Theme 7 Improving Diagnosis and Prognosis

P181 RARE FORMS OF SPORADIC 4R-TAUOPATHIES WITH PROMINENT MOTOR NEURON FEATURES EASY TO MISTAKE FOR ALS-FTD

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Keywords: 4R tauopathies, MND-like syndromes, FTD

Background: ALS-FTD is usually associated with TDP-43 or FUS pathology. FTD as determined by 4 repeat (4R) tauopathies can, in rare cases, show prominent motor neuron disease (MND)-like features. In such sporadic cases, the diagnostic criteria of classic progressive supranuclear palsy (PSP) or cortico-basal syndrome (CBS) are not necessarily fulfilled. Histopathologically, these rare cases are characterized among others by a co-occurrence of astrocytic plaques, typical for CBD (Cortico-basal degeneration), in addition to tufted astrocytes, typical for PSP. Language and motor speech dysfunctioning and/or primary lateral sclerosis (PLS)-like features are acknowledged as parts of the clinical spectrum of atypical PSP.

Objectives: To describe rare forms of 4R tauopathies with prominent motor neuron features in two patients and distinguish them from ALS-FTD.

Methods: Clinical, imaging (MRI, FDG-PET), genetic, and neuropathological analysis.

Results: Case 1 describes a 77-year-old woman with a 15-year disease duration of slow progressive dysphagia, followed years later by dysarthria developed into mutism. A gradual progressive behavioral variant (bv) FTD became apparent 9 years after the bulbar onset of the disease. There was no asymmetric parkinsonism. The MRI displayed prominent right-sided temporal lobe atrophy. No mutation was detected in the microtubule-associated protein tau (MAPT) gene. The neuropathological criteria for CBD were fulfilled. Unusually, however, several tufted astrocytes were also detectable in affected cortical regions. Case 2 describes a 76-year-old woman with a 7-year disease duration, which began with progressive non-fluent aphasia (PNFA) and apraxia of speech (AOS) and later also developed into bvFTD. Furthermore, right-sided dominant bulbospinal upper motor neuron syndrome was observed. MRI showed pronounced cerebral atrophy, which was not, however, concentrated in the brainstem. No mutation was detected in the MAPT gene. FDG-PET showed a left frontal glucose hypometabolism. The neuropathological diagnosis was FTLD-TAU (PSP-subtype), with a distribution of the PSP pathology corresponding to atypical PSP.

Discussion and conclusions: The cases presented here demonstrate that MND-like syndromes with prominent bulbar or PLS-like features belong to the clinical manifestations of rare forms of sporadic 4R tauopathies and can lead to false ALS-FTD assessments. A lateralized cortical syndrome or a focal cortical pathology support the likelihood of tau pathology and render both TDP-43 and FUS pathology less likely. In our two cases, the focal features were as follows: in the atypical CBD case, right temporal atrophy; in the atypical PSP-case AOS, PNFA, and left frontal hypometabolism. Histopathologically, both of our cases are atypical forms of 4R tauopathies: in the CBD case, this is due to the additional tufted astrocytes; in the PSP case, owing to the shift of the tau pathology from the brainstem to the neocortex.

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P182 PREDICTION OF OUTCOME AND MONITORING OF CLINICAL COURSE BY LABORATORY INVESTIGATIONS

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Keywords: diagnosis, monitoring, prediction

Background: Laboratory investigations are of great importance in clinical practice for ALS, in support of the clinical diagnosis, when evaluating possible clinical effects of experimental treatment, but also as a tool in information to patients of the possible prognosis and future course of their disease. We have followed a large number of patients during a 25-year period by monitoring clinical disease activity in relation to laboratory parameters with an expanding set of assays in plasma, serum, and cerebrospinal fluid (CSF).

Methods: Patients were followed by repeated blood and CSF monitoring with CSF NFL, beta-amyloid, GFAP, Tau, NSE, and S100 protein, with serum and CSF autoantibodies, glycolipid antibodies and a broad spectrum of analyses in serum and CSF as well as assessment by clinical rating scales.
Results: We have used CSF NFL for 20 years. It is inversely related to the survival time of patients from the first symptoms of ALS until death. The diseased survival expectancy was further related to other biological between patients. Increased immunoglobulin levels (IgG Index and IgM indexes) hormonal, metabolic and inflammatory changes in serum and CSF.

Conclusions: Increased CSF levels of NFL are closely related to disease activity in ALS and are inversely correlated to life expectancy after diagnosis of ALS. It seems fairly stable during the course of disease in each patient, but is very variable between patients. Increased levels of IgG Index, IgM Index, and complement levels are related to remaining life expectancy. Analyses of hormonal changes show changes that might be of importance. Immunoglobulin and complement levels might be pertinent to perform in parallel with NFL assays in CSF and to clinical rating scales to reveal possible changes in response to different strategies, enabling an early switch from one possibly ineffective treatment into another possibly more effective disease retardation medication.

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P183 EARLY DETECTION OF BULBAR SYMPTOMS IN ALS

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Keywords: dysarthria, dysphagia, speech acoustics

Background: The current gold standard diagnostic tests for dysarthria (i.e. impaired speech intelligibility/rate) and dysphagia (swallowing dysfunction) are insensitive to the onset of bulbar involvement in ALS1. Therefore, there is a critical need to develop an assessment battery capable of early detection of bulbar onset, tracking bulbar deterioration as the disease advances, and quantifying treatment outcomes relative to bulbar function. Toward this goal, we focused on speech and swallowing tasks that show promise as sensitive indicators of bulbar decline and which would be readily amenable to acoustic waveform analysis, as manual analysis methods are impractical for widespread use in clinical settings.

Objectives: This study has two primary aims: (a) to identify which tasks detect bulbar deterioration associated with healthy aging versus early ALS; and (b) to identify which tasks have the highest inter-rater reliability for subsequent automated acoustic analysis.

Method: To establish normative values for our test battery, we first recruited healthy adult participants between 20–99 years of age, from each decade across the adult life-span. The battery consisted of four non-invasive behavioral tests of speech and swallow function that elicit distinct acoustic waveforms: diadochokinetic (DDK) speech rate test, mastication rate test, swallow rate test, and a novel tongue tick rate test that corresponds with lick rate, which we recently identified as the first clinical indicator of bulbar dysfunction in a mouse model of ALS2. We also measured tongue strength using the Iowa Oral Performance Instrument (IOPI), which is known to correlate with age- and ALS-related lingual dysfunction. Acoustic signals were digitally recorded and manually analyzed by two independent reviewers using a freeware speech acoustics program called PRAAT. We are currently recruiting participants in the early stages of ALS (n=10) for comparison with age- and gender-matched controls.

Results: Our preliminary results from 165 healthy adults revealed that older participants (>60 years) have significantly reduced tongue strength, slower rates for DDK and tongue tick tasks, increased fatigue during the tick rate task compared to the speech rate task, and longer oral preparation time during the mastication rate task. Two of the four tasks had the highest inter-rater reliability: DDK speech rate and tongue tick rate, providing rationale for their inclusion in our initial automation efforts.

Discussion and conclusions: Waveform analysis on acoustic signals obtained during speech and swallow tasks can detect subtle age-related changes in healthy people over 60 years of age. We expect similar outcomes for people in the early stages of ALS. While acoustic data collection is quick to perform, manual data analysis is labor intensive and impractical for a clinical environment. To overcome this barrier, we are developing a Smartphone app for automated acoustic analysis in real-time.

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P184 EVALUATION OF OROFACIAL MUSCULATURE FATIGUE AS A CLINICAL MARKER IN PATIENTS WITH BULBAR MOTOR NEURON DISEASE

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Keywords: fatigue, stomatognathic system, speech

Background: Fatigue is a very common symptom in patients with MND and should be carefully considered during the therapeutic process that involves motor activities. In speech therapy, orofacial motor function exercises may be recommended, with emphasis on mobility; being contraindicated by any activity, type of exercise or dose that are creating fatigue.

Objective: To evaluate the occurrence of fatigue in orofacial musculature and review the relationship with scales of functionality in patients with a diagnosis of MND.
Methods: A total of 121 patients were evaluated, being 90 appendicular onset (43 women and 47 men), with average diagnosis time 22.28 months; and 31 with bulbar onset (21 women and 10 men), with average diagnosis time 13.61 months. The following instruments were applied: ALSFRS-R and ALSSS functionality scales, speech intelligibility scale and clinical evaluation of orofacial musculature, with analysis of fatigue of the muscles of lips, tongue (movements of lateralization, tip, and dorsal of the tongue), soft palate and masticatory muscles. During the series of movements, the number of series in which the muscle showed the first sign of fatigue was recorded, especially evidenced by the loss of quality of the movement.

Results: The patients with appendicular onset (ALS) had median score of 7 on a scale of speech intelligibility, 8 (bulbar field of ALSFRS-R), and 7 (speech and swallowing of ALSSS fields) and, during isotonic movements series, were assessed for fatigue, with median score of 8 for lips, 11.5 for lateralization of tongue, 5 for lifting tip of tongue, 10 for lifting back of tongue, 10 for soft palate, and 11.5 for masticatory muscles. Patients with bulbar onset (PBP) had median score of 4 on the scale of speech intelligibility, 5 (bulbar field of ALSFRS-R), and 5 (speech and swallowing fields of ALSSS) and, during isotonic movements series, were assessed for fatigue, with median score of 5 for lips, 4 for lateralization of tongue, 2 for elevation of tip of tongue, 2 for elevation of back of tongue, 6 for soft palate, and 8 for masticatory muscles.

Discussion and conclusions: Patients with bulbar onset (PBP) showed reduced exercise tolerance, with earlier indices of fatigue of orofacial musculature, with impact on swallowing, and speech functions. These values also indicate that in speech and language therapy, the therapist must advocate a series of exercises that are inside this range pack containing a variety of measures, including the

ALS Functional Rating Scale-revised (ALSFRS-R), scored as three domains of Bulbar, Respiration, and Mobility, ranging from: 0 to 12, 0 to 12, and 0 to 24, respectively, scored such that a high score represents few problems.

