DSP-01: A multi-centre longitudinal biofluid biomarker appraisal in ALS: The AMBRoSIA analysis.

Dr Elizabeth Gray1, Dr Alexander G Thompson1, Dr Nick Verber3, Ms Yoana Bobeva2, Dr Vittoria Lombardi2, Dr Stephanie R Shepheard1, Dr Ozlem Yildiz1, Dr Emily Feneberg1, Dr Lucy Farrimond1, Dr Thanuja Dharmadasa1, Mrs Pamela Gray1, Dr Evan C Edmond1, Dr Jakub Scaber1, Dr Delia Gagliardi1, Professor Janine Kirby3, Dr Thomas Jenkins3, Dr Pietro Fratta2, Professor Christopher McDermott3, Professor Kevin Talbot3, Professor Andrea Malaspina2, Professor Dame Pamela Shaw3, Professor Martin R Turner1

1University of Oxford, Oxford, United Kingdom, 2Queen Mary University of London, London, United Kingdom, 3SITRAN, University of Sheffield, Sheffield, United Kingdom

Background:
The development and integration of objective markers of disease activity in ALS is recognised as a key aim in advancing therapeutic development.

Objectives:
To appraise leading candidate biofluid biomarkers in the stratification and potential therapeutic monitoring of ALS patients.

Methods:
Blood, urine and cerebrospinal fluid (CSF) samples were collected at 3-6 monthly intervals in 258 patients diagnosed with ALS across three specialist tertiary referral clinics, with single timepoint sampling of 80 disease controls and 101 healthy controls. CSF levels of neurofilament light chain (NFL, using the MSDTM platform), chitotriosidase 1 (CHIT1) and P75 neutrophin receptor extracellular domain (P75ECD); plasma levels of NFL (MSDTM), complement C3, C4, creatine kinase (CK), ferritin and C-reactive protein (CRP); and urinary P75ECD levels were measured.

Results:
CSF NFL, CHIT1 and plasma NFL, CK and ferritin were all significantly elevated in ALS patients compared to other groups. Levels of P75ECD, C3, C4 and CRP did not differ significantly between patients and controls. Plasma NFL level, CSF NFL and CHIT1 levels were strongly associated with faster rate of disability progression, with weak associations noted with plasma C3 and C4. First visit plasma NFL level had a strong association with survival, independent of clinical prognostic factors. Individual longitudinal CSF NFL levels remained stable throughout, but a small increase was seen in plasma levels of those sampled within 12 months of symptom onset. An increase in CSF CHIT1 level was observed longitudinally. Modelling the inclusion of plasma NFL as a therapeutic trial outcome measure suggested earlier detection of response with smaller group sizes compared to reliance on a functional rating score.

Discussion and conclusion:
Through the unique power of a large multi-centre longitudinal cohort, the emerging value of plasma NFL measurement for the objective stratification of those diagnosed clinically with ALS has been strengthened. Furthermore, the modelling in this study now strongly supports the inclusion of plasma NFL levels in therapeutic trials as a potentially more sensitive marker of early disease-modifying effect.
DSP-02: A study validating the Italian version of self-administered ALSFRS-R scale

**Dr Luca Solero**, Dr Umberto Manera, Dr Sara Cabras, Dr Margherita Daviddi, Dr Rosario Vasta, Dr Maria Claudia Torrieri, Dr Francesca Palumbo, Dr Alessandro Bombaci, Dr Maurizio Grassano, Dr Laura Peotta, Dr Barbara Iazzolino, Dr Antonio Chiò, Dr Cristina Moglia

1Neuroscience Department, Turin University, Torino, Italy

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Objectives:
To assess the accuracy and validate the Italian version of self-administered ALSFRS-R (1), taking into account both the caregivers’ help and the patients’ clinical and cognitive features.

Methods:
From 27th March 2020 to 5th May 2020, a series of ALS patients were recruited during regular telemedicine follow-up assessments, performed in this modality by the Turin ALS Centre as a consequence of the lockdown measures. All patients met the revised El Escorial Criteria for defined, probable and probable-laboratory supported ALS. Through the analysis of the results of 70 paired self-administered vs standard telephone-administered ALSFRS-R, overall score, single items scores, ALSFRS-R domain scores, King’s and MiToS stage inter-rater agreement and reliability were calculated using different validated methods. We drafted the Italian version of self-administered ALSFRS-R following ENCALS recommendations (2).

Results:
Seventy patients (43 females, 61.4%) accepted to take part in the study. Correlation between the two scales was 0.94 and no systematic directional bias was found. Intraclass correlation coefficient (ICC) was very high (>0.90) for the vast majority of the considered classification criteria, especially King’s total score (0.96) and MiToS score (0.94). The overall ICC for ALSFRS-R did not differ according to sex or cognition, although it was slightly higher when patients answered the ALSFRS-R with the help of the caregiver (0.91 vs 0.95); patients who needed caregiver assistance in filling in the ALSFRS-R assessment were significantly older, had a more aggressive disease phenotype, higher motor impairment and/or impaired cognition.

Discussion:
In this study, we established that the self-assessed ALSFRS-R score is an accurate and reliable tool to monitor disease burden and progression. Furthermore, we demonstrated that its reliability increases with the possibility to complete the assessment with the assistance of a caregiver, since ALS patients present frequently with cognitive impairment even in the early stages of disease (3).

Conclusions:
Online self-administered ALSFRS-R scale is a valid tool to stratify ALS patients into clinical stages and to carry out telemedicine monitoring.

References:
DSP-03: A young girl presenting with unusual bulbar symptoms: a diagnostic and therapeutic challenge.

Dr Sara Cabras1, Dr Maurizio Grassano1, Dr Alessandro Bombaci1, Dr Antonio Canosa1,2, Prof Andrea Calvo1,2,3, Prof Adriano Chiò1,2,3,4, Dr Cristina Moglia1,2
1“Rita Levi Montalcini” Department of Neuroscience, University of Turin, Turin, Italy, 2Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy, 3Neuroscience Institute of Turin (NIT), Turin, Italy, 4Institute of Cognitive Sciences and Technologies, C.N.R., Rome, Italy

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Objective:
We report the case of a young girl presenting with unusual bulbar involvement to highlight the complexity of differential diagnosis and therapeutic attempts.

Case report:
A 23-year-old girl, with a history of bilateral hypoacusis, developed an important tongue oedema, along with consequent sialorrhea, speech and swallowing impairment following tonsillectomy. A local pharyngeal inflammation was hypothesized and treatment with antibiotics and steroids was started, without benefit. Few weeks later, she developed neck weakness, therefore neurophysiologic studies were performed, showing a neuromuscular junction disorder. As a confirm, myasthenia specific antibodies were tested and therapy with acetylcholinesterase inhibitors and steroids was attempted, with negative results. Electromyography (EMG) was then repeated, showing widespread denervation pattern. In the suspicion of an inflammatory neuropathy, both intravenous immunoglobulin and plasmapheresis were administered, without clinical response. The diagnostic process was completed with brain magnetic resonance, lumbar puncture, visual and brainstem auditory evoked potentials, total-body positron emission tomography (PET), tongue biopsy, infectious markers and autoantibodies: all investigations resulted normal.

During hospitalization, the patient presented a generalized tonic-clonic seizure following an acute dyspnœa, with need for oral intubation and tracheostomy for mechanical ventilation, as well as circulation support for an unexpected cardiovascular instability, then regressed. Based on the clinical findings, genetic testing for Brown-Vialetto-Van Laere syndrome and juvenile Amyotrophic Lateral Sclerosis (ALS) was requested, while riboflavin supplementation was started, although without benefit. Four months later, the presence of both lower and upper motor neuron signs with EMG demonstrating a lower motor neuron disorder, along with the positivity for FUS/TLS (fused in sarcoma/translocated in liposarcoma) mutation, confirmed the suspicion of juvenile ALS.

