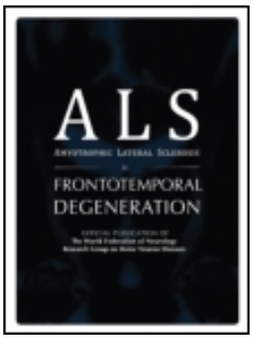
Taylor & Francis
Taylor & Francis Group




Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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

# THEME 1 IMPROVING DIAGNOSIS, PROGNOSIS AND DISEASE PROGRESSION

**To cite this article:** (2014) THEME 1 IMPROVING DIAGNOSIS, PROGNOSIS AND DISEASE PROGRESSION, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 15:sup1, 57-67, DOI: 10.3109/21678421.2014.960174

**To link to this article:** https://doi.org/10.3109/21678421.2014.960174

Published online: 10 Nov 2014.

Submit your article to this journal

Article views: 1430

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://informahealthcare.com/action/journalInformation?journalCode=iafd20

# THEME 1 IMPROVING DIAGNOSIS, PROGNOSIS AND DISEASE PROGRESSION

## P1 RED FLAGS FOR MUSCLE WEAKNESS: EXPLORING GP DECISION-MAKING AND REFERRAL PATHWAYS

MCDERMOTT CJ[1], BAXTER S[1], BEDFORD J[2]

[1]*University of Sheffield, Sheffield, UK,* [2]*Motor Neurone Disease Association, London, UK*

*Email address for correspondence: s.k.baxter@sheffield.ac.uk*

*Keywords: referral, diagnosis, referral pathway*

**Background:** Motor neurone disease is heterogeneous in clinical presentation, its clinical course is variable, and several clinical variants are recognized making early referral and diagnosis challenging (1).

**Objectives:** The data reported here forms part of the evaluation of a checklist for GPs to use with patients that present with muscle weakness. The aim of this phase of the work was to: i) explore GP decision-making processes; ii) to explore factors underpinning referral pathways for patients with muscle weakness.

**Methods:** The study used qualitative methods to investigate the views and experiences of GPs who have recently referred patients with muscle weakness, and those who have not. Semi-structured interviews were carried out over the telephone, recorded and examined using methods of thematic analysis.

**Results:** Eighteen GPs were interviewed from a spread of UK regions with a range in level of experience. 13 GPs had referred patients in the last year, and five had not. The most common description of patients who had been referred, or those that were likely to be referred was that of a patient who 'just did not fit' any familiar presentation, and GPs described their feeling of uncertainty, of a pattern that they were unable to explain. The priority was perceived to be referring the patient on to the expert rather than attempting to make a differential diagnosis.

The most commonly described sign that would trigger a referral was the presence of fasciculation. Familiarity with the patient was highlighted as a potentially important element in a GP's ability to assess disease progression. GPs described basing decisions on knowledge mostly acquired during initial training, and identified a range of online resources that they had found helpful. Participants described the challenge of having to make a decision with the patient in front of them, and also the potential impact of mentioning MND. While the majority of referral stories told by participants were of patients being directed rapidly to appropriate pathways, five patients had more convoluted routes to specialist MND services.

**Discussion and conclusion:** This study highlights the challenges in diagnosis and referral of patients with muscle weakness from primary to specialist care. The presence of fasciculation tended to trigger referral directly to a specialist MND service however patients presenting with other symptoms could experience referral to a range of other agencies. This work provides baseline data prior to the introduction of the Red Flags Checklist by the Royal College of GPs. A second wave of data collection will examine any impact of this tool on decision-making and referral pathways for patients with muscle weakness.

**Acknowledgements:** This project was funded by the Motor Neurone Disease Association (UK).

**Reference:**

1. Vermer A, Bradley W. Semin Neurol. 2001; 21(2): 177–188.

DOI: 10.3109/21678421.2014.960174/001

## P2 FOUNDATION OF THE NETHERLANDS ALS CENTRE IN 2003: REDUCING THE DIAGNOSTIC DELAY?

VISSER AE, SEELEN M, VELDINK JH, VAN DEN BERG LH

*University Medical Center Utrecht, Utrecht, The Netherlands*

*Email address for correspondence: a.visser-13@umcutrecht.nl*

**Background:** There is no diagnostic test to confirm the diagnosis of ALS. Due to the relatively low incidence and prevalence of ALS and unfamiliarity with symptoms by general practitioners and other physicians, there is a considerable diagnostic delay.