Results: A total of 465 people with MND/ALS had returned complete baseline questionnaires by the end of 2015. Their mean age was 64.9 years (SD 10.8), mean duration of disease 28.4 months (SD 37.5). 60.6% were male. Bulbar onset was recorded for 24%. Median scores on the ALSFRS-R were 9 (Bulbar), 11 (Respiration), and 14 (Mobility). A significant difference was observed for each domain across type of onset (Kruskal Wallis p < 0.001). Those with Bulbar onset had much worse (lower) scores for Bulbar and Respiratory symptoms, but better scores for Mobility. Including a grouped age-of-onset variable into a univariate ANOVA, with duration as a covariate, showed that the main effects of onset type and age-of-onset were significant for Bulbar symptoms (F 21.8; p < 0.001). The estimated marginal mean for Bulbar symptoms among those with age of onset at 55 years and below, was 9.0, compared to 6.8 (i.e. worse) for those aged 70 years and over, controlling for duration. For Bulbar onset, the estimated marginal mean was 4.8, compared to 9.8 (i.e. better) for limb onset, controlling for duration. Type of onset was dominant in the model; however, there was no significant interaction between the two factors. Thus, for example, those with onset at over 70 years of age, and of the bulbar onset type, did not incur a further worsening of the bulbar symptoms because of this interaction.

Discussions and conclusion: Both type- and age-of-onset independently influenced the level of bulbar symptoms experienced by those with MND/ALS. While the onset type appeared dominant for the experience of bulbar symptoms, age also retained a significant effect, adjusted for duration.

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P186 QUANTITATIVE LABIAL, TONGUE SPEECH AND SWALLOWING RATE MEASUREMENTS AT DIAGNOSIS CORRELATE WITH ALS FUNCTIONAL RATING SCALE – REVISED (ALSFRS-R) BULBAR SUB-SCORE AND BULBAR SUB-SCORE ITEM SCORES BUT NOT WITH ALSFRS-R TOTAL SCORE – INTER-RATER RELIABILITY – PRE-POST NUDEXTA EFFECTS ON SPEECH AND SWALLOWING

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Keywords: bulbar function, speech swallow rates, Nuedexta treatment

Background: Labial articulation rate (LAR) and tongue articulation rate (TAR) (words-per-minute (WPM) or words-per-minute-per-breath (WPMPB)) changes over time significantly prior to intelligibility changes. Liquid swallowing rate (LSR) (mL-per-swallow-per-minute (mLPSM)) or mL-per-swallow-per-minute-per-breath (mLPSMPB)) changes prior to video fluoroscopic swallowing changes and predicts oral feeding safety capacity across a wide-range of causes of neurogenic dysphagia.

Objectives: Determine inter-rater variability for LAR, TAR, and LSR in a sub-group of ALS-MND patients at diagnosis. Determine the relationship of LAR, TAR, and LSR to ALSFRS-R total score and ALSFRS-R bulbar sub-score total and bulbar sub-score speech, salivation, and swallowing item-score.

Methods: LAR was measured by repeating “pepper” and TAR was measured by repeating “ticker” 10 times and recording the start and completion time in seconds. The number of breaths required to complete the task were recorded. LSR was measured by recording the time for swallowing 90 mL (3oz) water from the initiation of liquid leaving the cup at the lips to the completion of the final swallow of liquid in seconds. The number of breaths required to complete the task were recorded. WPM, WPMPB, mLPSM, and mLPSMPB were calculated and statistical analysis was performed with MedCalc software version 12.2.1 (www.medcalc.org).

Results: At diagnosis in 250 ALS-MND patients LAR, TAR, and LSR were measurable in 212 patients. LAR, TAR, LSR measured as WPM and mLPSM distributed differently than LAR, TAR, LSR measured as WPMPB and mLPSMPB and were not normal. LAR and TAR correlated significantly across patients (R2=0.995; p<0.001). LAR and TAR correlated significantly with LSR across patients (R2=0.762; 2=0.883; p<0.01). Inter-rater reliability in 88 paired tests was excellent (Spearman rho LAR=0.889; TAR=0.881; LSR=0.773; p<0.01). LAR, TAR, LSR did not correlate with ALSFRS-R total score. LAR (R2=0.891) or TAR (R2=0.848) significantly correlated (p<0.01) with ALSFRS-R bulbar sub-score speech item score. LSR (R2=0.788) significantly correlated (p<0.01) with ALSFRS-R bulbar sub-score swallowing item-score. A clinic-based observational study of LAR, TAR, and LSR post administration of Nuedexta in 42 ALS patients with pseudobulbar affect demonstrated a significant change in LSR (mLPSMPB) (pre-79.4±86.2/post-104.7±62.9; paired-t-test, p=0.02) but not into the normal range. Rate improvements did not correlate with changes in ALSFRS-R, vital capacity or other clinimetrics. Factors affecting the persistence of improvement will be presented.

Conclusions: LAR, TAR, and LSR are robust quantitative bulbar clinimetrics that provide specific outcome measurements correlating with bulbar functional milestone scales in the ALSFRS-R, but not with the ALSFRS-R total score. LAR, TAR, LSR will provide more precision in assessing response to treatment in speech and swallowing domains of patients with ALS.

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P187 LONGITUDINAL NATURAL HISTORY OF OROFACIAL MUSCLE STRENGTH CHANGES IN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS

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Keywords: bulbar function, orofacial muscle strength, bulbar clinimetric scales

Background: There is next to nothing in the literature on the longitudinal natural history of orofacial (facial, lingual-oro-pharyngeal) muscle strength measurements by clinical scales compared with the ALS Functional Rating Scale-Revised Bulbar subscale (Speech, Salivation, and Swallowing) in patients with Amyotrophic Lateral Sclerosis (ALS) or Bulbar-Spinal Muscular Atrophy. Other groups have proposed clinical strength rating scales validated by quantitative strength measurements (1).

Objective: Present natural history of 75 patients with ALS followed prospectively over 12 months from entry into a clinical trial.

Methods: Forehead wrinkling, eye closure, pursing lips, puffing out cheeks, platysma contraction, clinically assessed tongue strength was rated (0-no movement, 1-minimal movement, 2-full movement gravity-eliminated, 3-full movement against gravity, 4-full movement but not
full resistance, 5-full resistance), tongue click was rated (0-absent, 1-minimal, 2-more than minimal, 3-moderate, 4-hard click, 5-maximal click), presence of gag reflex were assessed, Functional Rating Scale-Revised was completed at 3 month intervals in 75 patients (21 bulbar onset; 54 limb onset).

**Results:** Median ALSFRS-R Bulbar subscore declines 4.5 (−5.8 to −1.3 95% CI) units in bulbar onset patients and 0.5 (−2.1 to 0.0) units in limb onset patients over 12 months (p=0.0068). Tongue click which is actually higher in limb onset patients declines faster by 1.5 (−2.0 to −0.9 95% CI) units compared with bulbar onset patients −0.3 (−1.6 to 0.0 95% CI) units in 12 months. Change in tongue click correlated significantly with change in tongue strength (r=0.8324; p=0.005) over 12 months. Change in ALSFRS-R Bulbar subscore correlated significantly with change in platysma strength (r=0.5933; p=0.006).

**Conclusions:** The natural history of orofacial muscle strength measured clinically correlates with ALSFRS-R Bulbar subscale and other measurements offering a novel set of new clinimetrics to assess new treatment regimens in the bulbar domain.

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**PI188 PERCEPTUAL, INSTRUMENTAL, AND SELF-DETECTION OF EARLY BULBAR CHANGES IN ALS**

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Keywords: bulbar, early detection, speech

**Background:** Bulbar symptoms in ALS substantially impact quality of life and lead to shortened survival; however, there are currently no agreed standards for early detection of bulbar changes. Recent efforts have identified several performance-based measures (i.e. acoustic and articulatory kinematic) that appear sensitive to early bulbar changes (1). While these quantitative metrics promise for early detection, they have not been directly compared to perceptual judgments of speech-language pathologists (SLPs) and patients’ own perceptions of speech changes associated with the disease.

**Objectives:** The purpose of this study was to determine if patients and clinicians detect changes in speech prior to currently used instrumental-based measures of speech performance, and to determine which measures best detected early changes in bulbar function.

**Methods:** Thirty-six individuals with early-stage ALS and 17 healthy control participants were included. Six acoustic and kinematic speech measures were obtained: percent of pause time (PPT), articulation rate, maximum fundamental frequency, nasalance, maximum velocity of lip opening, and diadochokines (DDK) rate. The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) (2) was administered, and a bulbar subscore was derived to assess patients’ awareness of early bulbar changes. Two certified SLPs provided perceptual ratings of speech samples. To determine whether patients and clinicians detected early bulbar changes reflected in instrumental measures, patients were first grouped as “pre-symptomatic” and “symptomatic” separately based on patient self-report and clinician assessment. ANOVAs were used to assess group differences in gold-standard instrumentation-based speech measures. ROC analysis was used to compare the sensitivity and specificity of perceptual, acoustic, and kinematic measures for detecting bulbar changes in pre-symptomatic individuals with ALS.

**Results:** Pre-symptomatic persons with ALS (based on self-report and clinician rating) had significantly longer PPTs and significantly faster lip velocities than healthy adults (p<0.05). ROC analyses indicated that PPT was the best measure for differentiating healthy controls from self-rated pre-symptomatic individuals with ALS (sensitivity = 68%, specificity = 94%, AUC = 0.83).

**Discussion and conclusions:** Overall, findings suggested that individuals with ALS and SLPs did not detect early changes in bulbar function apparent in kinematic and acoustic measures.