Discussion:
Despite the help of laboratory and instrumental investigations, diagnostic definition can be challenging. For example, low-frequency repetitive nerve stimulation and single-fiber EMG could result both positive in ALS cases, especially when examining proximal muscles in rapid progressors. Moreover, in our case the young age of the patient, not typical for ALS onset, the strange tongue oedema, in contrast to the classic atrophy, and the absence of upper motor neuron signs in the initial phase complicated the diagnostic process.

Conclusion:
In patients with complex diagnostic definition, considering different therapeutic strategies could be helpful not only to try everything possible to limit disabling symptoms, but also to support the final diagnosis excluding other possible causes responsive to treatments performed.

References:
DSP-04: ALS prediagnostic BMI trajectory diverges from controls and associates with poorer ALS survival

Dr Stephen Goutman¹, Mr. Jonathan Boss¹, Dr. Bhramar Mukherjee¹, Dr. Eva Feldman¹
¹University of Michigan, Ann Arbor, United States

Background:
Body weight and body mass index (BMI) have important associations with ALS. Body weight is inversely associated with ALS risk and weight loss is also associated with a poorer survival.

Objectives:
To determine if patterns of BMI change in ALS cases differ from controls in the 10 years prior to diagnosis and how these patterns associate with survival.

Methods:
ALS case and control participants were recruited from University of Michigan and provided written informed consent. Participants self-reported estimated body height and weight 10 years prior, 5 years prior, and at the time of diagnosis for cases and at the time of consent for controls. Generalized estimating equations compared the difference in BMI trajectories between cases and controls. Next, to determine prognostic significance of BMI trajectories in cases, longitudinal clustering of these trajectories was performed. Participants were then further divided by baseline BMI tertile. All-cause mortality was assessed in these cluster*BMI tertile groups via Cox proportional hazard and accelerated failure time (AFT) models. Models were adjusted for age, sex, and other ALS covariates.

Results:
Data from 373 ALS cases and 265 controls were available beginning with BMI 10 years prior. Average BMI at -10, -5, and 0 years for cases was 27.3, 28.0, and 26.3 and for controls 26.5, 27.6, and 27.6 kg/m² respectively, with a significant difference in trajectory between cases and controls (p<0.001). Longitudinal clustering of BMI trajectories in ALS cases defined 3 groups: participants with 1) overall increasing BMI, 2) overall stable BMI, and 3) overall decreasing BMI at the -10, -5, and 0 year intervals. Cox proportional hazard models violated proportional hazards, thus AFT models were used. ALS participants in the decreasing BMI trajectory cluster with a baseline BMI in the middle and upper tertiles had a reduction in survival of about 30% (p<0.05). Interestingly, ALS participants in the increasing BMI trajectory cluster that had a BMI in the upper tertile also had a marginally significant reduction in survival of 26% (p=0.109).

Discussion:
Our data show that ALS participants in the 10 years prior to diagnosis have a different BMI trajectory compared to control participants, and that importantly this trajectory changes within 5 years of diagnosis. Further, we find that participants with a decreasing BMI trajectory in the middle and upper BMI tertiles and with an increasing BMI trajectory in the upper BMI tertile may have a reduced ALS survival. Further replication of these findings with prospective cohorts is encouraged.
DSP-05: Anxiety shows a higher prognostic role in Amyotrophic Lateral Sclerosis than depression

Dr Umberto Manera1, Dr Barbara Iazzolino1, Dr Laura Peotta1, Dr Antonio Canosa1, Dr Francesca Palumbo1, Dr Paolina Salamone1, Dr Rosario Vasta1, Dr Cristina Moglia2, Prof Andrea Calvo2, Prof Adriano Chiò1

1Department Of Neuroscience, University Of Torino, Torino, Italy

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Background:
Psychological status has already been related to clinical outcome in ALS (1), without considering the specific role of anxiety and depression.

Introduction In the Turin ALS Centre, from 2008 to 2018, we collected all Hospital Anxiety and Depression scale (HADS) questionnaires administered at diagnosis to patients who underwent a wide neuropsychological evaluation. We assessed the prognostic role of anxiety and depression in ALS patients, adjusting for different motor and cognitive confounders.

Materials and Methods:
Survival analysis were performed for both depression (HADS-D) and anxiety (HADS-A) domains, using Cox proportional hazard models, adjusting for age, sex, education, ALSFRS-R score, ΔALSFRS-R, onset-diagnosis interval, cognitive categories and Kaplan-Maier curves.

Results:
Five hundred sixty-nine patients with HADS questionnaire and all complete data were collected. Survival was calculated until 1st January 2020. Median HADS-A score was 7 (IQR 5-10) and median HADS-D score was 5 (IQR 3-8): both scores showed moderate correlation (0.485, p<0.001). Depression was significantly correlated to age, total ALSFRS-R score and cognitive impairment, while anxiety showed only a minimal correlation to ALSFRS-R score (-0.108, p=0.022). Using standard cut-offs, 53.8% of patients resulted normal, 25.0% borderline, and 21.2% abnormal for HADS-A, while 71.8% of patients resulted normal, 17.4% borderline, and 10.8% abnormal for HADS-D. Cox proportional hazard model using raw scores showed that HADS-A, was related to overall survival (HADS-A: HR 1.040, CI 1.012-1.069, p=0.005; HADS-D: HR 1.013, CI 0.976-1.052, p=0.497) but not HADS-D. The best discriminating cut-off for both HADS-A was 6 (HR HADS-A>6 1.453, CI 1.151-1.835, p=0.002; log-rank test p=0.012): interestingly, HADS-D raw scores resulted to be prognostic only in patients with HADS-A >6 (HR HADS-D raw scores 1.059, CI 1.009-1.112, p=0.020; HR HADS-D>6 1.568, CI 1.078-2.281, p=0.019; log-rank test p=0.014).

Discussion:
Our results confirmed that anxiety is more frequent than depression in ALS patients at diagnosis (2) and, unlike depression, seems not to be related to particular motor or cognitive features or to disease duration (3). We pointed out that anxiety is not a simple epiphenomenon related to diagnostic challenge, but rather an independent prognostic factor, similarly to what is found in other non-neurological disease (4).

References:
DSP-06: Cardiovascular comorbidities in Amyotrophic Lateral Sclerosis

Doctor Marta Gromicho, Mariana Pereira, Ana Henriques, Ana Catarina Pronto-Laborinho, Julian Grosskreutz, Magdalena Kuźma-Kozakiewicz, Susanne Petri, Hilmi Uysal, Michael Swash, Mamede de Carvalho

Instituto De Medicina Molecular João Lobo Antunes, Faculdade De Medicina, Universidade De Lisboa, Lisbon, Portugal, Departamento de Estatistica e Investigação Operacional, Faculdade de Ciências, Universidade de Lisboa, Lisbon, Portugal, Hans-Berger Department of Neurology, Jena University Hospital, Jena, Germany, Department of Neurology, Medical University of Warsaw, Warsaw, Poland, Department of Neurology, Hannover Medical School, Hannover, Germany, Department of Neurology, Akdeniz University Faculty of Medicine, Antalya, Turkey, Barts and the London School of Medicine, Queen Mary University of London, London, UK, Departamento de Neurociências e Saúde Mental, Hospital de Santa Maria - Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

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Background:
The role of cardiovascular risk factors in amyotrophic lateral sclerosis (ALS) is controversial. A favourable profile has been found in ALS patients, but previous studies have not specifically considered the profile in different disease phenotypes.