**Objective:** We evaluated whether the founding of the Netherlands ALS centre in 2003, consisting of the University Medical Centre Utrecht and the Amsterdam Medical Centre, and a national awareness campaign resulted in the reduction of the diagnostic delay.

**Methods:** The Prospective ALS study the Netherlands database provided data such as the date and site of onset, the date and hospital of diagnosis, El Escorial Criteria (EEC) and additional clinical characteristics of patients with ALS and PMA. The diagnostic delay was calculated in months and $Chi^2$ tests were performed. Hypotheses on site of onset and EEC influencing the diagnostic delay were analysed.

**Results:** Out of 2350 patients, we found a reduction in mean diagnostic delay of 1.1 months when comparing diagnostic period 2003–2007 with 2008–2012. In addition, within these periods, more patients were diagnosed within 12 months after symptom onset ($p < 0.001$). Finally, specifically within the group of patients with less clinical certainty (probable - laboratory supported and possible EEC) and in the group of patients with a spinal site of onset, more patients were diagnosed within

ISSN 2167-8421 print/ISSN 2167-9223 online © 2014 Informa Healthcare
DOI: 10.3109/21678421.2014.960174

12 months after symptom onset between 2008–2012 compared to 2003–2007 ($p = 0.002$ and $p = 0.004$ respectively).

**Discussion and conclusion:** After the foundation of the ALS centre in 2003, more patients were diagnosed within 12 months. This is the result of the expanding expertise and well-organised diagnostic workup, especially in those patients where there is less clinical certainty about the diagnosis. A shorter diagnostic delay leads to earlier treatment with Riluzole, and provides a greater opportunity to become enrolled in clinical trials and for the appropriate planning of care.

DOI: 10.3109/21678421.2014.960174/002

## P3 EXTENDING THE PHENOTYPE OF FOSMN SYNDROME: AN IMPORTANT ALS MIMIC

BROAD R, LEIGH PN

*Brighton and Sussex Medical School, Falmer, East Sussex, BN1 9RY, UK*

*Email address for correspondence: r.broad@bsms.ac.uk*

*Keywords: FOSMN, blink reflex, trigeminal nuclei*

**Background:** Facial Onset Sensory Motor Neuronopathy (FOSMN) is a rare disorder (1) presenting with facial numbness, facial weakness, and bulbar symptoms and progressing to involve the neck, shoulder girdle, and limb muscles (1–5). The pathogenesis of FOSMN remains unknown, however, evidence supports a neurodegenerative process with early involvement of the trigeminal nuclei (2–4). A link between FOSMN and amyotrophic lateral sclerosis (ALS) has been proposed (2,4,5) and as the number of reported cases increases, the phenotypic spectrum of FOSMN continues to expand (1–5).

**Objectives:** To study the phenotypic heterogeneity in FOSMN and to highlight a case of motor onset FOSMN masquerading as an ALS mimic.

**Methods:** Six patients with FOSMN were identified following thorough clinical assessment and investigation.

**Results:** All cases were male, aged between 42 and 66 years. Five presented with features of central trigeminal sensory dysfunction. All patients had facial and neck weakness. Four had additional limb weakness. Three patients suffered with severe neck pain. Creatine Kinase was mildly elevated in two patients. Blink reflexes were delayed or absent. Disease duration ranged from 18 months to over ten years.

In one case, FOSMN was altered with a predominantly motor syndrome presentation.

**Case study:** In this incident, a 55 year-old man presented with a decade of progressive facial and arm wasting and developed significant neck pain. The patient experienced mild difficulty swallowing and had lost over a stone in weight. Examination revealed wasting and mild weakness of facial, neck, shoulder girdle, and proximal arm muscles. Tendon reflexes were brisk at the knees with bilateral adductor jerks. EMG studies showed chronic partial denervation of the upper limbs and the cervical paraspinal muscles with some fasciculation. Blink reflexes showed bilaterally delayed responses.

**Discussion and conclusion:** FOSMN may appear as an atypical case of ALS, particularly when features are predominantly motor and there is upper motor neurone involvement. TDP-43 inclusions have been demonstrated in one case of FOSMN (4) and heterozygous D90A SOD 1 mutation was reported in another case of FOSMN (5) supporting a link FOSMN and ALS. However, FOSMN can usually be distinguished from ALS. Neck pain is a striking feature and blink reflex abnormality is diagnostically useful (1–5).

The case described in this study, expands the phenotype of FOSMN to include a predominantly motor syndrome and highlights the importance of considering FOSMN as an ALS mimic.