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**PI189 THE ASSESSMENT OF BULBAR FUNCTION IN ALS**

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Keywords: clinical trial endpoints, bulbar function, clinical assessment

**Background:** Historically, clinical trials in ALS have emphasized survival rather than symptomatic improvement as an endpoint. When symptomatic benefit is
assessed, it generally focuses on the integrity of limb musculature. In fact, to our knowledge, objective measurements of bulbar functions, such as timed swallowing, have never been measured in a clinical trial.

**Objective:** To evaluate the utility of measures, which assess bulbar function in ALS: the ALSFRS-R, CNS-BFS (a self-report scale), visual analog scales (VAS), and timed measures of speech and swallowing.

**Methods:** Bulbar function was assessed in up to 120 subjects with probable or definite ALS as determined by El Escorial criteria. A clinical observer made a diagnosis of impaired speech, swallowing and salivation by making direct observations of the subjects. For example, the patients’ speech was determined to be normal or abnormal based on three criteria: intelligibility, loudness, and nasality. Subsequently, subjects completed the self-administered CNS-BFS and VAS tests, and were also evaluated by raters who scored the various items comprising the ALSFRS-R. Speech rate for each subject was determined by reading a test passage, and the time to swallow both liquids and solids was recorded. Further, correlations were made between clinician diagnosis and each of the measures that were assessed. Based on this, we ranked ordered each of these measures for their potential utility in a clinical setting.

**Results:** The self-report CNS-BFS was highly correlated with the bulbar subscale of the ALSFRS-R ($r = -0.896$, $p < 0.001$). Both the ALSFRS-R bulbar subscale and the CNS-BFS speech, swallowing, and salivation subscales were highly predictive of clinician assessment of bulbar dysfunction. The CNS-BFS subscales for swallowing and salivation were more highly correlated with the VAS than with the corresponding ALSFRS-R subscales. The CNS-BFS swallowing subscale was better correlated with the timed swallowing of liquids and solids than were the ALSFRS-R and VAS swallowing subscales.

**Conclusions:** Both the CNS-BFS and the bulbar domain of the ALSFRS-R accurately predict impaired bulbar function in ALS patients, comparing favorably to clinician diagnosis. In general, the recently developed CNS-BFS outperforms both the ALSFRS-R and the VAS when correlations are made between these scales and timed reading and swallowing tests. Although the ALSFRS-R is the most frequently used scale, it is a rater-administered scale, a disadvantage in that the data is generated by an observer rather than the patient. The variability between raters does not need to be taken into account in the instance of a self-report scale, a considerable advantage since data provided by a patient is not filtered through an observer. At a minimum, the CNS-BFS could become a useful adjunct to the clinical assessment of bulbar function.

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**P190 THE LATENT STRUCTURE UNDERLYING THE ALSFRS-R: A CROSS-SECTIONAL STUDY**

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**Keywords:** ALSFRS-R, exploratory factor analysis, confirmatory factor analysis

**Background:** The latent structure of the amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R) has caused inconsistent results in the literature. Both models with a four-factor structure comprising a bulbar function scale, a fine motor function scale, a gross motor function scale, and a respiratory function scale and a three-factor structure in which the two motor scales are collapsed into one motor function scale have been examined. However, there is currently not one distinct strategy to calculate ALSFRS-R factor scores.

**Objectives:** To explore and to evaluate the latent structure of the ALSFRS-R.

**Methods:** ALSFRS-R data of ALS patients was obtained from the Prospective ALS study in the Netherlands (PAN) database. To obtain the broadest possible cross-section and avoid dependency in the data, only the most recent observation per individual was included in the study. The sample ($n = 1674$) was split randomly into a training set and a validation set. The latent structure of the ALSFRS-R was investigated in the training set using exploratory factor analyses (EFA) and confirmatory factor analyses (CFA). Confirmatory models were derived from the literature and respelled based on modification indices and theoretical knowledge. All confirmatory models were cross-validated in the validation set. Analyses were performed both with WLS-MV and ML-MV estimators. Both estimators produced similar results. ML-MV results are reported to facilitate model comparison based on AIC and BIC.

**Results:** Both the three-factor and the four-factor model with uncorrelated latent variables demonstrated poor model fit. Their equivalent with correlated latent variables showed improved, but still poor model fit. The three-factor model with correlated latent variables was respelled to include correlated errors of items 4 and 5 (Handwriting and Cutting food and handling utensils), and items 8 and 9 (Walking and Climbing stairs), which demonstrated acceptable model fit ($\chi^2 = 269.21$, $df = 49$, $p < 0.001$, RMSEA = 0.07, CFI = 0.94, TLI = 0.92, SRMR = 0.05). The four-factor model with correlated latent variables was respelled to include cross-loading item 6 (Dressing and hygiene) on the gross motor function scale and item 7 (Turning in bed and adjusting bed
clothes) on the fine motor function scale, which showed good model fit ($\chi^2 = 135.89$, $df = 46$, $p < 0.001$, RMSEA = 0.05, CFI = 0.98, TLI = 0.97, SRMR = 0.04). Model comparison indicated that the respecified four-factor model provided the best fit to the data.

**Discussion and conclusion:** CFA of the ALSFRS-R have demonstrated that both the three-factor and the four-factor model improved after respecification of the latent structure. Furthermore, the respecified four-factor model with cross-loading items 6 and 7 fitted the data best. Future studies should therefore adjust the calculation of factor scores to reflect this respecified latent structure for valid inference.

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**P191 AN EXAMINATION OF LONGITUDINAL CHANGES IN INDIVIDUAL ITEMS OF ALSFRS-R**

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**Keywords:** ALSFRS-R, ordinal regression, Cox model, clustering analysis

**Background:** The total score of revised ALS functional rating scale (ALSFRS-R) is a widely used outcome measure in ALS studies. To our knowledge, individual items of ALSFRS-R, especially their longitudinal changes, are rarely analyzed. Since each item interrogates a unique aspect of a patient’s functional status, a detailed examination of the longitudinal change of each individual item can provide further insights into the nature of ALS disease progression.

**Objectives:** To examine individual items of ALSFRS-R and to identify patient subgroups based on their longitudinal profiles.

**Methods:** We used longitudinal data on ALSFRS-R collected over 12 months from 943 patients in the EMPOWER study. Data for each item of ALSFRS-R was analyzed using ordinal logistic regression. Cox model was employed to evaluate the relationship between survival and baseline values of each item of ALSFRS-R. Each item’s predictability of patient survival was assessed through the ranking of chi-square test statistics. All analyses were adjusted for effects of age, sex, symptom duration since onset, stable use of riluzole, and disease onset site. Hierarchical clustering of longitudinal data on individual items of ALSFRS-R was conducted and the result was summarized using a heat map.

**Results:** At study entry, patients showed differing degrees of functional decline (in terms of distributions of scores 0–3) over 12 items: most patients ($\geq$75%) showed abnormalities on each of items 4–9 (motor function), while the fewest patients ($\leq$30%) reported abnormalities on items 10–12 (respiratory function). For the distribution of score 0 over 12 items, item 9 (climbing stairs) had the highest proportion (12%), followed by item 6 (dressing and hygiene) (2.7%). For the predictability of survival, the top three items were 1 (speech), 7 (turning in bed), and 8 (walking). Longitudinally, significant functional decline was observed on each item. The log-odds of changing to a lower score over time was linear for each item, with item 12 (respiratory insufficiency) having the largest slope while item 2 (salivation) having the smallest slope. The clustering analysis of all items showed 4 distinct patterns of patient subgroups: minimal abnormality on all items, abnormalities on items 1–3, abnormalities on items 4–9 and abnormalities on all items.

**Discussion:** At study entry, items 4–9 of ALSFRS-R had the highest proportions of patients showing functional impairments, which is consistent with the limb onset dominance of ALS. Over time, more patients reported abnormalities in respiratory functions. The time effect in the log-odds scale was linear. Clustering analysis of individual items showed distinct patterns of patient subgroups in disease progression.

**Conclusions:** Individual items of ALSFRS-R are informative to disease progression. They also provide richer information than the total score of ALSFRS-R on progression patterns of patient subgroups.

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**P192 ASSESSING THE UTILITY OF DIAGNOSTIC DELAY TO PREDICT ALSFRS-R DECLINE IN PEOPLE DIAGNOSED WITH ALS**

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**Keywords:** ALS functional rating scale, prognosis, disease progression

**Objectives:** Diagnostic delay is associated with survival in ALS. However, it is not clear whether diagnostic delay is also related to functional decline. Questions about disease progression and functional decline are common in the clinical setting. We sought to determine whether diagnostic delay can be used as a predictor for functional decline in ALS.

**Materials and methods:** The South East ALS register includes all people with a diagnosis of MND in a defined area of South East England. We analyzed cases with a confirmed diagnosis of ALS where ALSFRS-R had been recorded in the register. Rate of decline in ALSFRS-R was estimated by linear extrapolation from two time points. R was used to model the data using linear regression of ALSFRS-R decline on diagnostic delay.

**Results:** A total of 141 cases with a confirmed diagnosis of ALS and ALSFRS-R were identified. After excluding for missing variables 138 cases were included in the analysis. The median age of onset was 64 years, male to female ratio was 1.3:1, bulbar v limb onset was 0.53:1.
The untransformed data were not normally distributed, neither were the residuals of the data from a regression analysis, but log transformation corrected the distribution. A linear regression model on the log transformation of the variables showed that diagnostic delay can predict ALSFRS-R decline ($p < 0.001$, $R^2 = 0.22$).

**Conclusion:** Diagnostic delay can be used to predict functional decline in ALS, but there remains a lot of variation in the data. This variation may be explained by other factors that affect function.

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**P193 THE SPREADING OF SYMPTOMS AT DIAGNOSIS IN ALS IS A MARKER OF PROGNOSIS: A POPULATION-BASED STUDY**

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**Keywords:** phenotype, prognosis, ALSFRS-R

**Background:** In ALS, the time of disease spread is probably linked to the intensity of the neuro-axonal degeneration and consequently to the rate of progression and survival. Recent studies have tried to find a correlation between the disease generalization trend and the patient’s outcome, to better define the ALS natural history and to provide new primary outcome measures for clinical trials (1).