Methods:
Demographic data, smoking habits, lifetime exercise, and medical history including diabetes mellitus, hypertension, hypercholesterolemia, hypertriglyceridemia, stroke, and cardiac events, were analysed in ALS patients and in controls with other neurological disorders, utilising a standardized questionnaire applied by the same neurologist. In ALS patients the results were analysed according to their different phenotypes. Univariate analyses and multinomial logistic models were applied to estimate the odds ratios (ORs) and confidence intervals (CIs) for covariates, to test potential modifiers and their effects.

Results:
500 consecutively assessed adult ALS patients (mean age 65.6, 47% women, and 136 bulbar-onset) and 327 age and gender-matched controls were studied. Hypertension was more frequent in women with bulbar-onset ALS (p=0.006). Patients with spinal-onset ALS took more exercise (p=0.012), reported less hypertension (p=0.002) and had fewer cardiac events (p=0.012) and, for these two comorbidities in men, differences were observed (hypertension, p<0.001; cardiac events, p=0.015). Multinomial regression analysis indicated that hypertension as comorbidity had a potential protective effect against the development of spinal and bulbar-onset ALS in men.

Conclusions:
Gender as a modifier of hypertension may have a protective effect in ALS, since men without hypertension have an increased risk of disease. However, a protective effect of vigorous exercise cannot be excluded. Future research should consider these factors in the different ALS phenotypes.
DSP-07: Methodology of a pilot study of endurance tasks to measure performance fatigue in ALS

Katherine Burke¹, Mackenzie Keegan¹, Zoe Scheier¹, Ella Collins¹, Minhaj Rahman¹, Dr. James Berry¹, Dr. Sheena Chew¹
¹Massachusetts General Hospital Healey Center for ALS, Boston, United States

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Background:
Fatigue is a prevalent, bothersome, and undertreated symptom in patients with amyotrophic lateral sclerosis (ALS). Measuring fatigue is challenging because multiple factors may contribute to the patient experience of fatigue, such as tiredness, mental fatigue, and motor fatigue.

Objective:
This pilot study will evaluate the feasibility of using three endurance tasks to evaluate motor performance fatigue, defined as a temporary decline in aspects of motor performance such as peak force, power, speed and accuracy. We hypothesize that motor performance fatigue is a key component of the general experience of fatigue in patients with ALS.

Methods:
We will enroll 15 participants with ALS and 15 age-matched healthy volunteers. Participants with ALS must have a score of 14 or higher on the Neurological Fatigue Index – Motor Neuron Disease (NFI-MND) scale and have the ability to ambulate without assistance from another person. Participants will complete questionnaires measuring patient-reported fatigue, complete routine ALS clinical measures including the Revised ALS Functional Rating Scale (ALSFRS-R) and slow vital capacity, and perform the three endurance tasks (endurance shuttle walk test, endurance shuttle box and block test, and endurance shuttle nine hole peg test).

For each of the endurance tasks, participants will complete an estimation of maximal performance followed by a submaximal endurance task at 75% maximal intensity for as long as possible, up to 20 minutes. Perceived exertion will be asked throughout the tasks. Participants will be asked to rate acceptability, comprehensibility, perceived burden and perceived fatigue for each of the tasks. Digital tools will be utilized to collect physiologic data and measurements of body movements in three dimensions.

Results:
If enrollment has begun, results to date will be presented.

Discussion/Conclusions:
If the endurance tasks are feasible and acceptable, a follow-up study would be proposed to measure motor fatigue and its relationship to ALS disease characteristics and patient-reported fatigue in patients with ALS compared to healthy volunteers. Developing and validating objective measures of motor performance fatigue that relate to the patient experience of fatigue in ALS will enable an assessment of efficacy of therapeutics aimed at treating fatigue in ALS.
Background:
Studies concerning young-adult amyotrophic lateral sclerosis (yALS) are uncommon, due to the rarity of this condition.

Objectives:
We aimed to investigate this subject.

Methods:
A retrospective-prospective study was conducted in our ALS center, including 1278 ALS patients followed longitudinally. We included patients with the initial diagnosis of progressive muscular atrophy and ALS. ALS patients attained the categories of definite, probable, probable laboratory-supported and possible disease, as defined by the revised El Escorial criteria and supported by the Awaji guidelines, during the clinical follow-up. Patients with other neurological conditions and without progression were excluded. Familial ALS was defined by at least one first- or second-degree affected relative; the remainder patients were classified as sporadic. Patients were divided in two groups - yALS (onset ≤40 years) and adult-onset ALS (aALS, onset >40 years). We analyzed phenotype, survival and genetics. Comparisons between yALS and aALS were performed using Chi-square and Fisher’s exact test for categorical variables, and Student’s t-test for continuous data. Survival was defined as the time from symptom onset to death. December 31, 2019 was considered as the censor date. Univariate survival modelling was performed using Kaplan-Meier log-rank test. The Cox proportional hazards regression model with a backward stepwise method was used to assess the effects of confounders on survival. A p value of <0.05 was considered as statistically significant.

Results:
Sixty-three out of 1278 (4.9%) patients were included in yALS group, while the majority were categorized as aALS (1215, 95.1%). Juvenile ALS (onset <25 years) represented 14.3% (9 patients) of yALS. In yALS group mean onset age was 32.5±6.6 years (14–40) and 68.3% were men. Spinal-onset was significantly more frequent in yALS (p<0.001), while bulbar onset was more common in aALS (p=0.002). Diagnostic delay was longer in yALS group (p=0.02). yALS patients survived longer than aALS (88.2±81.9 versus 41.1±34, p<0.001), and functional decay was the only independent predictor found in the younger group (p=0.007). No other significant differences were found, including familial history of ALS. Three yALS patients (4.8%) had C9orf72, SOD1 and FUS mutations identified by single-gene testing. A panel of 50 ALS-related genes investigated with next-generation sequencing in 9 yALS patients revealed no pathogenic mutation.

Conclusions:
yALS is a rare and specific ALS group. Disease progression is slower and survival longer in yALS, moreover and bulbar-onset phenotype is less common than in aALS. These observations are relevant to inform patients and for clinical trials design.
DSP-09: Comparison of individual disease courses in partner centers of the ONWebDUALS project applying the D50 model

Mrs Beatrice Stubendorff¹, Marta Gromicho², Katarzyna Szacka³, Nora Hertel⁴, Mamede de Carvalho⁵, Magdalena Kuźma-Kozakiewicz³, Susanne Petri⁴, Hilmi Uysal⁶, Julian Grosskreutz¹

¹Hans-Berger Department of Neurology, Jena University Hospital, Jena, Germany, ²Instituto de Medicina Molecular, Instituto de Fisiologia, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal, ³Department of Neurology, Medical University of Warsaw, Warsaw, Poland, ⁴Department of Neurology, Hannover Medical School, Hannover, Germany, ⁵Department of Neurosciences and Mental Health, Hospital de Santa Maria-CHLN, Lisbon, Portugal, ⁶Department of Neurology, Akdeniz University Faculty of Medicine, Antalya, Turkey

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Background:
Amyotrophic Lateral Sclerosis (ALS) is characterized by profound phenotypic heterogeneity including different genetic and environmental risk factors. By incorporating data sets from different European countries, ONWebDUALS aimed to understand ALS related risks and prognostic factors in order to enhance patient characterization.

Objectives:
To analyze randomly collected clinical data from 5 European 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 D50 model uses available ALSFRS-R scores to describe disease progression in a sigmoidal state transition from full health to complete functional loss. The model yields parameters of overall disease aggressiveness: D50, dx and descriptors of local disease activity: calculated functional loss (cFL) and functional state (cFS). Normalizing individual D50 values yields relative D50 (rD50), a value describing disease course covered. rD50 allows aligning of different disease courses in a normalized framework and categorizing of patients into disease phases. Kaplan-Meier curves and log-rank test were used for “time-to-event” analysis. Statistical significance was set at p<0.01.