**References:**

1. Vucic S. *et al.* Brain 2006; 129(12): 3384–3390.
2. Fluchere F. *et al*. Muscle Nerve. 2011; 43: 136–140.
3. Vucic S. *et al.* Neurology 2012; 3(79): 73–70.
4. Sonoda K. *et al*. J Neurol Sci. 2013; 332: 148–153.
5. Dalla Bella E. *et al.* J Neurol Neurosurg Psychiatry. 2014; Mar 3.

DOI: 10.3109/21678421.2014.960174/003

## P4 SPORADIC LOWER MOTOR NEURON DISEASE WITH A SNAKE EYES APPEARANCE ON THE CERVICAL ANTERIOR HORNS BY MRI: A NEW CLINICAL SUBTYPE?

SASAKI S

*Tokyo Women's Medical University, Tokyo, Japan*

*Email address for correspondence: ssasaki@nij.twmu.ac.jp*

*Keywords: lower motor neuron disease (LMND), snake eyes appearance, new clinical subtype*

**Background:** Lower motor neuron syndromes are characterized by progressive, asymmetrical lower motor neuron symptoms and largely classified into two subgroups: one in which motor neurons are primarily affected (lower motor neuron diseases: LMNDs), and the other, in which motor axons and their surrounding myelin are predominantly affected, leading to muscle weakness and atrophy, fasciculation and muscle cramps. These syndromes include various diseases. Thus, 'LMND' is the term generally used to describe diseases in which only LMN signs are detected.

**Objectives:** To elucidate whether certain patients with slowly progressive, asymmetric, pure lower motor neuron upper limb weakness showing a snake eyes appearance by MRI constitute a new clinical subtype of LMND.

**Methods:** For more than 5 years, the author regularly followed up two unique unprecedented LMND patients with a longstanding clinical course of more than 10 and 7 years (aged 52 and 40 years at onset), who presented with proximal dominant and distal dominant spinal muscular atrophy localized in the upper extremities, respectively, with unilateral predominance and a snake eyes appearance by MRI.

**Results:** Patients were characterized by 1) longstanding slow progression or stability of lower motor neuron signs over a long period of time localized exclusively in the upper extremities with unilateral predominance and distal or proximal preponderance; 2) the absence of upper motor neuron signs, bulbar signs, sensory disturbances and respiratory involvement; 3) a snake eyes appearance on the anterior horns of the cervical cord by axial T2-weighted MRI; 4) neurogenic change with denervation potentials such as fasciculation confined to the affected muscles by EMG; 5) a normal creatine kinase

level. Patients neither fall into any existing category of LMND such as progressive muscular atrophy or flail arm syndrome, nor indicate other lower motor neuron syndromes with or without a snake eyes appearance.

**Discussion and conclusion:** These two unique unprecedented LMND patients with a longstanding clinical course localized exclusively in the upper extremities showing a snake eyes appearance on the anterior horns of the cervical cord by axial T2-weighted MRI may constitute a new clinical subtype of LMND.

**Acknowledgements:** This study was supported by a Grant-in-Aid for General Scientific Research © from The Ministry of Education, Culture, Sports, Science and Technology (22590965).

DOI: 10.3109/21678421.2014.960174/004

## P5 AMYOTROPHIC LATERAL SCLEROSIS (ALS) WITH LABORATORY ABNORMALITIES OF UNKNOWN SIGNIFICANCE (LAUS)] – WHERE DOES IT BEGIN AND WHERE DOES IT END?

BROOKS BR[4], BRAVVER EK[1,4], DESAI UG[1,4], STORY SJ[1,4], LINDBLOM SS[2,4], PACICCO TJ[2,4], BOCKENEK WL[3,4], SANJAK MS[1,5], WARD AL[1,6], WRIGHT KA[1], LANGFORD VL[1], HOLSTEN SE[1], FISCHER MP[1], LARY C[1], NEMETH J[1], BELCHER SL[1], NICHOLS MS[1], SMITH NP[1], LUCAS NM[1], OPLINGER H[1]

[1]*Carolinas Neuromuscular/ALS-MDA Center - Carolinas Medical Center - Department of Neurology – Carolinas Healthcare System Neurosciences Institute, Charlotte, North Carolina, USA,* [2]*Department of Internal Medicine - Carolinas Medical Center, Charlotte, North Carolina, USA,* [3]*Department of Physical Medicine and Rehabilitation - Carolinas Rehabilitation, Charlotte, North Carolina, USA,* [4]*University of North Carolina School of Medicine – Charlotte Campus, Charlotte, North Carolina, USA,* [5]*Department of Kinesiology, University of North Carolina - Charlotte, Charlotte, North Carolina, USA,* [6]*Cabbarus College of Health Sciences - Occupational Therapy, Concord, North Carolina, USA*