**Objectives:** To assess in a population-based series of ALS patients the pattern of disease involvement of different body regions (upper limbs, lower limbs, bulbar, and respiratory) at diagnosis and its relationship to survival.

**Methods:** Of a total of 879 ALS patients incident in the period 2007–2012 in Piemonte and Valle d’Aosta regions, 810 (92.2%) were included in the study (382 women and 428 men, mean age at onset 66.3 years (SD 10.9)). The time of involvement of different regions was obtained from ALSFRS-R score performed during the follow-up visits, considering the site as affected upon the loss of one point from the maximum sub-score awarded to that region (ALSFRS-R domains 1, 2 and 3 for the bulbar region, 4 and 5 for the upper limbs, 8 and 9 for the lower limbs, and 10, 11 and 12 for the respiratory muscles). The different involvement patterns were analyzed according to sex, age at onset, site of onset, PEG, NIV, tracheostomy, and survival.

**Results:** In 367 patients (45.3%) only one region was affected at diagnosis, two regions were involved in 217 patients (26.8%), three in 152 patients (18.8%), and four in 74 patients (9.1%). The number of affected regions at diagnosis progressively increased with the increase of the age at onset ($p=0.0001$). This trend was not correlated with a delayed diagnosis because the symptom onset-diagnosis interval (overall mean 0.97 years, SD 0.96) did not change according to the number of affected regions at diagnosis ($p=0.48$) and the different age groups ($p=0.30$). Moreover, the number of affected regions at diagnosis was related to survival (1 region, median survival time 3.1 years, 2.1–5.6; 2 regions 2.6 years, 1.7–4.2; 3 regions, 1.8 years, 1.2–3.1; 4 regions, 1.5 years, 0.8–2.4; $p=0.0001$) and was independent from the duration of the onset-diagnosis interval ($p=0.0001$) and the age at onset of patients ($p=0.0001$).

**Conclusions:** The different spreading patterns and the symptom burden at diagnosis in ALS patients are related to overall survival and can help to better define disease outcome.

**References**

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P194 PHENOTYPE HETEROGENEITY AND ALS FUNCTIONAL IMPAIRMENT AT DIAGNOSIS: CONSEQUENCES FOR CLINICAL TRIALS ENROLMENT

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Keywords: ALSFRS-R slope, Airlie House diagnostic criteria, diagnostic delay

Objective: (i) Describe the phenotypic heterogeneity of amyotrophic lateral sclerosis (ALS) patients diagnosed in 2012 in 11 ALS centers, (ii) to look at the associations between ALSFRS-R score and ALSFRS-R slope (ΔFS) at time of diagnosis with diagnosis delay, ALS phenotypes, and Airlie House diagnosis criteria (AHDC), (iii) Describe the rate of progression on ΔFS, according to a stratification on diagnosis delay.

Methods: Incident ALS cases diagnosed in French ALS referral centers were included. The rate of progression (ΔFS) was evaluated as follows: ΔFS = (48 – ALSFRS-R at time of diagnosis)/duration from onset to diagnosis (months). Fast, and slow progressors were defined by a ΔFS > 1 and <0.5, respectively.

Results: At time of diagnosis patients were classified into eight phenotypes: bulbar (33.0%), spinal lumbar (28.2%), spinal cervical (23.1%), flail leg (4.4%), ALS/FTD (4.2%), possible flail arm (4.0%), respiratory (2.1%), dropped-head (1.0%). The overall median of ΔFS was 1.0 (0.5–2.0). ΔFS was associated with AHDC (p = 0.009), but not with clinical phenotype (p = 0.902).

The stratification on diagnosis delay (<12 months or ≥ 18 months) allows to differentiate fast progressors from slow progressors.

Conclusions: At time of inclusion in a therapeutic trial closed to diagnosis, ΔFS discriminate the rate of progression.

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P195 GLOBAL COLLABORATIONS, PATIENT CENTRICITY AND BIG DATA IN ALS

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Keywords: collaboration, big data, NeuroGUID

Objective: Implement global collaborative patient-centered environment, methodology, processes, incentives, and distributed infrastructure for creating “Big Data” in ALS/MND.

Background: PRO-ACT approach proved its efficiency and serves as a de-facto reference knowledgebase with tens of published papers and developed models.

Design and methods: Four interlocking patient-centered platforms create an environment for global collaboration: NeuroGUID (patient Global Unique Identifier for neurological diseases) allows unique patient identification across clinical research continuum, information aggregation, from phenotypical data to biospecimens, patient-reported outcomes, omics, genetic files, and images across clinical visits and research projects, regardless where/when information was captured; PRO-ACT, the first open-access ALS/MND dataset (10,723 subject-reports) merges data from global clinical trials serving as the reference dataset for disease modeling and outcomes optimization with 500+ registered users and tens of scientific discoveries; NeuroBANK, a patient-centered accelerated clinical research environment with standardized patient-centric approach to clinical research, in which information about People with ALS (PALS) is linked across studies, locations and modalities; PRO-ACE, a new platform that “closes” the gap of existing clinical data underutilization: similar to PRO-ACT it

allowed clinicians to submit historical phenotypical/clinical patient data, which is cleaned, harmonized, de-identified, and serves as a foundation for studying the natural history of ALS/MND, unbiased to clinical trials’ PALS selection and uninfluenced of placebo effects, formed analyses to its credit. Identification and development of new sources and approaches for large datasets are critical for identifying statistically significant and biologically relevant observations, creation of disease models and potential therapy development. Implemented approach and platforms for
Results: Standard operating procedures (SOPs), common data elements (CDEs), consent language and technology unify multiple participants in clinical care and research (physicians, researchers, industry, patients and non-profits), and informational components (clinical data captured at bedside and from health records, research data, disease-specific consortia, and patient-reported outcomes, and data from completed clinical trials) into single disease-specific research continuum. Several thousand NeuroGUIDs uniquely identify PALS across clinical and research continuum. Distributed “virtual” biobanks are connected to clinical and research data, image banks, and GWAS files, with information residing in NeuroBANK. 100+ sites in Europe and Americas utilize NeuroBANK for 18 research projects. CDEs and SOPs lead to accelerated studies review, approval, deployment, and patient enrollment, while preserving PALS’ privacy. Standard consent language lays out the foundation for information sharing and data aggregation within particular studies and between multiple projects.

Conclusions: Extremely powerful concept of Patient Centricity in clinical research paired with modern technology and incentives to collaborate and create clinical research continuum from bedside to clinical trials and back.

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P196 ALS IN A POST-PRO-ACT ERA: POOLED RESOURCE OPEN-ACCESS ALS CLINICAL RESEARCH (PRO-ACE) DATABASE

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Keywords: big data, analytics, NeuroGUID

Objective: Implement a global collaborative shared clinical dataset to allow investigators in ALS/MND to utilize Big Data to better understand the disease, to develop disease natural progression models, and to identify disease sub-populations, which may bring us into the age of Precise Medicine.

Background: The PRO-ACT open-access ALS/MND dataset proved its efficiency and serves as a de-facto reference knowledgebase with tens of published papers, several disease models, staging systems, and performed analyses.

Identification and development of new sources for large clinical datasets are critical. We implemented The Pooled Resource Open-Access Clinical Research (PRO-ACE) platform to facilitate: retrospective collection of clinical research data in a structured and secure system; harmonization, de-identification, aggregation, storage, and open-access distribution of data for secondary analyses.

Design and methods: Data from completed single-site and multi-site, national, and international ALS Natural History studies, retrospective clinical assessments and existing clinical datasets are eligible for inclusion in PRO-ACE ALS database. Data Use Agreements (DUAs) are executed to define terms of data sharing between the PRO-ACE team and each contributing Data Donor. Data Donors represent and certify that Institutional Review Board (IRB) or Ethical Review Board (ERB) review and approval were obtained. If PIs represent multisite collaborations, they warrant that DUAs between PIs and participating sites are in place. Data Donors (Principal Investigators (PIs), data owners or key decision makers) donate existing retrospective clinical datasets. Following contribution, Data Donors join the PRO-ACE Consortium and benefit by securing authorship rights and first-access to the PRO-ACE Dataset. Common sense data cleaning is performed and units and text values are standardized. Original Datasets are de-identified following HIPAA PHI conventions. Following aggregation and harmonization of the Original Datasets, the uniform PRO-ACE Dataset is made available for secondary analyses. The PRO-ACE Data Access Committee reviews data requests. Requestors from any national or international entity may request access to the PRO-ACE Dataset that contains only de-identified data.

Results: Standard PRO-ACE DUAs, operating procedures, common data elements (CDEs), consent language and technology platform are implemented. Datasets with more than 15,000 patient records are identified and first five Data Donors provided data from clinical encounters. The PRO-ACE Dataset contains data devoid of placebo effects and clinical trial selection bias, thus representing the general disease population in more natural disease progression.

Conclusions: PRO-ACE allows for aggregation of existing publicly- and privately-collected datasets from multiple sources including completed Natural History studies, retrospective data from clinical assessments and other existing clinical datasets. The PRO-ACE platform and services provided by the PRO-ACE Core team at the NCRI generate an invaluable open-access resource for accelerating discovery in a specific disease field.

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P197 ALS RESISTANCE IS REGIONAL AND NOT EXPLAINED BY DEMOGRAPHICS, MEDICATIONS OR LABS

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Keywords: resistance, reversal, progression

Background: Brief periods of ALS stability (plateaus) or small improvements in motor functions (reversals) are not uncommon. Long plateaus and large sustained reversals are rarer, and potentially important. Further study of these will be challenged by lack of an operational definition, expected small numbers of cases, and arguments about whether these are “real” or due to noise in the scale used to measure progression (ALSFRS-R).