Results:
The D50 model was used to simulate the disease course of 1459 patients from 5 European centers. A significant correlation between D50 and dx was noted (r=0.97). Forty-two and 55% of all consultations occurred in disease phases I and II, respectively. All disease-related events could be relatively staged from disease onset i.e. rD50: 1st consultation at rD50=0.06; spread to 2nd region at rD50=0.14; formal diagnosis at rD50=0.20; spread to 3rd region at rD50=0.24; invasive ventilation at rD50=0.58; and death at rD50=0.70. Finally, cFS and cFL calculation resulted in 46±3 and 0.6±0.7 at 1st consultation; 44±5 and 0.7±0.9 at spread to 2nd region; 43±6 and 0.8±1.0 at spread to 3rd region; 41±6 and 0.9±1.0 at formal diagnosis; 22±11 and 1.4±1.5 at invasive ventilation and 17±10 and 1.1±0.8 at death.

Discussion:
The D50 model provides meaningful descriptors of overall disease aggressiveness, local disease activity, and a unified linear scale to describe disease progression. It allows the staging of individual events; provides a way to pseudo-longitudinally interpret cross-sectional data and efficiently compares the composition of cohorts from different geographic regions. Furthermore, it enables to distinguish between disease progressors and to analyze disease related events in a relative way revealing novel perspectives of the disease. This might be helpful in order to develop new strategies for ALS treatment.

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DSP-10: Development of Novel Dexterity Sensor in Amyotrophic Lateral Sclerosis

Mr Conor D Hayden¹, Dr. Bruce P Murphy¹, Dr. Dara Meldrum¹, Prof. Orla Hardiman¹,², Dr. Deirdre Murray¹,²
¹Trinity College Dublin, Dublin 2, Ireland, ²Beaumont Hospital, Dublin 9, Ireland

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Background:
The Finger Tapping Test (FTT) is a widely used measure in neurological practice (Ashendorf et al., 2009). The index finger is tapped against the thumb, while the clinician judges whether the movement is normal or abnormal by visual examination of the movement. This visual grading is subjective and insensitive to small but meaningful changes.

Objective:
To develop and test a novel sensor device that digitises the FTT and provides a sensitive, objective measure of hand function, that is clinically meaningful and practical.

Methods:
A novel dexterity device containing a magnetic encoder was developed, which is placed on the thumb and index finger. During FTT with the device, a sinusoidal wave is produced, from which the frequency, amplitude, velocity and accuracy are determined. Initial testing was completed on a small group of patients and healthy controls, who provided informed consent. Patients’ upper limb function was quantified using traditional methods, including 9-hole peg test (9HPT) and the DASH questionnaire. The time to complete 10 taps (TTC) and the average finger extension height (EH) were examined. The study was approved by Beaumont Hospital and Trinity College Dublin ethics committees.

Results:
10 healthy controls (ages 24 –70, 6 males) and 8 patients (ages 49 - 73, 5 males, 3 PLS, 5 ALS) completed the assessment. There was wide variation in the level of upper limb impairment (9HPT mean score 31.1±14.8 seconds (2 unable), DASH 41.2±29.7). The TTC for the healthy controls and patients (n=6 completed), using their right hands, were 5.4 ± 0.7 seconds and 17.9 ± 0.8 seconds respectively (p=0.016) and the EH were 11.4 ± 1.9 cm and 9.9 ± 3.6.cm respectively (p= 0.394). The test required less than 5 minutes.

Discussion:
Initial testing on a small group of healthy people and patients with MND showed that the novel dexterity device was able to distinguish between them. Two patients were unable to complete the test due to severe hand weakness, indicating a floor effect. The patients who completed the FTT achieved similar amplitudes (EH) to the healthy controls, but took significantly longer to complete the task, which was most likely due to weakness and / or spasticity. Differences in EH between patients’ weaker and stronger hands was noted. A final prototype has now been developed based on this testing and user feedback, which requires extensive testing, but shows potential as a sensitive, accurate and clinically practical tool, which will allow objective measurement of changes in hand function.

References:

Acknowledgements:
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DSP-11: Genetic modifiers and phenotypic heterogeneity within ALS kindreds

Dr Marie Ryan1,2, Mr Mark Heverin1, Prof Russell McLaughlin3, Prof Niall Pender4, Prof Orla Hardiman1,2
1Academic Unit of Neurology, Trinity College Dublin, Dublin, Ireland, 2Department of Neurology, Beaumont Hospital, Dublin, Ireland, 3Smurfit Institute of Genetics, Trinity College Dublin, Dublin, Ireland, 4Department of Psychology, Beaumont Hospital, Dublin, Ireland

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Background:
While genetic factors play an important role in one’s risk of developing ALS (1), less is known about the relative importance of genetic modifiers to the clinical phenotype. Familial forms of ALS are both associated with a greater burden of ALS risk genes and are clinically characterised by younger mean age of symptom onset (2). However, while clinical heterogeneity is a consistent feature of ALS, those with familial ALS may harbour expectations that their clinical presentation and course will mirror that of their affected relative.

Objective:
To determine the extent of clinical heterogeneity within ALS kindreds.

Methods:
130 familial ALS kindreds were identified using the Irish ALS register (1995 – 2020). First-degree relative ALS pairs with complete data on both relatives were analysed in respect to age of symptom onset, site of onset and survival from diagnosis. Intrafamilial difference in age of onset and survival from diagnosis was determined by calculating the difference in age of onset and survival for each patient from that of their paired relative. C9orf72 repeat expansion testing using repeat-primed PCR was performed on all available DNA samples.

Results:
37 ALS first-degree relative pairs were identified (27 sibling-sibling, 10 parent-offspring). 22/34 (65%) pairs carried the pathogenic C9orf72 repeat expansion. Sibling pairs showed strong correlation in age of onset of ALS symptoms, independent of C9orf72 status (mean age onset 60.4 years [95%CI 57.3 – 63.5], mean intrafamilial difference age onset 8 years [95%CI 5.7 – 10.3], p=0.02). Parent-offspring pairs showed marked variability in age of symptom onset (mean intrafamilial difference age onset 19 years [95%CI 11.1 – 26.9], interquartile range 6.0 – 30.3). 12/32 (37%) pairs were discordant for site of onset of ALS and marked intrafamilial variability in survival from diagnosis (mean intrafamilial difference survival 15.3 months 95%CI 9.9 – 17.9) was observed. Neither individual site of onset or survival from diagnosis were predictive of same in relatives (site onset p=0.16, survival from diagnosis p=0.21).

Conclusion:
Marked phenotypic heterogeneity exists within ALS kindreds. Age of onset of ALS symptoms showed the strongest clinical correlation between relatives, independent of C9orf72 status, supporting the important role for ALS modifier genes play in determining age of disease onset.