*Email address for correspondence: benjamin.brooks@carolinashealthcare.org*

*Keywords: ALS-LAUS, MGUS, anti-ganglioside antibody*

**Background:** Amyotrophic lateral sclerosis (ALS) with laboratory abnormalities of unknown significance (ALS-LAUS), characterized by upper and lower motor neuron signs together with LAUS, has been categorized as a diagnostic classification category by the World Federation of Neurology Research Group on Motor Neuron Disease/ALS (1). Lower motor neuron syndromes (LMNS) with LAUS may be separated out as ALS-Mimics (2,3).

**Objectives:** To define the prevalence/natural history of ALS-LAUS at an ALS Multidisciplinary Clinic in the Southeastern USA.

**Methods:** Patient Database review from 2010–2014 of 457 patients referred for ALS diagnosis.

**Results:** ALS-LAUS was seen in 17.2 % (79/457) of evaluated patients with probable-laboratory supported, clinically probable and clinically definite ALS by Revised El Escorial criteria (1). GM1 ganglioside/HS6S/SGPG Antibodies (Abs) (12/79 = 15.2%); Monoclonal Gammopathy of Unknown Signficance (MGUS)/Waldenstrom (16/79 = 20.3%); Voltage-Gated Calcium or Potassium Channel Abs (7/79 = 8.8%); hypo/hyper-gammaglobulinemia/cryoglobulinemia (12/79 = 15.2%); Acetylcholine Receptor/Ganglionic Acetylcholine Receptor/Skeletal muscle Abs (3/79 = 3.8%); Anti-phospholipid Abs (2/79 = 2.5%) comprise a pattern of possibly immune-mediated motor neuron pathogenesis (52/79 = 65.8%). Concurrent infection with virus (WNV, HCV, HPV, Rubella, 5/79 = 6.3%) and borrelia burgdorferi (1/79 = 1.3%) was also identified. Methylmalonic academia (4/79 = 5.1%) and aluminum toxicity (4/79 = 5.1%) were identified and treated.

In addition to standard Riluzole, patients with ganglioside Abs (10/12 = 83.3%), MGUS/Waldenstrom (2/16 = 12.5%); VGCC/KC Abs (4/7 = 57.1%) or hyper-or hypo-gammaglobulinemia/cryoglobulinemia (1/12 = 4.8%) were treated with IVIg and/or other regimens. On IVIg treatment, ALSFRS-R deterioration showed no change over 12 months in 1/2 MGUS/Waldenstrom patients and slowed in 3/10 ganglioside Abs patients. Pulmonary embolism rate (5/79 = 6.3%-ALS-LAUS; 20/377 = 5.3%-ALS) was comparable in both groups.

**Discussion and conclusion:** Further detailed analysis of progression rate by site of onset, sex, age, treatment will require the assimilation of clinic-based datasets of properly analysed ALS-LAUS patients from multiple clinic sites. The appropriate role of IVIg in ALS-LAUS patients requires further study following clarification of the natural history of these patients compared with non-ALS-LAUS patients. The determination as to whether auto-antibodies to additional antigens may play a role in the progression rate of ALS-LAUS compared with sporadic ALS needs to be systematically studied (4,5).

**Acknowledgements:** ALS and Neuromuscular Garden-Carolinas Garden of Hope Funds, Carolinas ALS Research Fund, Pinstripes ALS Foundation, Carolinas Health Care Foundation, Muscular Dystrophy Association - ALS Division.

**References:**

1. Brooks BR. *et al.* Amyotroph Lateral Scler Other Motor Neuron Disord. 2000; 1(5): 293–9.
2. Lawton KA. *et al.* Amyotroph Lateral Scler Frontotemporal Degener. 2014; 1: 1–9.
3. Traynor BJ. *et al.* Arch Neurol. 2000; 57(1): 109–13.
4. van Blitterswijk M. *et al.* Amyotroph Lateral Scler. 2011; 12(6): 430–8.
5. Hwang CS. *et al.* Neurobiol Dis. 2013; 58: 13–8.