Objectives: (a) To develop an acceptable operational definition of “ALS resistance”, which captures patients with unexpectedly long plateaus or large and sustained reversals; (b) To determine whether ALS resistance is regional (occurring across multiple ALSFRS-R questions related to the same body part) or random (and thus more likely to be due to noise); (c) To look for differences in demographics, medications, and laboratory values between resistant patients and those with more typical progression.

Methods: We used the Origent algorithm to predict ALSFRS-R progression for 3742 participants in the PRO-ACT database with ALSFRS-R records. We explored different potential definitions of ALS resistance according to the number of data points above the 97.5% confidence interval for predicted progression and the time interval between these. We then determined which individual ALSFRS-R items were improving in these resistant patients, and how these items were correlated with each other. We reasoned that higher correlations between improving items within a given region (bulbar, cervical, lumbar or respiratory) would support a biological effect as opposed to random noise in the ALSFRS-R scale. ALS resistance was not explained by demographics, medications or available lab data. There may be a genetic component, as in HIV elite controllers.

Results: Increasingly restrictive definitions yielded smaller numbers of resistant participants. 80 PRO-ACT participants had ALS resistance defined as 2 ALSFRS-R data points at least 6 months apart that were above the 97.5% confidence interval for predicted progression. The most commonly improving ALSFRS-R item across these patients was handwriting (n=24) and the least commonly improving item was respiratory insufficiency (n=3). Correlations between improving items within a given region were higher than correlations across regions. No differences in demographics, medications or labs were found between resistant participants and those with more typical progression.

Conclusions: We created an operational definition of ALS resistance that identified a small but interesting group of PRO-ACT participants whose disease course was at least two standard deviations better than expected. A wide range of ALSFRS-R items improved over time in this group. Correlations between improving items were higher within a given anatomical region, suggesting that they were due to a real biological effect rather than random noise in the ALSFRS-R scale. ALS resistance was not explained by demographics, medications or available lab data. There may be a genetic component, as in HIV elite controllers.

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P198 IMPROVING ALS PREDICTIVE MODELS FOR THE DESIGN AND CONDUCT OF CLINICAL TRIALS

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Keywords: hierarchical modeling, PRO-ACT, clinical trial planning

Background: A predictive model which utilized 3 month progression on the ALS Functional Rating Scale (ALSFRS) to predict what happens at 12 months would be important for ALS clinical trials, allowing more efficient multiple imputation for missing data, and could provide a framework for adaptive clinical trial designs.

Objective: To test multiple modeling approaches for ALS progression using a Bayesian statistical framework.

Methods: We used the Pooled Resource Open-Access ALS Clinical Trials database (PRO-ACT, n=1301 placebo participants) to compare the following hierarchical models using a Bayesian framework: linear (similar to random effects), mixture (mixture of two normal distributions), and onset-anchored (utilizes an additional data point at time of disease onset). We explored the predictive power of clinical features provided by PRO-ACT. The models were compared by measuring the mean-square-error of the model fit in repeated cross validation.

Results: The onset-anchored model vastly outperformed the linear and mixture models in predicting the 12 month change in the ALSFRS. Additionally, no clinical features other than time of disease onset consistently resulted in significant improvement to the onset-anchored model's mean-square-error.

Conclusions: An onset-anchored Bayesian predictive model of disease progression could improve the efficiency of handling missing data and help guide adaptive trial designs for future ALS clinical trials. Only time of disease onset improved model performance.

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**P199 USING HISTORICALLY CONTROLLED TRIALS IN TREATMENT DEVELOPMENT FOR ALS**

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Keywords: clinical trials, randomization, historical controls

**Background:** Most phase II clinical trials in ALS have a placebo control group at the expense of increased sample size and patient dissatisfaction. One of the arguments against historically controlled trials is that there is a trial effect, from variation in the patient population and other factors which is not accounted for when the results of a trial are compared to a placebo group from a previous trial.

**Objectives:** To develop methods for planning and analyzing historically controlled trials that account for the variation among trials.

**Methods:** A hierarchical model was used to analyze ALSFRS slopes among control-group participants from trials in the PRO-ACT database. We calculated what would constitute a significant difference from the “control group” slope, incorporating the variability in slopes both among participants within a trial and among trials. We used this to calculate the power and required sample size of a historically controlled study and compared it to what would be required for a concurrently controlled study.

**Results:** If a treatment slowed the decline in ALSFRS by 25%, then a historically controlled trial that enrolled 100 participants would have 57% power while the approach ignoring among-trial variance would incorrectly calculate a power of 80%. Whether or not a historically controlled trial would require fewer participants than a concurrently controlled trial depends on the difference the trial is designed to detect. Historically controlled and concurrently controlled trials would both require the same sample size (270 participants) for 80% power when the true effect of treatment is a 27% slowing of ALSFRS decline. For larger effects, a historically controlled trial will require fewer participants. To detect a 50% effect, a historically controlled trial would require 26 participants vs. 80 for a concurrently controlled trial, a reduction in sample size of 68%. The minimum treatment effect at which historically controlled trials would be more efficient is smaller when outcomes can be predicted from baseline patient information. If a predictor reduced both the within-trial and among-trial standard deviations by 10%, then a historically controlled trial would require 180 participants to detect a 25% slowing of ALSFRS decline, 100 fewer participants than a concurrently controlled trial.

**Discussion:** Proper analysis of a historically controlled trial requires accounting for unexplained among-trial variation. We show that historically controlled trials are more efficient when a large treatment effect is expected. Other issues with historically controlled trials are the possibility of secular trends in the ALS rate of progression and the possibility that such trials will enroll a completely different population. Historically controlled trials have a place in the development of intensive treatments that would require a large treatment effect to be practical.

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**P200 MONITORING AMYOTROPHIC LATERAL SCLEROSIS DISEASE PROGRESSION WITH PLASMA CREATININE LEVELS**

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Keywords: clinical trials, outcomes, plasma creatinine

**Objective:** The aim of this study is to determine the potential value of plasma creatinine to monitor disease progression during clinical trials.

**Methods:** Clinical trial data from the Dutch lithium study and the open source PRO-ACT database were used for this study. Longitudinal ALSFRS-R scores and plasma creatinine values were available for 893 patients in the PRO-ACT database and for 40 patients in the lithium study. Linear mixed models were used to estimate between-subject slope variations, patterns over time, and extrapolation to disease onset.

**Results:** Both plasma creatinine and the ALSFRS-R declined significantly over time (p<0.001) and showed significant slope heterogeneity between subjects (p<0.001). However, there was more slope heterogeneity in the ALSFRS-R (60.1% (CI: 57.7–62.4)) than in plasma creatinine (23.0% (CI: 18.8–26.9)) (p<0.001). The longitudinal changes in plasma creatinine and ALSFRS-R had a non-linear correlation (p<0.001) showing that disease progression is earlier shown in plasma creatinine levels than in ALSFRS-R.

**Conclusions:** Plasma creatinine is a relatively low-cost objective measure and may be a more sensitive marker than the ALSFRS-R. The reduced heterogeneity in plasma creatinine slopes between patients establishes more homogenous trials populations and may thus increase the power to detect treatment effects.

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P201 PREDICTING DISEASE PROGRESSION FOR ALS CLINIC PATIENTS

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Keywords: clinic patients, predictive algorithms, disease progression

Background: We have previously developed disease models using the Pooled Resources Open Access Clinical Trials (PRO-ACT) database of ALS clinical trials. It is not clear whether the predictive tools developed using data from a clinical trial research database are useful for the wider ALS patient population who does not enroll in clinical trials. Indeed, the patients in the PRO-ACT database are generally higher functioning and more homogeneous than the general clinic population. Clinical trial participants tend to have higher functional scores, are more likely to be male, are half as likely to have had bulbar onset, and are generally younger. Thus, ALS patients enrolled in clinical research trials are likely to exhibit slower disease progression with less severe symptoms as compared to a typical clinic population. We hypothesized that an accurate predictive model useful for a general clinical population can be trained using patient data from the PRO-ACT as long as the range of attributes in PRO-ACT was broad enough to encompass the range of the clinic population.

Objectives: We asked whether models trained using PRO-ACT could predict the disease progression of clinic patients and outperform the predictive accuracy of a commonly used non-parametric linear model (NPL Model) for calculating the slope of the ALSFRS-R. The ultimate goal of these studies is to develop a model useful for predicting the disease course for the full range of ALS patients encountered at a tertiary care clinic.

Methods: Patient data from PRO-ACT was used to train a non-linear non-parametric random forest model (RF Model) and a parametric generalized linear model (GL Model). Previous models have used up to a 3-month run in period, but we reasoned that for a clinic application, a model that uses just baseline data taken at the first patient visit would be most useful. Thus, we investigated the performance of baseline models for this report. Both models were compared against the NPL Model for accuracy, bias, and classification accuracy.

Results: The RF Model modestly outperformed both the GL Model and the NPL Model in terms of root mean square deviation (RMSD). Measures of mean prediction error indicated that the RF Model is substantially less prone to bias and overfitting when applied to the clinic population.

Discussion: We conclude that a non-parametric, non-linear machine learning model (NPL Model) trained using research patients enrolled in clinical trials could more accurately predict disease progression in a population of patients attending a tertiary care clinic than existing models despite the potential confounds of bias due to trial participation and differences in the clinical and demographic distributions of research vs. tertiary care clinic ALS patient populations.

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P202 IN SILICO STRATIFICATION OF ALS PATIENTS USING MACHINE LEARNING ALGORITHMS

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Keywords: stratification, predictive algorithms, clinical trials

Background: Patient disease heterogeneity is widely believed to be a confounding factor in the analysis of ALS clinical trials. In particular, deaths and, at the other extreme, slowly progressing patients may be the root cause of the observed heterogeneity.

Objectives: We hypothesized that computer models incorporating predictions for both survival and disease progression as measured by the ALSFRS-R score could serve as tools to stratify patients into slowly, average and rapidly progressing patients.