References:

Acknowledgements:
We would like to thank patients and their relatives for taking part in the study. Funding for this study was provided by Science Foundation Ireland and Research Motor Neurone.
Amyotrophic Lateral Sclerosis (ALS) is an inexorably progressive neurodegenerative condition with no effective disease modifying therapy at present. Given the striking clinical heterogeneity of the condition, the development and validation of reliable prognostic models is a recognised research priority. We present a prognostic model for functional decline in ALS where outcome uncertainty is taken into account. Patient data were reduced and projected onto a 2D space using Uniform Manifold Approximation and Projection (UMAP), a novel non-linear dimension reduction technique. Information from 3,756 patients was included. Development data were sourced from past clinical trials. Real-world population data were used as validation data. Predictors included age, gender, region of onset, symptom duration, weight at baseline, functional impairment, and estimated rate of functional loss. UMAP projection of patients showed an informative 2D data distribution. As limited data availability precluded complex model designs, the projection was divided into three zones defined by a functional impairment range probability. Zone membership allowed individual patient prediction. Patients belonging to the first zone had a probability of 83% (+/- 3%) to have an ALSFRS score over 20 at one year follow up. Patients within the second zone had probability of 89% (+/- 4%) to have an ALSFRS score between 10 and 30 at one year follow up. Finally, patients within the third zone had a probability of 88% (+/- 7%) to have an ALSFRS score lower than 20 at one year follow up. This approach requires a limited set of features, is easily updated, improves with additional patient data, and accounts for results uncertainty. This method could therefore be used in a clinical setting for patient stratification and outcome projection.
DSP-13: Neck flexors weakness at diagnosis predicts respiratory impairment in Amyotrophic Lateral Sclerosis

**Dr Rosario Vasta**1, Dr. Maria Claudia Torrieri1, Dr. Fabrizio D'Ovidio1, Ms Alberta Circiello1, Dr. Filippo De Mattei1, Dr. Umberto Manera1, Dr. Antonio Canosa1,2, Professor Andrea Calvo1,2, Professor Adriano Chio1,2, Dr. Cristina Moglia1,2

1ALS Center, Department of Neuroscience, University of Turin, Turin, Italy, 2Neurology 1, AOU Città della Salute e della Scienza di Torino, Turin, Italy

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**Background:**
The prediction of the exact evolution of ALS remains elusive and many elements are likely to be involved(1). Few studies suggested that weakness of neck flexors muscles at diagnosis could be prognostic in ALS(2-4).

**Objectives:**
To assess the prognostic role of neck muscles weakness at diagnosis in Amyotrophic Lateral Sclerosis (ALS) patients with respect to survival and respiratory impairment.

**Methods:**
We conducted a retrospective cohort study. All ALS patients seen in the Turin ALS Center from 2007 to 2014 were included. Muscles strength at diagnosis was evaluated using the Medical Research Council (MRC) scale. Survival was considered as time from diagnosis to death or tracheostomy; time to respiratory impairment was considered as the interval from diagnosis to the first event among ALSFRSr 10 item <4, forced vital capacity <70%, start of non-invasive ventilation or tracheostomy. Time from diagnosis to dysarthria, dysphagia and walking impairment were considered as secondary outcomes. Cox proportional Hazard regression models adjusted by sex, age at diagnosis, diagnostic delay, onset site, genetics status and other muscles groups MRC scores were used to assess the prognostic role of neck muscles.

**Results:**
A total of 370 patients were included in the study. Fifty-nine (15.9%) patients showed neck flexors weakness at diagnosis; MRC values were mostly concord for neck extensors. Neck flexors were the only muscles able to predict survival (HR 0.49, 95% CI 0.28 – 0.86; p=0.01). Furthermore, neck flexors normal strength decreased the risk of respiratory impairment (HR = 0.46, 95% CI 0.22-0.96; p=0.04) but did not influence any secondary outcomes.

**Discussion:**
Neck flexors weakness at diagnosis predicts survival and respiratory impairment in ALS. We believe this result could be valuable for both planning of patients’ interventions and clinical trials’ design.

**References:**
DSP-14: TBK1 mutation in patients with Amyotrophic Lateral Sclerosis: a genotype/phenotype heterogeneity.

Dr Fabiola De Marchi1, Dr Lucia Corrado2, Dr Roberta Croce2, Dr Alice Di Pierro2, Dr Nadia Barizzone2, Prof Roberto Cantello1, Prof Sandra D’Alfonso2, Dr Letizia Mazzini1

1Department of Neurology and ALS Centre, University of Piemonte Orientale, Maggiore della Carità Hospital, Novara, Italy, 2Interdisciplinary Research Center of Autoimmune Diseases, "Amedeo Avogadro" University of Piemonte Orientale, Novara, Italy

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Background:
Mutations in TANK-binding kinase 1 (TBK1) are typically associated with Amyotrophic Lateral Sclerosis/ Frontotemporal Dementia (ALS/FTD). TBK1 is a serine/threonine protein kinase involved in many signaling pathway acting as key player in autophagy and innate immunity. Insufficient regulation of TBK1 activity can lead to autoimmune, neurodegenerative diseases or tumor-igenesis. Many ALS-linked TBK1 mutations are already described in literature (i.e. missense, splicing, non-sense). In this case series, we have investigated the clinical genotype/phenotype heterogeneity of 4 patients with different mutations in TBK1.

Material:
Patient 1: a 52-year-old man presented with a two-year history of progressive dysarthria, dysphagia and right arm hypotrophy. He had a history of relapsing-remitting multiple sclerosis (age of diagnosis: 26 years). His younger sister has optic neuritis, his father has myasthenia gravis. Neurological examination disclosed upper cingulate hypotrophy and weakness, bilaterally, dysphagia and dysarthria. Neurocognitive evaluation shown frontotemporal mild cognitive impairment (ALS-bi). Genetic analysis revealed the presence of c.922 C>T, p.R308X (NM_013254) mutation in heterozygous status in exon 8 of TBK1 gene (new mutation).

Patient 2: a 71-year-old man presented with a muscle weakness and hypotrophy in the upper limbs, bilaterally (> left) and mood disorders in the last two years. His father died at age 47 from an unclear neurological disease. Clinically he showed a prevalent lower motor neuron syndrome, with diffuse muscle hypotrophy and weakness. The neurocognitive examination, showed severe deficit in mnesic, executive and behavioral (apathy) functions (ALS-FTD). Genetic analysis revealed the presence of the c.992+1G>A heterozygous splicing mutation in exon 8 donor site causing an in-frame exon skipping.

Patient 3: a 64-year-old woman presented with mild muscular weakness in the left leg, dysarthria and occasional dysphagia. No history of neurodegenerative or psychiatric disease was present in her relatives. She had a history of a late-onset Obsessive-Compulsive disorder with high state of anxiety, egodystonic obsessions and repetitive behaviors. Clinically, she had a spastic diplegia, mild weakness of proximal muscles and asymmetric pyramidal signs in upper and lower limbs side. The neurocognitive examination was compatible with FTD. Genetic analysis revealed the presence of the c.358+3A>G heterozygous splicing mutation in intron 4 of TBK1 gene resulting in partially intron 4 retention and frameshift.

Discussion:
Our clinical data support and confirm the hypothesis that TBK1 pathogenic variants have considerable geno- phenotypic heterogeneity within the ALS/FTD spectrum, both in terms of age of onset (52-71 yrs), clinical presentation (upper or lower motor neuron), phenotype (spinal or bulbar) and type of cognitive/behavioral involvement.
DSP-15: Using Active Digital Phenotyping to Quantify Function and Cognition in Amyotrophic Lateral Sclerosis (ALS)

Mackenzie Keegan1, Zoe Sheier1, Ella Collins1, Katherine Burke1, Kelley Erb2, Tairrmae Kangarloo2, Dr. Krzysztof Gajos3, Dr. Sheena Chew1, Dr Anoopum Gupta1, Dr James Berry1

1Massachusetts General Hospital, Boston, United States, 2Biogen, Inc, Cambridge, United States, 3Harvard School of Engineering and Applied Sciences, Cambridge, United States

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Background: Amyotrophic lateral sclerosis (ALS) clinical trials employ traditionally accepted outcome measures such as the revised ALS Functional Rating Scale (ALSFRS-R), vital capacity (VC), and handheld dynamometry (HHD). Active digital phenotyping (ADP), in which human phenotype data is gathered during diagnostic tasks that people perform on digital devices may provide less subjective, more quantitative, and more granular measurements of function than these traditional outcomes.

