis (ALS): a case report

Helena Noemi Moreira Sierra[1,2], Rosana Mara Borges[1,2], Luciana Maria Frabasile[1,2], Percília Cardoso Lopes Alves[1,2,3], Juliana Wanderley Cidreira Neves[1,2], Cristina Cleide dos Santos Salvioni[1,2,4], Acary Souza Bulle Oliveira[1,2], Adriana Leico Oda[1,2,4]

[1]Federal University of São Paulo, São Paulo, Brazil, [2]Brazilian Association of ALS, São Paulo, Brazil, [3]Santa Marcelina Hospital, São Paulo, Brazil, [4]Neuroqualis, São Paulo, Brazil

Email address for correspondence: *adrileico.oda@uol.com.br*

Keywords: communication, speech, Foreign Accent Syndrome

Background: The Foreign Accent Syndrome (FAS) is a disease of the Central Nervous System (CNS) affecting the non-dominant hemisphere in which the person speaks a native language with a foreign accent.

Objectives: To describe the Foreign Accent Syndrome (FAS) in an Amyotrophic Lateral Sclerosis (ALS) patient.

Methods: This is a descriptive case report of a 59-year-old female patient, resident in the city of São Paulo-Capital, diagnosed with ALS and referred to a 2-year and 7-month disease time. It started presenting predominant Castilian accent 2 years and 1 month, being that it never maintained convivial with people or communities that speak Spanish. A clinical evaluation was done using the following clinical scales: Functional Oral Intake Scale (FOIS), S/Z Relation, evaluation of pneumo-phono-articulatory coordination, phonetic and phonological evaluation; maximum phonation time (MPT), spontaneous conversation voice recording, word repetition (Orofacial myofunctional evaluation - MBGR protocol), oral diadochokinesia (DDK), Edinburgh cognitive and Behavioral ALS Screen (ECAS), orofacial motricity assessment and auditory perceptual evaluation (GRBASI).

Results: The following changes were found regarding the voice: in auditory perceptual evaluation (GRBASI), tense voice quality - Grade 1; Acute pitch; Loudness adequate, mild degree laryngopharyngeal resonance. Maximum Phonation Time (TMP)/a/= 10.3 “/i/= 11”/u/= 7.3 “. Mean S/Z ratio =5.3 “. In relation to speech: orofacial motricity alteration of the lips, tongue, and cheeks, in mild degree and masticatory musculature in moderate degree. Pneumo-phono-articulatory incoordination (ICPFA) with very short inspiratory time, pulling of the wishbone and use of accessory musculature; decreased velocity and overarticulate; Phonological and phonological alteration due to unsystematic alterations: omission of the vowel / i /, distortion of the vowel / o / by / w /; distortion of closed vowels /ɪ̃/ by / ẽ̞/, change of phoneme/v/by/b/; exchange of vowel / and / by / i /; systematic distortion of the / r / isolated and in group and occurrence of abrupt vocal attack; dysprosody characterized by a change in speech rhythm and intonation, with phonemes’ prolongation at the beginning and middle of the word and a change in the tonicity of words; evidence of vocal addition at the end of sentences introducing the vowel / ã /; Diadococinesia Oral (DAC) reduced, with emission number for 5 seconds: / pa / = 16; / ta / = 17; / ka / = 15; / pataka / = 7. In the cognitive evaluation, by the (ECAS), there was impairment in the tasks of executive functions, language (spelling) and memory of evocation.

Discussion and conclusions: The patient presented alterations of the neuromuscular control, which are compatible with the Motor Neuron Disease, together with prosodic alterations, which agree with the description of FAS. This is the first case report of Amyotrophic Lateral Sclerosis with FAS.

DSP-16 What matters most to patients with ALS: initial validation of the ALS Health Index (ALS-HI), a multi-faceted patient reported outcome measure

Christine Zizzi[1], Ellen Wagner[1], Michael Benatar[2], Chad Heatwole[1]

[1]Department of Neurology, University of Rochester, Rochester, NY, USA, [2]Department of Neurology, University of Miami, Miami, FL, USA

Email address for correspondence:
chad_heatwole@urmc.rochester.edu

Keywords: disease burden, QoL, therapeutic trials

Background: As therapeutic trials are planned for patients with ALS, it is important to better understand the symptoms that have the greatest impact on ALS patients' lives and to have instruments that are capable of measuring small but relevant changes in these symptoms over time.

Objectives: To utilize direct patient input to identify the symptoms that generate the greatest disease burden in the ALS patient population.

Methods: During the initial phase of this study, we interviewed 15 adults with varied ALS phenotypes. Using open-ended questions, participants were asked to identify the symptoms and issues that have the greatest impact on their lives. Patient interviews were recorded, transcribed, and analyzed using a qualitative framework technique, triangulation, and an investigator consensus approach.