Methods: We first developed Random Forest (RF) and Gradient Boosting Machine (GBM) predictive models for ALSFRS-R and survival, respectively, using the appropriate packages in the R programming language. A randomly selected sample from the Pooled Resources Open Access Clinical Trials (PRO-ACT) database was selected as an “industry standard” in silico trial population for detailed analysis and the models were trained using the remaining PRO-ACT records. The one year predicted 10% highest mortality patients were defined as rapid progressors while the 25% slowest progressors by predicted ALSFRS-R change in one year were defined as slow progressors. The remaining group was defined as average progressors. We plotted out the actual observed Kaplan–Meier survival curves of the rapidly, average and slowly progressing patients. We plotted out the actual observed Kaplan–Meier survival curves of the rapidly, average and slowly progressing patients, compared them to each other and to the original starting group of 425 patients.

Results: The predicted slowly progressing group had an observed ALSFRS-R slope of −0.44 pts/month and ~90% survived one year. In contrast, the predicted rapidly progressing group had an observed slope of −1.80 pts/month and a median survival of 5.8 months. The average progressing group closely resembled the starting group of 425 and had an observed slope of −1.18 pts/month and a median survival of 15.9 months.

Discussion: We conclude that ALS patients can be successfully stratified using a combination of algorithms that predict survival and ALSFRS-R progression.

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**P203 MACHINE LEARNING MODEL FOR THE PREDICTION OF SLOW VITAL CAPACITY**

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**Keywords:** tirasemtiv, predictive algorithm, SVC

**Background:** This report is the first step of a research collaboration that aims to retrospectively validate an ALS disease progression computer model leveraging data from the BENEFIT-ALS clinical trial of tiasenitiv. The PROACT database is a rich source of Forced Vital Capacity (FVC) records, but Slow Vital Capacity (SVC) records are relatively sparse. The BENEFIT-ALS trial used SVC as an outcome, thus we asked whether a reliable SVC predictive model could be developed using a training dataset rich in FVC records.

**Objectives:** To develop a model that predicts slow vital capacity using the PRO-FACT database.

**Methods:** Three different machine learning techniques including Random Forest (1), Gradient Boosting Machine (GBM) (2), and Xgboost (3) were used to predict slow vital capacity (SVC) using, for training, either forced vital capacity (FVC) alone or in combination with SVC records. Finally, the performance of the three models was compared.

**Results:** We initially asked whether FVC and SVC were correlated and found a strong linear correlation between the two, thus providing a strong rationale for using FVC records in the training dataset. We compared Root-Mean Squared Deviation (RMSD) and R2 for RF, GBM and Xgboost models trained with either FVC alone or with combined FVC and SVC records. The Xgboost option was discarded because it exhibited both a higher RMSD and lower R2 value than the other algorithms. Upon additional testing, it was revealed that the GBM model slightly outperformed the RF model.

**Discussion:** The goal of this study was to examine the possibility of using FVC records to predict SVC scores of ALS patients using machine learning techniques. Our results support our hypothesis and showed acceptable correlation. GBM outperformed other models and we selected GBM as our core model for developing a tool to predict SVC.

**Acknowledgments:** This work was supported by a grant (D.L.E.) from the Amyotrophic Lateral Sclerosis Association (17-LGCA-333).

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**P204 STRATIFYING ALS PATIENTS BY CLUSTERING DISEASE PROGRESSION PATTERNS FROM DATA**

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**Keywords:** disease progression, heterogeneity, stratification

**Background:** Several issues have complicated clinical research and trials regarding ALS. A predominant problem in understanding the disease and with designing clinical trials is the heterogeneity of the ALS population with respect to disease onset site, progression rate, and pattern of progression that vary among patients so that it is often extremely difficult to reach statistically sound conclusions in clinical trials, and large numbers of participants are required for these.

**Objectives:** Our goal is to suggest a new method of stratifying ALS patients by clustering from data disease progression patterns that characterize different disease functionalities of the patients.

**Methods:** First, using the PROACT database, we represented patients based on deterioration rates of their amyotrophic lateral sclerosis functional rating scale (ALSFRS) scores in performing functions of five body segment groups: bulbar, upper limbs, lower limbs, full body, and respiratory. Second, we clustered these representations using the k-means algorithm and selected the best clustering scheme using the Davies-Bouldin index (DBI). DBI minimizes the ratio between the scatter within the clusters and that between clusters, and thereby guarantees compact clusters that are far apart. Third, we identified the most predictive features for a patient cluster and predicted a progression rate for a patient assigned to that cluster using information about the cluster and its predictive features.

**Results:** We show that stratification yields an informative division of patients into four distinct groups. The groups are differentiated not only by the rate of disease progression (i.e. fast, moderate, and slow progressors), but also by the pattern of progression. Among the groups, one shows fast deterioration in all functions, another demonstrates slow progression in all functions, a third exhibits a moderate progression, but rapid bulbar deterioration, and the fourth is of patients with moderate progression but fast limb functionality deterioration. By plotting 2D rate scatter plots for pairs of the five body segment groups, we could identify which combination of the five can distinguish the four patient groups the best. By comparing characteristics of the groups, we detected the most predictive features for each patient cluster. Using the PROACT data, we then suggested and evaluated three methods for predicting a patient’s future progression pattern using features from early stages of the disease and cluster information. We showed that incorporating information from the clustering scheme improves performance of models in predicting the future rate of disease deterioration.

**Discussion and conclusions:** Our work suggests two important results: (a) clustering disease progression
patterns from data yields a novel, informative, and useful means of stratifying patients, and (b) this stratification can then be used to improve the prediction of disease progression rates by fitting a prediction model for each patient cluster separately.

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**P205 THE ALS STRATIFICATION CHALLENGE – USING BIG DATA SCIENCE TO IDENTIFY CLINICALLY SIGNIFICANT ALS PATIENT SUBPOPULATIONS**

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Keywords: disease progression, survival, classification

**Background:** Amyotrophic lateral sclerosis (ALS) shows significant heterogeneity in progression and survival. Patients show highly variable disease development paths that pose a challenge for clinicians devising care strategies, researchers exploring disease mechanisms, and pharmaceutical companies planning and interpreting clinical trials. Therefore, identifying and characterizing meaningful sub-groups of ALS patients is of great significance for advancing ALS research and improving patient care.

**Objectives:** The DREAM ALS Stratification Prize4Life Challenge was a crowd sourcing initiative that aimed to address the problem of ALS patient heterogeneity with regards to two important clinical targets: ALSFRS progression and patient survival.

**Methods:** The challenge ran during summer 2015, and used ALS clinical data from the PRO-ACT database, as well as data from National/regional ALS registries from Italy and Ireland. Participants were asked to derive meaningful sub-groups of ALS patients, identify the most informative clinical features from the dataset and use them to predict disease progression and survival. The challenge drew in 288 participants and 70 final submissions. Submitted algorithms used statistical and machine learning approaches to classify patients and make progression and survival predictions.

**Results:** The Winning algorithms in the challenge outperformed all other methods and currently available benchmarks. The most informative features for both survival and progression predictions were overall ALSFRS score, ALS onset site (limb/bulbar), weight, and time from symptoms onset, while age was most informative for survival predictions only. Twenty-two submissions included clustering of patients into subgroups based on clinical features or outcomes. While algorithms that did not cluster the patients generally performed better in making predictions on the general patient population, models that did choose to cluster gave better predictions for the more extreme cases — mainly the very fast progressing patients. We used participants’ clustering results to detect patients which were consistently grouped together and identified four reliable clusters. These novel subgroups of patients had distinct clinical, physiological, progression, and survival profiles. A few of the most distinctive features separating the clusters were symptoms onset location (limb/bulbar), time from disease onset, functional scores for different modalities (hands, legs, trunk, mouth), breathing measurements, and disease progression rate. We will present a full description of the clusters and use the data and challenge outcomes from ALS national registries to demonstrate how our results may be applicable to the overall ALS patient population and applied to the day to day patient care in the clinical setting.

Discussion and conclusions: Algorithms submitted to the challenge were able to consistently identify clinically significant subpopulation of patients, and use this information to accurately predict disease progression and survival. These results demonstrate the value of large datasets and crowd sourcing challenges for developing a better understanding of ALS natural history, prognostic factors, and for improving ALS clinical development.

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**P206 A POPULATION DISEASE PROGRESSION MODEL FOR AMYOTROPHIC LATERAL SCLEROSIS – RESULTS OF THE TREEWAY SUMMER CHALLENGE 2015**

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Keywords: disease model, disease progression, prediction

**Background:** Amyotrophic lateral sclerosis disease progression is monitored by means of the ALS Functional Rating Scale (ALSFRS), evaluating the ability to perform several physical tasks. However, disease progression, as assessed by this symptomatic scale, is highly variable between patients, thus complicating accurate estimation of patient’s prognosis and clinical trial design and analysis.

**Objectives:** During the 10-week Treeway Summer Challenge 2015, a group of 9 MSc and PhD students aimed to gain more insight in the complex pathobiology of
ALS and to develop a disease progression model to better understand patient heterogeneity and predict disease progression on population and individual level.

**Methods:** Longitudinal ALSFRS scoring data was obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. Patients from both active and placebo treatment arms, but not those on riluzole were included. Using these criteria data from 1069 ALS patients and a total of 8365 ALSFRS evaluations were available for the fitting of the longitudinal disease progression model.

**Results:** Similar to the only available ALS disease progression model in literature (1), disease progression was best described by the Weibull function. Subsequent stepwise covariate model building resulted in the inclusion of baseline ALSFRS (BAS) on all three function parameters and site of onset as a covariate on the time-dependent parameter (td). With this model, the occurrence of two distinct subpopulations could be explained by the site of onset, bulbar- vs. limb-onset.

**Discussion and conclusions:** The current model provided an adequate model to describe the longitudinal disease progression as measured by the ALSFRS score and could distinguish two subpopulations with distinct disease progression rates based on site of onset. Still, there remains a high degree of unexplained residual variability which should be explored in further research.