Methods: The study consists of two in-person visits separated by one week. At each visit, participants complete traditional ALS outcome measures. They also complete cognitive assessments designed to evaluate executive function on a tablet-based platform (TabCAT) and digital phenotyping using recordings from high frame-rate video and research-grade accelerometer/gyroscope devices during tasks such as computer mouse clicking. Participants then complete motor and cognitive tasks run on an Apple Watch and iPhone on alternating days between their two visits. The study is currently being revised to add 24 weeks of remote monitoring, where participants complete the tasks on the Apple Watch and iPhone. Available data from both study designs will be presented.

Results: Eight participants have completed the study (6 ALS and 2 control). Multiple computer mouse task features have a test-retest reliability > 0.8 and correlate well (r>0.8) with at least one of the relevant ALSFRS-R questions or muscle strength recordings. These features include movement time, click duration, execution time, movement direction changes, and normalized jerk. The Social Norms Questionnaire (SNQ) on TabCAT shows a test-retest reliability of >0.9 and correlates with ALSFRS-R total score (r=0.84). iPhone-based alternating finger tapping is also reduced in PALS and associated with ALSFRS fine motor scores.

Discussion: This deep phenotyping study is helping to understand the utility of a variety of digital tools in ALS, to compare these tools to traditional ALS outcome measures, and to extend our ability to assess cognition in people with ALS. Early results suggest at least a subset of the digital tests included in this study may have promise as reliable measurements of function and cognition in people with ALS.
Background and Objectives:
Mutations in SOD1, C9orf72, TARDBP, and FUS/TLS genes have been associated with familial amyotrophic lateral sclerosis (FALS). Our objective was to determine the distribution of the most commonly mutated genes, and genotype/phenotype associations in Chinese FALS patients.

Methods:
We collected the clinical data of 103 ALS families in a study of genetic linkage from 2008 to 2012. 58 families have been screened originally for SOD1 molecular genetic analysis, 39 SOD1-negative probands were screened for TARDBP, and 34 SOD1- and TARDBP-negative samples were screened for FUS. To detect abnormal C9ORF72 repeat expansion in all samples using a repeat-primed PCR assay. Ultimately, we performed phenotype-genotype correlations with mutation in Chinese patients with FALS.

Results:
Clinical data could be partially recovered for up to 559 relatives belonging to the total 103 analyzed families, and the male-to-female ratio was 1.3:1, with a mean age of onset of 43.8±13.0 (95%CI 38.8-48.6), from 11 to 80. The average duration from the symptom to diagnosis was 56.9±61.6 (95%CI 51.0-62.5) months. The average duration from the symptom to death or censoring (information traced to Apr, 2015) was 97.2±73.3 (95%CI 86.4-108.2) months. A mean lifespan (age at death or censoring) was 51.7 years, from only 16 years to 82 years. 20 pathogenic missense mutations from 32 different families were found in 32 probands (19 SOD1 (32.8%), 1 C9orf72 (1.7%), 5 TARDBP (8.6%) and 7 FUS (12.1%)) and all were not detected in controls. The survival of FALS cases seemed longer, but bulbar-onset ALS and the male-to-female ratio were lower than reported. Clinical comparison of SOD1, TARDBP, FUS and other familial ALS patients revealed differences in site of onset (predominantly upper limbs for SOD1 and FUS and bulbar for TARDBP mutations), age of onset (older with SOD1 and TARDBP mutations), and in lifespan (shorter for FUS mutation). Our SOD1 patients had heterogeneous survival time with bimodal distribution and FUS also had rapid disease duration.

Conclusion:
We showed genetic associations with ALS and provide phenotype-genotype correlations with mutation in Chinese patients with FALS. This study substantially advances the understanding of the clinical features and epidemiology of this rare disease.
DSP-17: Family history of neurodegenerative disorders in patients with amyotrophic lateral sclerosis: population-based case–control study

Catarina Falcão Campos, Marta Gromicho, Hilmi Uysal, Julian Grosskreutz, Magdalena Kuzma-Kozakiewicz, Susana Pinto, Susanne Petri, Mamede de Carvalho

1Instituto De Medicina Molecular João Lobo Antunes, Faculdade De Medicina, Universidade De Lisboa, Lisbon, Portugal, 2Department of Neurosciences and Mental Health, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa-Norte, Lisbon, Portugal, 3Department of Neurology and Clinical Neurophysiology, Akdeniz University Faculty of Medicine, Antalya, Turkey, 4Hans Berger Department of Neurology, Jena University Hospital, Jena, Germany, 5Neurodegenerative Disease Research Group, Medical University of Warsaw, Warsaw, Poland, 6Department of Neurology, Hannover Medical School, Hannover, Germany

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Background:
A positive family history of neurodegenerative disorders (NDs) can be associated with amyotrophic lateral sclerosis (ALS) development. We aimed to describe the family aggregation of ND within the group of patients with ALS and to estimate the risk of ALS development in patients with a positive family history of ND, such as, ALS, frontotemporal dementia (FTD), Alzheimer’s disease (AD) and Parkinson’s disease (PD).

Methods:
A prospective case-control study was conducted during 2005-2018 in a Portuguese reference ALS clinic. Information about family history of ALS, FTD, AD and PD, concerning ALS patients (n=496) and controls (n=304) was obtained through a standardized questionnaire. Adult Portuguese patients with definite, probable laboratory-supported and possible ALS according to the revised El-Escorial criteria, progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS) were included. Subjects referred to our ALS clinic, in whom motor neuron disease or other ND diagnosis was excluded, were used as controls (e.g., patients with spinal cord lesion, root lesion, plexopathy, nerve entrapment, motor neuropathies, benign fasciculations syndrome, myasthenia gravis, inclusion body myositis and unspecific symptoms). Student t-test or the Mann-Whitney U-test was used as appropriate to compare continuous variables and Chi-square test to compare categorical data between populations. Adjusted ORs were calculated through a logistic regression analysis in order to assess the risk of ALS in subjects with a positive family history of ND, namely, ALS, FTD, AD and PD. A p value of <0.05 was considered statistically significant.

Results:
Approximately 8.5% of patients with ALS were classified as familial ALS/FTD, but a positive familial history was observed in only 3% of the patients with PMA. A positive family history of ALS and FTD was significantly higher in the ALS group, including the first-degree relatives, as compared with controls. However, patients with ALS did not have an increased prevalence of other NDs, namely, AD and PD. Even after adjusting for potential confounders, the risk of developing ALS in subjects was significantly higher in patients with a positive family history of ALS (OR 7.3; 95% CI 2.2-24.1) and FTD (OR 8.7; 95% CI 1.2-66.5).

Conclusion:
A positive family history of ALS/FTD, but not PD and AD, increases the risk of ALS, supporting the definition of ALS/FTD continuum. The absence of association between family history of AD or PD and ALS suggests distinct etiopathogenic mechanisms among these disorders. These findings may be considered for proper counselling of patients with a positive family history of ND, regarding the risk of ALS development.
DSP-18: Progressive muscular atrophy with likely inflammatory component partially responsive to immunomodulatory treatment

Dr Alessandra Govoni1, Dr Costanza Simoncini1, Dr Erika Schirinzi1, Dr Lorenzo Fontanelli1, Dr Elena Caldarazzo Ienco1, Dr Lucia Chico1, Dr Chiara Pizzanelli1, Prof Gabriele Siciliano1
1Neurological Clinics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

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Due to the lack of suitable biomarkers, differential diagnosis within the different forms of involvement of lower motor neurone is often difficult and challenging. We present the case of a 50 year old man who developed, from the age of 44 year, progressive distal weakness at left lower leg with contralateral leg and also proximal districts upper limbs involvement over the years. He has been wheelchair bound since the age of 46 and he never manifested bulbar involvement. Diagnostic investigations highlighted clinical and electromyographic alterations compatible with involvement of the lower motor neuron. The patient has not family history for motor neuron diseases (MND). He had previously diagnosed for hemochromatosis (heterozygosity of variant H63D) and treated with bloodletting until the age of 39. SOD, FUS, TDP43, NEFL, MFN2, GDAP1, SMA and AR genes analyses were normal.

