

## SESSION 3B CLINICAL PHENOTYPES AND DISEASE PROGRESSION

### C21 MRI-BASED NEUROIMAGING AS A SURROGATE MARKER IN ALS AND OTHER MOTOR NEURON DISORDERS: PROSPECTS AND PITFALLS

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Computerised magnetic resonance imaging (MRI)-based techniques are increasingly used to analyse the structural and functional pathoanatomy of the brain in neurodegenerative diseases such as ALS and other MND *in vivo*. Besides volumetric approaches in regions-of-interest and magnetic resonance spectroscopy, especially whole brain-based techniques are accepted advanced neuroimaging tools for cross-sectional or longitudinal investigations, such as morphometric 3-D T1-weighted MRI analysis (e.g. voxel-based morphometry) and diffusion tensor imaging (DTI) which provides insights into white matter microstructure at group or individual level. Most promising for the *in vivo* mapping of structural MRI-based computational neuropathology are multiparametric protocols with multiple neuroimaging techniques in combination. For a correlational or direct analysis of the functional impact, it has been shown that the inclusion of covariance analysis with clinical parameters or the co-registration with task-specific functional mapping (functional MRI) might give complementary information.

The application to ALS but also to other MND entities with different clinical phenotypes of upper or lower MN affection has successfully been used to identify lesion patterns of central motor and extra-motor areas and thus provided the option to map the alterations of MND patients' brains *in vivo* - at least at group level. That way, it has been possible to define pathomorphological grey matter or white matter 'fingerprints' of various types of MND. Furthermore the post-processing techniques allow for a quantitative comparison of MRI data from MND patients with controls, including tract-based statistics of DTI data. It has to be considered, however, that with respect to being used as a diagnostic tool at the individual patient's level, the above-named techniques face severe limitations in applicability, sensitivity and specificity. One important aim in MND beyond gaining a deeper understanding of the disturbed neuroanatomical and functional networks will be the establishment of (combined) MRI protocols as a ('dry') biomarker (i) in natural history studies with MND patients who are well-defined in all aspects of their clinical presentation and (ii) in potential disease-modifying multi-center trials. For that purpose, there is not only a need for a higher number of longitudinal studies but also for more uniformity in the acquisition and especially post-processing of computer-based neuroimaging data in order for the methods to be both reproducible and valid. This aim is to be realised in large quality-controlled multi-national databases.

### C22 NEW DIAGNOSTIC CRITERIA FOR PRIMARY LATERAL SCLEROSIS: A PROSPECTIVE VALIDATION STUDY

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*Keywords: PLS, HSP, prognosis*

**Background:** Diagnosis of primary lateral sclerosis (PLS) is by exclusion and current diagnostic criteria include a disease duration of  $\geq 4$  years to exclude ALS and a negative family history to exclude hereditary spastic paraparesis (HSP). However, sporadic presentation of HSP is not rare while genetic testing for many HSP forms is currently not available. We have previously shown that differentiation of sporadic HSP from PLS based on clinical characteristics is unreliable, although bulbar region UMN symptoms may support diagnosis of PLS.

**Objectives:** To prospectively assess the diagnostic and prognostic value of new criteria for clinical diagnosis of PLS, incorporating different levels of certainty of diagnosis of PLS instead of sporadic HSP.

**Methods:** Ninety one patients were included and classified according to our new PLS diagnostic criteria. Inclusion criteria were a gradually progressive, adult-onset ( $\geq 18$  years), UMN syndrome, of  $\geq 6$  months duration. Exclusion criteria were a positive family history, clinical or electrophysiological evidence of generalized LMN involvement, and evidence of other causes.

**Results:** Included were 22 patients with 'suspected PLS' (duration  $< 4$  years), 30 with 'possible PLS' (duration  $\geq 4$  years, UMN signs only in legs), 13 with 'probable PLS' (duration  $\geq 4$  years, UMN signs in arms and legs), and 26 with 'definite PLS' (duration  $\geq 4$  years, UMN signs in at least bulbar region), according to our criteria. After a median follow-up of 3.0 years (range 0.1-4.3), 27 (30%) had shifted to a more certain PLS diagnosis, 7 (8%) fulfilled criteria for ALS, and 3 patients (3%; 2 'possible PLS', 1 'probable PLS') were re-diagnosed with another disorder (2 HSP, 1 corticobasal degeneration (CBD)). Conversion to ALS did not occur in 'possible PLS'. In 3 'suspected PLS' patients conversion to ALS was associated with clinical LMN signs and with typical short survival (median 2.7 years, range 2.3-3.7). Overall, rate of disease progression was variable and not related to EMG findings. At last verification 21 patients had died: 4 died of

ALS, 1 of CBD, 11 died indirectly related to PLS, and 5 died of unrelated causes.