**Acknowledgements:** We thank Prize4Life for providing the raw data to conduct this study and Stichting ALS Nederland, Stichting “aan ALS komt een eind” and Heincken for financially supporting the summer challenge.

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**P207 EVALUATION OF AN ALS STAGING SYSTEM IN A US POPULATION**

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**Keywords:** ALS staging, prognosis, clinical tools

**Background:** Validated staging systems for ALS can increase understanding of the disease prognosis, help with resource management and research design. Recently, a staging system was proposed for ALS in a UK population (1) using clinical milestones for disease progression. Milestones were defined as symptom onset in one region (bulbar, upper limb, lower limb or diaphragmatic) (Stage 1), diagnosis (2a), involvement of a second region (2b), third region (3), and finally gastrostomy (4a) and non-invasive ventilation (4b). These stages/milestones occurred at predictable times when examined over the course of the illness with Stage 2a at 35%, stage 2b at 38%, 3 at 61%, 4a at 77%, and 4b at 80%. To date, this staging system has not been validated in a US population.

**Objectives:** To validate this proposed staging system in a US population.

**Methods:** We reviewed 84 clinical records at Drexel University College of Medicine (DUCOM) in order to compare the stage durations between our DUCOM and the UK population. We identified the percentage of time in each stage for both bulbar and limb onset, demographics and survivals in order to compare the results of the two populations. Survival analysis included Kaplan-Meier plots and results between the US subjects and UK subjects were analyzed with t-tests.

**Results:** DUCOM subjects included 56 limb (23F, 33M), and 28 bulbar onset (11F, 17M). The average age of onset was 62.4 years (Y) (62.6Y F, 62.2Y M), 63.9Y (62.1Y M, 66.5Y F) for bulbar onset and 61.5Y (61.85Y M, 61Y F) for limb onset. In the DUCOM population 2a occurred at 44%, 2b at 31%, 3 at 39%, 4a at 59%, and 4b at 62% through the disease course. Compared to the UK population, 2a occurred later, 2b occurred before 2a, and more time was spent between stages 2a and 2b. In both, stages 4a and b occurred at a similar point during course of disease, but in DUCOM subjects, this occurred at 59 and 62%, respectively, while in UK subjects it occurred at 75 and 76%, respectively. Survival was similar in both (37.3 vs 42.3 months).

**Conclusion:** The clinical staging system was easily applied to this population and similar to UK, Stage 4a and 4b occurred at the same time and likely can be collapsed into a single stage. Differences in overall results may relate to definitions of time of diagnosis and there may be a need to harmonize how the system is applied. While further validation and prospective studies will be needed, we agree that this staging system holds promise in guiding prognosis, use of resources and clinical research.

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**P208 AN ASSESSMENT OF TREATMENT GUIDELINES, CLINICAL PRACTICES, DEMOGRAPHICS, AND PROGRESSION OF DISEASE AMONG INDIVIDUALS WITH AMYOTROPHIC LATERAL SCLEROSIS IN JAPAN AND THE UNITED STATES**

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Keywords: clinical practice, treatment patterns, disease progression

Background: There continues to be a need for new therapies to treat amyotrophic lateral sclerosis (ALS). Edaravone (MCI-186) has been investigated in Japanese patients with ALS using the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R).

Objectives: Assess clinical practice and treatment guidelines, and compare the progression of disease among patients with ALS in Japan and the US.

Methods: To assess relative similarities and differences that might exist between Japanese and US medical practice for ALS, we reviewed country-specific practice guidelines. We also performed a literature review to compare the demographics and baseline characteristics of ALS for Japanese and US populations. Using reference studies of ALS in the US and edaravone studies in Japan, progression of ALS disease was assessed in patients receiving placebo using a random coefficient model, with an assumption that ALSFRS-R score declines in a linear fashion within each patient. The changes per month in ALSFRS-R score were calculated and compared between the studies. These results were also compared with published longitudinal data from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database.

Results: Overall, diagnostic criteria, recognition of ALS symptoms, comorbidities, use of riluzole as the first-line therapy, nutrition, and respiratory support were similar between the Japanese and US guidelines (1–4). Regarding demographic and baseline characteristics of the published literature, there were no clear differences in the incidence of sporadic ALS (93% vs 94–96%) and bulbar onset (25–30% vs 32–33%), time from onset to diagnosis (11 months vs 11–12 months), and use of percutaneous endoscopic gastrostomy (29–33% vs 9–27%) among the Japan and US populations, respectively. However, use of tracheostomy-based invasive respiratory support was higher in Japan (29–34%) than the US (4%).

Progression of disease, as assessed by ALSFRS-R score in patients receiving placebo, was similar between the reference studies including the US population (range across 6 studies, –0.89 to –1.28 points/month) and edaravone studies in the Japanese population (range across 3 studies, –0.98 to –1.21 points/month). These results parallel with published data from the PRO-ACT database (–1.02 ± 2.3 points/month) (5).

Discussion: Clinical practice and treatment guidelines for ALS between Japan and the US are similar with the exception of tracheostomy use. Progression of disease, as assessed by ALSFRS-R, appears similar between Japanese and US patients with ALS.

Conclusion: In Japan and the US, there are comparable clinical practices, treatment guidelines, and disease identification and progression for ALS populations, apart from the higher use of tracheostomy in Japan.

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P209 A MODEL-BASED ADJUSTMENT METHOD FOR THE ANALYSIS OF LONGITUDINAL MUSCLE STRENGTH DATA IN ALS

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Keywords: muscle strength, hand-held dynamometry, model-based adjustment

Background: Measures of muscle strength provide critical information on ALS onset and disease progression. Muscle strength can be affected by many factors, such as the size of a muscle, and an individual’s age, sex, and body weight. Analysis of strength data needs to adjust for differences in these factors to allow for comparison between muscles and between individuals. Two popular adjustment methods in ALS are z-scores and percent predicted values using normalization equations. However, z-scores are not easily interpretable and tend to obscure varying degrees of strength loss for different muscles in ALS patients at study entry. Percent predicted strength depends on normalization equations, which may not be available in the literature for some muscles. Therefore, there is a need for an alternative adjustment method that can address these issues.

Objectives: In this study, we propose and describe a model-based adjustment method for the analysis of longitudinal muscle strength data in ALS.

Methods: We used longitudinal quantitative muscle strength data collected using hand-held dynamometry (HHD) on 18 muscles (9 bilaterally) from 943 patients in the EMPOWER study. A linear mixed-effects model (LMM) with random subject effect and autoregressive within-subject covariance structure was employed to analyze the data. Month of follow-up was treated as a categorical variable. The estimated variance components from LMM were added to obtain the total variance. The estimated effects of strength loss were then standardized from LMM were added to obtain the total variance. The estimated effects of strength loss were then standardized based on normalization equations, which may not be available in the literature for some muscles. Therefore, there is a need for an alternative adjustment method that can address these issues.

Objectives: In this study, we propose and describe a model-based adjustment method for the analysis of longitudinal muscle strength data in ALS.

Methods: We used longitudinal quantitative muscle strength data collected using hand-held dynamometry (HHD) on 18 muscles (9 bilaterally) from 943 patients in the EMPOWER study. A linear mixed-effects model (LMM) with random subject effect and autoregressive within-subject covariance structure was employed to analyze the data. Month of follow-up was treated as a categorical variable. The estimated variance components from LMM were added to obtain the total variance. The estimated effects of strength loss were then standardized based on normalization equations, which may not be available in the literature for some muscles. Therefore, there is a need for an alternative adjustment method that can address these issues.

Results: All muscles showed significant strength loss over time and the absolute magnitude of the loss varied between muscles. The largest strength loss occurred on the first dorsal interosseous muscles (–0.54), while the smallest strength loss occurred on the knee extensor muscles (–0.32). Average strength loss showed a strong linear trend over time for each muscle and the slopes of
the linear lines ranged from $-0.045$ per month to $-0.065$ per month.

**Discussion:** The model-based adjustment method does not require data transformation and provides a unified framework for assessing both cross-sectional and longitudinal strength loss. The z-score method can be considered as a special case of model-based adjustment in that the sample mean is used in the former while a regression on age, sex, and body weight is employed in the latter.

**Conclusions:** The model-based adjustment method provides a systematic framework for adjusting for strength differences between muscles and between individuals.

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**P210 MAGNIFYING MOVEMENT: THE USE OF EULERIAN VIDEO MAGNIFICATION TO ENHANCE DETECTION OF MUSCLE FASCICULATIONS IN ALS**

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**Keywords:** fasciculations, Eulerian Video Magnification

**Background:** Muscle fasciculations is an early and typical lower motor neuron sign that is closely associated with amyotrophic lateral sclerosis (ALS). Detecting muscle fasciculations is difficult however, due to their often subtle and fleeting nature. Classically, this is done through clinical inspection, supplemented by needle EMG and ultrasonography (1). However, these techniques have significant limitations, including significant discomfort, the ability to screen a limited region of a single muscle at a time, and cost. Scientists at Massachusetts Institute of Technology (MIT) recently developed software known as Eulerian Video Magnification (EVM) that can reveal details in video footage that are otherwise invisible by exaggerating differences in pixels over time (2). The technology could potentially reveal fasciculations that go undetected by the naked eye, thereby enabling earlier diagnosis in ALS.

**Objectives:** To determine whether the use of EVM increases the detection of fasciculations in video footage of muscle groups of people with ALS (PALS), compared to direct clinical observation (DCO).

**Methods:** Seven PALS and seven controls with non-neuromuscular disorders were recruited, and thirty-second long video recordings were made of nine regions (bilateral arms, thighs, hamstrings, calves, and back). Fasciculations were also counted by DCO during the same thirty-second period. A total of 124 video recordings (61 ALS and 63 controls) were then motion-magnified, and both the original and magnified recordings were reviewed in random order by two independent assessors, who were asked to record the number of fasciculations visible per recording.