The recent neurophysiological observation confirmed total denervation in the majority of lower limb muscle districts and severe motor unit loss with neurogenic damage in still innervated muscles, while it detected impaired sensitive conduction at the ulnar nerve bilaterally and at left sural nerve, without alterations in sensitivity at physical examination. Patient then underwent new diagnostic tests: the CSF examination was normal, brain and spinal cord MRI did not show significant alterations along the pyramidal corticospinal tract, analysis of the TTR gene did not detect mutations and periumbilical fat sample resulted negative for amyloidosis. At blood test VEGF and light chains lambda values were increased (516 pg/ml and 314 mg/dl respectively), not associated with hematopoietic disorders according to hematological opinion. Neoplastic, paraneoplastic and infectious screenings were negative, while a weak positivity (1:80) for serum ANA autoantibody titer was found at rheumatologic screening. We decided to treat the patient with intravenous immunoglobulins (at a dosage of 0.4 g/kg/day) monthly. Soon after the second month patient showed improvement of clinical condition, he is now able to keep the knee flexed in bedrest position, as well as sensitive potentials’ amplitudes of the nerves studied at the lower limbs improved.

Although we could not perform a motor nerve diagnosis, the long duration of illness without involvement of the first motor neuron likely figures out the present case as progressive muscular atrophy. While the possible role of hemochromatosis in the pathogenesis of MND remains controversial, laboratory findings as well as improvement observed after immunomodulatory treatment seem to suggest that in this case part of the pathogenesis is determined by an inflammatory-based mechanism.
DSP-19: Sequence of arm muscle weakness suggests cortical/network influences over contiguous spread of neurodegeneration in ALS spinal cord.

Dr. Nimish Thakore¹, Dr. Brian Drawert², Dr. Brittany Lapin¹, Dr. Erik Pioro¹
¹Cleveland Clinic, Cleveland, United States, ²University of North Carolina, Asheville, USA

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Background:
Contiguous and network spread of neurodegeneration, cortical influences, and compensatory reinnervation influence evolution of extremity weakness in amyotrophic lateral sclerosis (ALS). Dissociated muscle atrophy is recognised, notably the ‘split hand’, and the recently proposed ‘split elbow’.

Objective:
Examine sequence of weakness in arm muscles from longitudinal handheld dynamometry (HHD) data in ALS for congruence with contiguous spread of neurodegeneration along spinal cord segments.

Methods:
Longitudinal HHD data from the Ceftriaxone clinical trial was examined using nonlinear mixed models, assuming a logistic trajectory from normal to zero strength. Time from onset to midway strength (TOMS) was estimated for each muscle group and TOMS ratios were examined to identify sequence of weakness, overall and by onset site.

Results:
Shoulder flexion (SF), elbow flexion (EF), elbow extension (EE), wrist extension (WE) and first dorsal interosseous (FDI) were measured on each side. Over a median of 36 weeks, 513 subjects provided 2,589 sets of HHD measures. TOMS increased sequentially in the following order: FDI, WE, SF, EF, and EE. TOMS ratios estimates with 95% CIs (adjusted for multiple comparisons) were: WE/FDI 1.32 (1.24-1.41), SF/WE 1.06 (1.01-1.10), EF/SF 1.06 (1.02-1.10), EE/EF 1.18 (1.12-1.23). Elbow flexors weakened sooner than did elbow extensors. The sequence of arm muscle weakness progression was similar regardless of onset site.

Conclusions:
Nonsegmental progression of arm muscle weakness that is similar for different onset sites favors cortical influence/network spread over contiguous spread of neurodegeneration in the spinal cord. Furthermore, this study confirms the ‘split elbow’ pattern.
DSP-20: Spectral EEG measures identify clusters of ALS patients not discoverable by clinical data

Stefan Dukic1,2, Roisin McMackin1, Emmet Costello1, Marjorie Metzger1, Teresa Buxo1, Antonio Fasano1, Rangarirayo Ash Chipika1, Marta Pinto-Grau1, Christina Schuster1, Michaela Hammond1, Mark Heverin1, Amina Coffey2, Michael Broderick2, Parameswaran Iyer1, Kieran Mohr1, Brighid Gavin1, Niall Pender1, Peter Bede3, Muthuraman Muthuraman5, Leonard van den Berg2, Bahman Nasseroleslami1, Orla Hardiman1,6,7

1Academic Unit of Neurology, Trinity College Dublin, Dublin, Ireland, 2Department of Neurology, University Medical Centre Utrecht, Utrecht, The Netherlands, 3Computational Neuroimaging Group, Trinity College Dublin, Dublin, Ireland, 4Trinity Centre for Bioengineering, Trinity College Dublin, Dublin, Ireland, 5Department of Neurology, Johannes-Gutenberg-University Hospital, Mainz, Germany, 6Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland, 7Department of Neurology, Beaumont Hospital, Dublin, Ireland

Results:
Statistical analysis of two cluster separability indices estimating the optimal number of phenotypes (k) was used. Neurophysiological, clinical and survival profiles were determined for the optimal number of clusters. Further, accuracy and robustness of the analyses were assessed by randomly leaving out five patients in each iteration. The accuracy was assessed by evaluating the left-out sample in each classification run [3], whereas robustness was tested by repeating the clustering pipeline with the remaining 55 patients [4].

Discussion:
This study paves the way for development of robust classification systems based on objective neurophysiological measures that capture both motor and cognitive network dysfunction. This methodology has the potential to provide both biologically-meaningful and replicable subphenotypes. Such a stable subphenotyping process could drive a precision medicine approach towards stratification in new clinical trials.

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DSP-21: Testing the new ALS ‘Gold Coast’ diagnostic criteria and longitudinal ALSFRS-R in a Queensland ALS clinical database (SALSA)

Miss Laura E Ziser1, Dr Viral Upadhyay2, Ms Susan Heggie2, Ms Kathryn A Thorpe2, Professor Naomi R Wray1, Ms Anjali K Henders1, Associate Professor Robert D Henderson2

1Institute For Molecular Bioscience, The University Of Queensland, St Lucia, Brisbane, Australia, 2Royal Brisbane and Women’s Hospital, Herston, Brisbane, Australia

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Background:
Clear diagnosis and stratification of disease progression is important for optimising ALS patient management and clinical trial recruitment. The Sporadic ALS Australian – Systems Genomics Consortium (SALSA-SCG) has built a national online platform to collect consistent clinical data for ALS patients and is part of the MiNDAUS consortium. Platform tools supporting diagnosis and patient management for clinicians are yet to be developed. Here we apply two updates to retrospective clinical data from the Queensland clinic to validate their use. The “Gold Coast diagnostic criteria” (1) have recently been proposed to reduce diagnostic ambiguity but require validation. Additionally, we test whether longitudinal collection of ALS functional rating scores (ALSFRS-R) can stratify patients to support management beyond diagnosis.

Objectives:
To investigate both the performance of the new diagnostic criteria and the stratification of ALSFRS-R progression rates throughout the disease course in a pre-existing Australian ALS cohort.