**Discussion:** Our new PLS diagnostic criteria help to identify patients in whom PLS diagnosis is less certain, either because they may still evolve to typically progressive ALS (in ‘suspected PLS’), or because they may still have sporadic HSP instead of PLS (in ‘possible PLS’ and ‘probable PLS’). Criteria for ‘definite PLS’ identify patients very unlikely to have sporadic HSP, although some of these patients may develop mild LMN signs or even fulfill EMG criteria for ALS, which in our study was not clearly associated with more rapid clinical deterioration.

**Conclusions:** These new PLS criteria have diagnostic and prognostic value in the differentiation between sporadic HSP, typical ALS, and PLS.

### C23 A RETROSPECTIVE ANALYSIS COMPARING FAST AND SLOW ALS PROGRESSION AND STUDYING FUNCTIONAL DECLINE AFTER INITIATING PEG AND BiPAP

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Keywords: ALSFRS-R, PEG, BiPAP

**Background:** ALS Functional Rating Scale-Revised (ALSFRS-R) is a commonly used outcome measure that may predict survival in ALS clinical trials. Determining which of the 12 ALSFRS-R questions best predicts survival is valuable information for both trials and clinical practice. Bi-level Positive Airway Pressure (BiPAP) and Percutaneous Endoscopic Gastrostomy (PEG) improve ALS survival but their impact on patients’ functional status is unclear.

**Objectives:** To determine patient characteristics and early ALSFRS-R answers that best predict future disease progression, and to compare the rate of functional (ALSFRS-R) and respiratory (FVC) decline before and after BiPAP and PEG placement.

**Methods:** This is a retrospective study of (519) ALS patients who participated in one of the following trials: celebex (n = 300), creatine (n = 104), arimoclomol (n = 84), and CoQ10 (n = 31). A linear mixed effects model was used to distinguish fast progressing (FP) and slow progressing (SP) patients compared to mean ALSFRS-R decline over time. A t-test was used to compare continuous variables and a Chi-Squared test was used to compare categorical baseline variables. A Cochran-Armitage test was used to test for trends of baseline ALSFRS-R questions. A stepwise-Cox regression model was used to investigate the relationship between ALSFRS-R answers and survival. A linear mixed effects model was used to compare ALSFRS-R and FVC slopes before and after starting BiPAP and PEG. Only subjects with at least two ALSFRS-R and FVC measurements before and after BiPAP or PEG were included in this analysis.

**Results:** There were 41% fast progressors (FP) and 59% slow progressors (SP). Site of onset and time from symptom onset to diagnosis were different between the two groups (p = 0.03) and (p = 0.004), respectively. There was no significant difference in other baseline characteristics including age, gender, family history, baseline weight, or riluzole intake. Answers to ALSFRS-R questions at baseline visit were all significantly different between SP and FP except for handwriting (p = 0.41)

and respiratory insufficiency (p = 0.17). Trial dropout rate of FP (41%) was 3.2 times more than SP (13%). Out of the 12 ALSFRS-R questions, climbing (p = 0.008), writing (p = 0.04), and salivation (p = 0.04) were the only predictors of survival. ALSFRS-R rate of decline was 0.35 units/month faster after BiPAP onset (p < 0.0001) and 0.32 units/month faster after PEG placement (p < 0.0004). These results remained significant after omitting ALSFRS-R “Swallowing” and “Respiratory insufficiency” questions for PEG (p = 0.01) and BiPAP (p = 0.001) analysis. The rate of FVC decline was not significantly different after BiPAP (p = 0.09) or PEG (p = 0.94).

**Discussion and Conclusion:** Slow ALS progressors are more likely to enroll in and complete clinical trials. Most ALSFRS-R questions are good early predictors of disease progression. Climbing, writing, and salivation ALSFRS-R questions are good predictors of survival and none of the “respiratory” questions are. Functional decline measured by ALSFRS-R is faster after PEG or BiPAP use.

### C24 TARDBP GENE MUTATION IN ALS PATIENTS: A GENOTYPE-PHENOTYPE CORRELATION STUDY

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Keywords: familial ALS, TARDBP, phenotype

**Objectives:** To describe the phenotype of ALS patients with TARDBP gene mutations and present genotype-phenotype correlations.