DOI: 10.3109/21678421.2014.960174/005

## P6 PARANEOPLASTIC SUBACUTE LOWER MOTOR NEURON SYNDROME ASSOCIATED WITH SOLID CANCER

VERSCHUEREN A[1], GALLARD J[1], ATTARIAN S[1], BOUCRAUT J[3], HONNORAT J[2], POUGET J[1]

[1]*Reference centre for neuromuscular diseases and ALS, Hôpital de la Timone, marseille, France,* [2]*French Reference Center on Paraneoplastic Neurological Syndrome, Hospices Civils de Lyon, lyon, France,* [3]*Laboratoire d'immunologie, Hôpital de la Conception, marseille, France*

*Email address for correspondence: annie.verschueren@ap-hm.fr*

*Keywords: LMND, paraneoplastic, solid cancer*

**Objectives:** To describe paraneoplastic lower motor neuron syndrome associated with solid cancer and/or anti-neuronal antibodies.

**Methods:** We retrospectively analysed three patients with pure lower motor neuron syndrome and who were followed for more than four years in our center. The investigations led to the diagnosis of paraneoplastic syndrome.

**Results:** The three patients shared several common clinical features, including a rapidly progressive lower motor neuron syndrome over the course of a few weeks leading to a severe functional impairment. The neurological symptoms preceded the diagnosis of a breast adenocarcinoma and a thymoma in the first two patients with anti-beta IV spectrin and anti-CV2/CRMP5 antibodies, respectively. Cancer was not detected in the third patient who had circulating anti-Hu antibodies. Electrodiagnostic studies revealed pure motor axonal involvement, abundant fasciculations, and acute denervation restricted to the lumbosacral, cervicothoracic, or both spinal segments, consistent with subacute lower motor neuron syndrome. Cerebral spinal fluid analysis showed an intrathecal synthesis of immunoglobulins in two out of three patients, but was otherwise normal. A final diagnosis of paraneoplastic syndrome was made after investigations for alternative causes of lower motor neuron syndrome. Early diagnosis, combined treatment of the underlying cancer, and immunomodulatory treatment, led to neurological improvement of the disease in two out of the three cases in which the cancer was diagnosed. The third patient, without cancer, died within a few months after the onset of neurological symptoms.

**Discussion and conclusion:** Cases of subacute lower motor neuron syndrome with rapid progression may occur as an expression of a paraneoplastic neurological syndrome, and an active research of cancer is justified in these cases. Anti-neuronal antibodies and CSF analysis can help to identify the autoimmune nature of the disease. Identification of these syndromes is important, as the treatment of underlying malignancy along with immunomodulatory treatment may result in a favourable long-term outcome of these potentially fatal diseases.

DOI: 10.3109/21678421.2014.960174/006

## P7 EXTRAPYRAMIDAL SYNDROME IN SPORADIC UPPER MOTOR NEURON-DOMINANT ALS WITH PURE TDP-43 PATHOLOGY

PRUDLO J[1], KASPER E[2], SCHUSTER C[3], KRAUSE BJ[4], BISKUP S[5], WALTER U[6], BENECKE R[6], BÜTTNER A[7], BESCHORNER R[8], NEUMANN M[8]

[1]*Department of Neurology, University of Rostock and DZNE, Rostock, Germany,* [2]*Department of Psychosomatic Medicine, University of Rostock, Rostock, Germany,* [3]*Academic Unit of Neurology, Trinity College, Dublin, Ireland,* [4]*Department of Nuclear Medicine, University of Rostock, Rostock, Germany,* [5]*Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, Tuebingen, Germany,* [6]*Department of Neurology,* [7]*Institute of Forensic Medicine, University of Rostock, Rostock, Germany,* [8]*Department of Neuropathology, University of Tuebingen and DZNE, Tuebingen, Germany*

*Email address for correspondence: johannes.prudlo@med.uni-rostock.de*

*Keywords: extrapyramidal, UMN-dominant, TDP-pathology*

**Background:** In amyotrophic lateral sclerosis (ALS), the cerebral TPD-43 pathology is spread beyond the pyramidal motor system. As regards the basal ganglia, this pathology is predominantly subclinical. However, the upper motor neuron (UMN)-dominant ALS variants, in particular, can clinically be associated with extrapyramidal features, suggesting overlap syndromes and distinct pathologies.

**Objectives:** To correlate clinical and pathological data in an unusual sporadic UMN-dominant ALS case with prominent extrapyramidal abnormalities.