Results: ALS participants provided 762 quotes, identifying 303 individual symptoms that have a significant effect on their daily lives. Symptoms represented 20 different symptomatic themes including: limitations with mobility or walking, proximal upper extremity weakness, lower extremity weakness, hand weakness, emotional issues, impaired body image, cognitive issues, social role limitations, social role dissatisfaction, activity limitations, swallowing and eating issues, speech and communication, fatigue, pain, sleep and daytime sleepiness, bowel function, respiratory function, bladder function, spasticity, fasciculations. Participants most commonly mentioned impaired walking, an inability to do things previously done, general fatigue, decreased independence, leg weakness, the need for assistive devices, and a change in body image as the issues that have the greatest impact on their lives.

Discussion and conclusions: There are many symptoms and symptomatic themes that have a significant effect on the lives of ALS patients. The second phase of this study is ongoing and includes a large, cross-sectional study, designed to obtain direct patient input from a larger patient population and to determine the relative importance and prevalence of each of the symptoms identified through the initial phase. Together, these two phases will provide a comprehensive overview of patient-reported disease burden in ALS. Data from these phases are being utilized to build and validate a patient relevant and sensitive clinical trial tool, the ALS-HI, for use as a measure of patient-reported disease burden in future ALS therapeutic trials.

Acknowledgments: Funding for this project was provided by the ALS Association. Research activities were conducted in collaboration with the CReATe consortium.

DSP-17 Early treatment effects of Riluzole in ALS-MND 2: isometric strength improvements in sentinel muscles

Benjamin Rix Brooks[1,2,3], Elena K. Bravver[1,2,3], Urvi G. Desai[1,2,3], Navid Jalali[1,2,3], William B. Dawson[1,2,3] and William L. Bockenek[1,3,4]

[1]Carolinas Neuromuscular/ALS - MDA Care Center, Charlotte, NC, USA, [2]Atrium Health Neurosciences Institute, Charlotte, NC, USA, [3]University of North Carolina School of Medicine - Charlotte Campus, Charlotte, NC, USA, [4]Atrium Health Carolinas Rehabilitation - Charlotte, Charlotte, NC, USA

Email address for correspondence:
benjamin.brooks@atriumhealth.org

Keywords: riluzole, disease progression, isometric muscle strength

Background: Riluzole has positive effects on survival and functional scales in ALS (1). Riluzole also had effect on isometric strength in the original clinical trial (2). Neck flexion, biceps, brachioradialis flexion, hip flexion, knee flexion have been identified as sentinel muscles in ALS-MND.

Objectives: Characterize isometric strength change in sentinel muscles in ALS-MND.

Methods: 128 consecutive ALS patients initiating riluzole therapy were assessed for ALS-FRS-R, respiratory function, isometric muscle strength measured by Medical Research Council scale. Subjects were examined before and at approximately 4 weeks following initiation of riluzole 50 mg twice daily, vitamin E 1200 units daily, vitamin B242 5000 micrograms daily, folic acid 2000 mcg daily, vitamin E vitamin D 5000 mcg daily. Statistical analysis employed MedCalc Software version 19.0.5 https://www.medcalc.org; 2019.

Results: 80/128 (62.5%) ALS patients showed improvement in one or more sentinel muscles following riluzole treatment and 48/128 (37.5%) ALS patients did not. Subjects in the 'strength improved' cohort demonstrated median survival =21.0 months (95% CI =17.0 to 23.0 months) that was significantly prolonged [$p = 0.001$ Kaplan-Meier Logrank test] compared with the subjects in the 'strength not improved' cohort median survival =12.0 months (95% CI =5.0 to 18.0 months).

Discussion and conclusions: A proportion of ALS patients receiving riluzole, vitamin E, vitamin B242, folic acid, vitamin D show improvement in isometric muscle strength in sentinel muscles observed within 4 weeks of treatment initiation that is associated with slower disease progression as measured by increased survival. Assessing early response to riluzole treatment may be an independent milestone that might be employed in prognostic models as well as prediction model based clinical trial analysis. Replication of this observation as well as further investigation of early non-responders with respect to riluzole pharmacokinetics may provide insights as to whether patients are treatment resistant or may need riluzole dose adjustment.

Acknowledgments: Supported by Muscular Dystrophy Association Care Center Grant, Atrium Health Foundation Carolinas ALS Funds as well as Pinstripes Foundation and ALS Charlotte Clinical Crew Funds.

References

Miller RG, et al. Cochrane Database Syst Rev. 2012;(3):CD001447.
Bensimon G, Lacomblez L, Meininger V. N Engl J Med. 1994;330(9):585–91.
Nakamura R, et al. J Neurol Neurosurg Psychiatry. 2013;84(12):1365–71.
Santos CL, et al. NeuroRehabilitation. 2016;38(4):395–400.
Slavin MD, et al. Arch Phys Med Rehabil. 1998;79(8):950–4.