**Background:** In approximately 10 to 20% of ALS cases, at least 2 cases are present within the pedigree, defining it as familial ALS (FALS). In 25% of those FALS cases a SOD1 mutation has been described as responsible for the disease. Recently, we and others have described TARDBP gene mutations in both sporadic and familial cases. While SOD1 mutations may modulate phenotype with rapid or slow evolution and with lower limb onset in the majority of the cases, the phenotype of ALS patients with TARDBP mutations has not been described, to date.

**Methods:** We describe phenotype and genotype of 9 ALS patients presenting with TARDBP gene mutations and their phenotype-genotype correlations.

**Results:** The five men and four women studied had the following characteristics: mean age of onset 58 ± 10 (range 46–78), 7 out of 9 had an upper limb onset, the disease was sporadic in 5 and within the 4 FALS cases (a mother and her son carried the same TARDBP mutation), mean disease duration was 71 months ± 53 (range 10–158), two patients are alive after 8 years and one of them had a tracheostomy after 5 years of ALS. Clinically all patients had both upper and lower motor neuron signs in 2 or 3 regions, with typical EMG features, without sensory conduction abnormalities. Three patients had transcranial magnetic stimulation (TMS) and single fibre EMG (SFEMG). In all cases these examinations were abnormal. Out of the 9 patients, 6 different mutations were found. Comparison between mutations, FALS and sporadic cases suggested that FALS cases have an earlier onset and a much longer course of ALS (103 months vs 39).

**Discussion:** Compared with classical ALS, patients carrying TARDBP mutation have few different characteristics. The apparently most significant difference lies in the site of onset as an upper limb onset is present in 7 out the 9 patients. However, mutated patients cannot be clinically distinguished from classical ALS cases. ALS is more slowly evolving in familial cases with TARDBP mutations, as already suggested in other FALS cases with or without SOD1 mutations. To date, our series is too limited to conclude that some specific TARDBP mutations are associated with a more rapid or slow ALS in opposition with that shown with SOD1 mutations.

## C25 TACKLING THE CHALLENGES OF ALS FROM A FAMILIAL PERSPECTIVE

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*Keywords: SOD1, pre-symptomatic, biomarkers*

**Background:** Amyotrophic lateral sclerosis (ALS) is a disease that remains shrouded in mystery. With the exception of rare mutations in genes such as superoxide dismutase (SOD1), the etiology of ALS is unknown. Little is known about environmental risk factors for ALS. Other than electromyography and motor unit number estimation, there are no biomarkers for ALS that might permit early diagnosis or be useful in monitoring disease progression or therapeutic response. Apart from riluzole there are no effective therapies. We contend that the systematic study of asymptomatic SOD1 positive (SOD1+) individuals, the only population known to be at risk for developing ALS and SOD1+ ALS patients, offers several unique opportunities to unravel many of the mysteries of this disease.

**Objectives:** To (1) characterize the pre-symptomatic phase of ALS, (2) identify environmental factors that may modify the age of disease onset and which may be relevant to the risk of sporadic ALS, (3) develop biomarkers for early diagnosis, and

(4) evaluate the safety and efficacy of arimoclomol in SOD1+ familial ALS patients.

**Methods:** We address these objectives through two parallel studies. The first, the Pre-familial ALS (Pre-fALS) study, is a prospective observational study. The second is a phase II/III randomized controlled trial (RCT) of arimoclomol, which targets a relevant pathophysiological mechanism and is effective in the SOD1 mouse when administered even after symptom onset. For Pre-fALS we offer genetic testing and counseling in order to identify and recruit presymptomatic SOD1+ individuals from familial ALS pedigrees. Study participants are evaluated annually using clinical, neurophysiological and neuroimaging techniques and environmental exposure assessment; biospecimens are also collected. For the RCT, we recruit individuals with recently diagnosed SOD1+ ALS. These individuals are randomized to receive arimoclomol or placebo and are followed serially over a 12-month period. The trial employs a novel 'remote evaluation' approach whereby most study procedures are performed in the study participant's home.

**Results:** As of May 2009, 68 subjects have been enrolled in Pre-fALS. Most participants who were previously unaware of their SOD1 gene mutation status, have elected to undergo genetic counselling and to learn their results. Over half of these subjects have completed their initial set of evaluations and some have already returned for their first annual follow-up visit. Twelve subjects have been screened for the arimoclomol trial and so far two subjects have been randomized.

**Discussion and Conclusion:** Pre-fALS is unique insofar as it prospectively follows asymptomatic people at risk for ALS using a broad range of investigative modalities. The arimoclomol RCT employs a novel 'remote evaluation' approach and focuses exclusively on the SOD1+ population. Progress to date is evidence of the feasibility of these studies. Although currently in their early stages, they hold promise to provide unique insights into disease biology and therapy.