Methods:
We used a pre-existing phenotypic dataset collected from ALS patients from Queensland recruited by SALSA-SCG since 2016. The dataset includes longitudinal measures of >100 variables, including ALSFRS-R scores, affected regions and ALS diagnosis using El Escorial criteria. Gold Coast criteria were applied with results compared to pre-existing diagnostic classifications. The rate of ALSFRS-R progression was calculated at each subsequent visit using (ALSFRS-R at current visit - ALSFRS-R at previous visit)/(months between visits).

Results:
The new diagnostic criteria were successfully applied to each primary visit (n=178). Of the 92 individuals presenting with classic ALS, 77% (n=71) met the new criteria, while 23% (n=21) were inconclusive due to missing data and no individuals failed to meet the criteria. In the unclassified ALS type (n=59), 44% (n=26) of individuals also met the new diagnostic criteria. ALSFRS-R progression rates were calculated at each subsequent clinical visit (n=403) and interpolated at one-month intervals from disease onset to generate a time profile for each individual.

Discussion:
We identify a similar number of classic ALS cases using the Gold Coast diagnostic criteria compared to El Escorial criteria. With few reclassified individuals, impact is expected to be minor for overall research outcomes but may be significant for a small number of individuals (for example, clinical trial recruitment for previously unclassified individuals). The value of ALSFRS-R progression rate is currently being assessed as we test different slow/fast progressing classifiers and examine changes across time. Our findings support adopting the Gold Coast criteria, and while yet to be realised, we believe ALSFRS-R progression metrics could be valuable for patient management.

References:

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DSP-22: The Comprehensive Analysis Platform To Understand, Remedy, and Eliminate ALS (CAPTURE ALS)

**Dr Sanjay Kalra**, Dr Tania Bubela, Dr Nicolas Dupré, Dr Angela Genge, Dr Russell Greiner, Dr Wendy Johnston, Dr Claire Magnussen, Dr Janice Robertson, Dr Ekaterina Rogaeva, Dr David Taylor, Dr Christine Vande Velde, Dr Lorne Zinman, Dr Hannah Kaneb

1Department of Medicine, University of Alberta, Edmonton, Canada, 2Department of Neurology and Neurosurgery, McGill University, Montreal, Canada, 3Department of Medicine, Université Laval, Québec City, Canada, 4Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada, 5Faculty of Science - Computing Science, University of Alberta, Edmonton, Canada, 6Department of Laboratory Medicine and Pathobiology, Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada, 7Department of Medicine, University of Toronto, Toronto, Canada, 8 ALS Society of Canada, Toronto, Canada, 9Department of Neurosciences, Université de Montréal, Montreal, Canada

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**Objective:**
The Comprehensive Analysis Platform To Understand, Remedy and Eliminate Amyotrophic Lateral Sclerosis (CAPTURE ALS) is an innovative initiative that will pool resources and talent in Canada to advance our understanding of the biological basis of ALS and address its heterogeneity.

**Background:**
ALS drug discovery has been hampered by the complexity of the disease, clinical heterogeneity and rare disease status. Key advances will be expedited through multisite, multidisciplinary collaborations and the sharing of data and materials. CAPTURE ALS will leverage and expand the existing clinical network and infrastructure developed by the Canadian ALS Neuroimaging Consortium (CALSNIC) to provide the most comprehensive picture of a person living with ALS. Led by a group of basic and clinician scientists, it will be driven academically, initially through four existing ALS centres in Edmonton, Toronto, Montreal, and Quebec City, with the vision for subsequent expansion to other clinics in the future.

**Design/Methods:**
CAPTURE ALS will provide the infrastructure and tools to enable the collection, storage, analysis and dissemination of standardized, longitudinal, multi-dimensional data and biosamples from patients with ALS, related disorders, and healthy controls across Canada. Participants will be followed prospectively to longitudinally collect detailed clinical, neurocognitive, speech, and imaging data. Biospecimens, including serum, plasma, peripheral blood mononuclear cells (PBMCs), cerebrospinal fluid (CSF), and urine will be collected at the same intervals, with postmortem material collected when possible. Capture ALS will be built with a strong focus on patient engagement, garnering the advice of a Patient Partner Advisory Council (PPAC) through the design and execution process. This will ensure a strong and engaged partnership between participants and researchers. CAPTURE ALS will incorporate ‘at home’ outcome measures and sample collections where possible in order to reduce on-site visit burden for participants. This is particularly relevant in a time where COVID-19 adds greater complexity and risk to on-site participant visits.

**Results:**
The rich datasets and samples collected through this platform will be used to develop and validate novel ALS biomarkers and enable the multidimensional stratification of ALS patients based on clinical phenotype, and imaging, genetic and cellular characteristics. Operating through Open Science principles, data and samples will be readily available to investigators and industry partners.

**Conclusions:**
CAPTURE ALS will contribute to global efforts to expedite ALS research, and provide hypothesis and data driven insights into disease mechanisms and clinical heterogeneity.

**Funding:**
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DSP-23: Using smartphones to quantify behavioral changes of people with ALS during the COVID-19 pandemic

Dr. Anna Beukenhorst¹, Ella Collins², Katherine Burke², Margaret Clapp³, Sai Charan Konanki¹, Dr. Sabrina Paganoni², Dr. Timothy Miller³, James Chan², Dr. Jukka Pekka Onnela¹, Dr James Berry²

¹Harvard TH Chan School of Public Health, Department of Biostatistics, Boston, United States, ²Massachusetts General Hospital Healey Center for ALS, Boston, United States, ³Washington University Medical Center, Department of Neurology, Saint Louis, United States

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Background:
The COVID-19 pandemic has changed behavior of the general population with required social distancing and stay-at-home-orders. The risk of severe COVID-19 infections is higher for people with serious underlying medical conditions, such as amyotrophic lateral sclerosis (ALS). Quantifying pandemic-related behavior change in people with ALS (PALS) is important for future studies into risk of contracting COVID-19 and understanding the impact of both ALS and social isolation on disease outcomes. Behavioral change can be difficult to quantify using traditional research methods. Smartphone sensors enable frequent passive measures of behavior, including mobility. This data can be used to construct a digital phenotype, quantifying a person’s behavior.

Objective:
Our objective was to quantify behavioral changes in PALS when COVID-19 measures were instated and compare behavioral changes between PALS with low versus high functional ability.

Methods:
Eight PALS used the Beiwe smartphone application which passively measured their location before and after the COVID-19 outbreak. We calculated daily home time and daily distance travelled. We used interrupted time series to quantify the effect of the COVID-19 pandemic on daily home time and on daily distance travelled.

Results:
Before the pandemic, median daily home time for PALS was 19 hours and median distance travelled was 42 km. The pandemic and resultant state of emergency had a significant effect on daily home time (+5.2 hours, 95% CI: + 0.75 to + 9.7) and daily distance travelled (-48 km, 95%CI: -77km to -19 km). There were also mobility and behavior differences between participants with low and high function according to the ALSFRS-R. The participant with the lowest functional ability spent more time at home and travelled less, both before and after the state of emergency. Compared to the participant with the highest functional ability, this participant changed behavior earlier and stayed at home even more during the COVID-19 pandemic.

Discussion:
We provide objective data that at baseline, PALS spend a significant amount of time at home. The COVID-19 pandemic and resultant state of emergency declaration reduced their mobility even further. Given their markedly high daily home time, there is reason to suspect that exposure to COVID-19 in PALS could be lower than the general population. Researchers investigating the impact of COVID-19 on people with neurologic disorders should account for a lower exposure to the virus because of low baseline mobility and high compliance with stay-at-home-orders. At the same time, the social isolation may have its own negative health implications. During the COVID-19 pandemic when all clinic-based observational research halted, digital phenotyping through smartphones provided continued data. The success of such digital phenotyping in providing outcome measures depends on the close collaboration of data scientists and clinical researchers for digital data collection, analysis and disease phenotyping.