**Results:** In muscle groups of PALS, the median fasciculation count was one by DCO (range 0–10) and three in the magnified recordings (range 0–15; p<0.0001). EVM revealed more fasciculations than DCO in 37 (61%) muscle groups; in nine of these fasciculations were detected with EVM where none were detected clinically. In muscle groups of controls, the median fasciculation count was 0 for both DCO (range 0–4) and EVM (range 0–6). EVM revealed more fasciculations than DCO in seven (11%) muscle groups; in four of these fasciculations were detected with EVM where none were detected clinically.

**Discussion and conclusions:** Compared to DCO, EVM significantly increased the detection of fasciculations in muscle groups of PALS, but not controls. If used to supplement clinical examination, EVM has the potential for earlier identification of fasciculations in ALS. The technique is non-invasive, requires no specialized equipment, and can be used to screen large areas of muscle at once. The potential contribution of EVM to earlier diagnosis in ALS certainly warrants further investigation.

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**P210A MEXILETINE FOR THE TREATMENT OF MUSCLE CRAMPS IN ALS: A RANDOMIZED DOUBLE-BLIND CROSSOVER TRIAL**

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**Keywords:** muscle cramps, symptom management, mexiletine
Background: Muscle cramps affect >90% of ALS patients, often so severely that they request medications. Muscle cramps are thought to be a consequence of hyperexcitability of peripheral motor axons through increased persistent sodium currents. Mexiletine is a selective persistent sodium current blocker. Mexiletine reduces cramp propensity in human lower motor neurons and reduces cramps in an unselected ALS cohort.

Objectives: To evaluate the effects of mexiletine on ALS patients suffering trouble muscle cramps.

Methods: Twenty ALS patients suffering muscle cramps completed a double-blind multicenter randomized crossover study. The primary outcome measure was daily cramp count. Secondary measures were 100 point visual analogue scale (VAS) cramp severity, and fasciculation severity. After a one week lead-in, patients were randomized 1:1 to mexiletine 150mg BID or placebo for a two week treatment epoch. This was followed by a one week washout. Patients were then crossed over to a second two week treatment epoch. We also monitored safety (EKG, blood chemistry) and tolerability. We used three methods to analyze the data: (A) Within a subject, mean responses using t-test. (B) A linear mixed effects model with random effects added to allow for different constants, placebo and drug effects in different patients. (C) We also tested for treatment, period, and order of treatment effects.

Results: Numbers of cramps: in 18 of 20 patients, the mean number of cramps was reduced. Thirteen were significant at two-sided p<0.05, nine of these at p<0.01. The probability for this occurring by chance is less than 10–10. Using the linear mixed effect model the average reduction was 1.8 (baseline 6) cramps per day p=0.001. The standard deviation of the random effect for treatment was 2.3, indicating a high variation in treatment effect. Analysis of the mean number of cramps for each patient in each phase also showed a significant treatment effect (p=0.008) while neither period nor sequence of treatments were significant (p=0.39 and p=0.7). Neither sex nor age played a role in predicting treatment effect. Cramp severity: the linear mixed effects model showed reduction in cramp severity across all patients. The estimated reduction was 15 points from a baseline of 46 on the 100 point VAS (p=0.011). Fasciculation Severity: none of the models found a treatment effect on the VAS.

Discussion and conclusions: Mexiletine at low dose (150mg BID) appears to be an effective treatment of muscle cramps in ALS, reducing cramp count and severity. However, the benefit varied from patient to patient, and in most patients cramps were not abolished completely. Mexiletine was ineffective at reducing fasciculations. No safety concerns were noted in this short duration randomized placebo-controlled study, consistent with the well-established safety profile of the medication at this dose.

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P211 UNDERSTANDING CRAMPS AND FASCICULATIONS

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Keywords: multicentered, long-term, symptoms

Background: Fasciculations are random involuntary muscle twitches, observed clinically as well as recorded by a needle electromyography (EMG) as fasciculation potentials. Cramps are involuntary, painful, rapid contractions of the skeletal muscles. Both fasciculations and cramps can occur in normal subjects as well as in several disease states, including ALS (1). In ALS, both are common early symptoms that often aide in the diagnosis (2), but little is known about how these symptoms change over time or affect clinical outcome.

Objectives: To improve the clinical relevance of cramps and fasciculations in an ALS cohort.

Methods: We analyzed data from 80 ALS patients (75 with complete data) enrolled in a 48 week multi-visit and multicenter non-intervention nutrition ALS study with over 10 years of survival data. We evaluated cramps and fasciculations in the context of related confounding factors including: gender, location of onset, forced vital capacity and fat free muscle mass. Paired t-tests were used to compare data sets. Both univariable and multivariable Cox proportional hazards model was used to assess the association between cramps and the overall survival (time to mortality) as well as between fasciculations and the overall survival. The unadjusted (from univariable model) and adjusted hazard ratios (HRs) were reported. The generalized estimating equation was used to examine the temporal trend of cramps and fasciculations over the entire follow up time. Statistical analysis was performed using Stata version 14.

Results: Fasciculations are statistically associated with the overall survival of ALS patients, with an unadjusted HR of 1.05 (95%CI: 1.01–1.11, p value = 0.018). This is to say, with 1 point increase in fasciculation index, the hazard of mortality for the ALS patients will be increased by 5%. No statistically significant association between cramps and mortality of ALS patient is found in both univariable and multivariable models (unadjusted HR = 0.97, 95%CI: 0.92–1.02, p value = 0.223). No statistically significant temporal trend was found for fasciculations or cramps. On average, cramps decreased by 0.0129 point per week (p value = 0.238) and fasciculations increases slight by 0.0008 point per week after baseline (p value = 0.949).

Discussion and conclusions: This large study with long-term survival data has identified associations with fasciculations and cramps in ALS not previously reported.
Based on our findings, cramps and fasciculations do not significantly change over the course of the disease. Fasciculations may be a useful marker for ALS survival, which has implications for clinical care and clinical trials.

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P212 EXTRAPYRAMIDAL SIGNS IN ALS PATIENTS: A PROSPECTIVE SURVEY

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Keywords: extrapyramidal, ALS, phenotype

Background: The most recent research findings, such as understanding the role of C9ORF72 gene’s pathological expansions in causing both ALS (Amyotrophic Lateral Sclerosis) and FTD (Frontotemporal Dementia), suggest that ALS could be considered as a spectrum of disease. A lot of clinical studies have reported cases of ALS patients presenting extrapyramidal signs and symptoms. These findings are supported by neuropathological studies describing the extrapyramidal system degeneration in these patients.

Objectives: To determine the presence of extrapyramidal signs in ALS patients, describe their clinical and diagnostic characteristics, and define a new phenotype of the disease.

Methods: A total of 114 patients were enrolled and underwent a three years’ clinical follow-up. During the first year, these patients were subjected to the following exams: analysis of the main ALS genes, brain MRI, and 18F-FDG-PET, a battery of neuropsychological tests. All the patients were examined by a Parkinson’s Disease specialist at the basal time and every three years; furthermore, once every year, they were assessed by a Parkinson’s Disease specialist using the UPDRS (Unified Parkinson’s Disease Rating Scale). A brain SPECT Scan was performed on all the patients with extrapyramidal signs and symptoms. During the second year of the study, all the patients underwent an analysis of the main Parkinson’s Disease-related genes.

Results: No significant phenotypic, neuropsychological and genotypic differences were reported between ALS patients with extrapyramidal signs and symptoms and those without them, except from a 25% excess of risk in men of developing extrapyramidal signs in concomitance with ALS. The more significant result was a marked hypermetabolism of putamen in ALS patients with extrapyramidal signs, which was absent in the remaining patients: this result was verified at a 1/1000 significance and is similar to the neuroimaging findings in patients affected by PD.

Conclusions: This is the first prospective cohort study with the aim to ascertain and describe an extrapyramidal phenotype of Motor Neuron Disease. The results show that, although no significant phenotypic and genotypic differences were described between the patients with and without extrapyramidal signs, there are specific functional changes typical of the first group of patients. 18F-FDG-PET, already considered a successful instrument for evaluating the entity of brain lesions in neurodegenerative diseases, has been of cardinal importance in demonstrating the presence of metabolic patterns typical of ALS patients with extrapyramidal signs; therefore it could play a major role in studying the multisystem involvement in ALS.

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P213 RECEIVING THE DIAGNOSIS OF MOTOR NEURONE DISEASE (MND): QUALITATIVE DATA FROM AN AUSTRALIAN SURVEY

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Keywords: diagnosis, qualitative research, communication

Background: The diagnosis of MND is not only challenging for neurologists to give, but also for those being given the diagnosis, and their family members. This devastating diagnosis requires great sensitivity in the manner in which it is communicated, in order for the person and their family to come to terms with what needs to be done as well as find support for the duration of the illness.

Objective: The overall objective of this study was to identify the experiences of people with MND and their family members in receiving the diagnosis.

Method: This consisted of an anonymous postal survey facilitated by all MND Associations across Australia, in 2014. Questions centered on the SPIKES protocol for
communicating bad news and each question contained an area for writing further responses.

**Results:** Two hundred and forty-eight responses were received from people with MND, estimated to be 29% of those receiving care from all Australian MND Associations. Three themes were identified from reading and re-reading the written responses to questions. These were: challenges in being diagnosed with MND; the emotions experienced; and links to further information and support. Receiving an MND diagnosis requires preparation and forethought on the part of the neurologist, including where and how the diagnosis is given; what supports should be in place so the person is not alone; and the timing, amounts and sources of giving information. The results also showed how the emotional reactions of the neurologist cause a lasting impression on those receiving a diagnosis of MND.

**Conclusion:** The diagnosis of MND requires sensitive and individualized care on the part of the neurologist. Guidelines from other medical disciplines may provide the basis for developing disease-specific guidelines to support neurologists in giving bad news.

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