**Case Report:** A 58-year-old male had difficulties walking and dysarthria, later experiencing numerous falls before becoming wheelchair-bound within 16 months. He showed bulbar-spinal spastic quadriparesis with slight extraocular and sphincter involvement; additionally, he demonstrated non-drug-induced bradykinesia, hand athetosis (swan-neck deformity), and foot and facial dystonia, all of which without a response to levodopa. He died three years after the disease onset. In the second year of this period, he developed lower motor neuron signs, thus fulfilling the criteria of definite ALS. Shortly before his death, he became mute, suffered from severe dysphagia (asphyxia by alimentary bolus) and displayed a marked pseudobulbar affect, behavioural changes (disinhibition), and restlessness. His cognition remained unaffected. The FTD criteria were not fulfilled.

**Results:** The dopamin transporter SPECT (DaTSCAN) showed an asymmetric reduction in striatal tracer uptake. Transcranial ultrasound showed a marked hyperechogenenicity of the substantia nigra. No mutations were detected in the ALS associated genes: SOD-1, Alsin, *C9orf72*, TARDBP, or FUS. At autopsy, degeneration of the pyramidal motor system (UMN$>$LMN) and a moderate degeneration of the substantia nigra pars compacta was observed. Immunohistochemistry revealed TDP-43 positive inclusions in neurons and oligodendroglial cells in these brain regions and also in the putamen and pallidum, while extramotor cortex (frontal, temporal, parietal) and hippocampus were devoid of TDP-43 pathology. No protein deposits characteristic for other neurodegenerative diseases such as Lewy bodies, neurofibrillary tangles or senile plaques were observed by immunohistochemistry for tau, alpha-synuclein, and b-amyloid.

**Discussion and conclusion:** The ALS-Plus syndrome presented here is not based on the coincidence of two independent neurodegenerative diseases. The striking extrapyramidal abnormalities were caused instead by pure TDP-43 pathology and correlated with the distribution and pronounced severity of the TDP-43 pathology in the basal ganglia and midbrain in this patient compared to that usually observed in cognitively normal ALS-patients. Our case is a further example of the clinical heterogeneity of pure TDP-43 proteinopathies (1).

**Reference:**

1. McCluskey LF, Elman LB, Martinez-Lage M. Arch Neurol 2009; 66: 121

DOI: 10.3109/21678421.2014.960174/007

## P8 MAGNETOENCEPHALOGRAPHIC EVIDENCE OF CORTICAL MOTOR DYSFUNCTION IN ALS

PROUDFOOT M[1], ROHENKOHL G[1], GOULD I[1], TALBOT K[1], WOOLRICH M[1], NOBRE AC[1], WUU J[2], BENATAR M[2], TURNER M[1]

[1]*University of Oxford, Oxford, UK,* [2]*University of Miami, Florida, USA*

*Email address for correspondence: malcolm.proudfoot@stx.ox.ac.uk*

*Keywords: magnetoencephalography (MEG), neurophysiology, biomarkers*

**Background:** Neurophysiological studies in ALS have supported evidence of cortical motor network dysfunction, most notably the phenomenon of hyperexcitability. The temporal sensitivity of magnetoencephalography (MEG) enables selective analysis of a brief period of motor preparation. Motor network activity is therefore measurable regardless of subsequent action completion, overcoming a key limitation of task-based functional MRI. The distortion-free MEG signal also permits more confident anatomical localization of oscillatory dysfunction.

**Objectives:** To pilot MEG in a study of affected ALS patients, including pre-symptomatic individuals at high genetic risk, with the goal of developing novel neurophysiological biomarkers that might improve patient stratification and ultimately would be relevant to future studies of disease prevention.

**Methods:** Eleven affected patients (8 ALS, 3 PLS; mean age $63.0 \pm 7.8$), 11 pre-symptomatic mutation carriers (10 SOD1, 1 *C9orf72*, mean age $52.2 \pm 10.2$) and 10 healthy controls (mean age $57.5 \pm 11.6$) were studied. Action preparation and completion was studied during MEG acquisition using a simple cued go/no-go task requiring manual responses with either index finger. A central visual cue incorporated both spatial and temporal information for the participant, indicating whether to use the left or right hand for the response, and whether to expect a one or two second interval from the cue to the go-no-go instruction. Data were analysed using a locally developed toolset based upon similar principles to functional MRI analysis, including independent component analysis artefact identification, established 'beamformer' reconstruction of whole brain cortical MEG sources, general linear model analysis of experimental and group contrasts, and threshold cluster statistics.

**Results:** The MND group had slower reaction times compared to controls (mean 525ms versus 453ms, $p < 0.001$), while the pre-symptomatic mutation carriers responded faster but also made more no-go errors compared to controls (mean reaction time 399ms versus 453ms; errors 26.2% versus 17.9%, $p < 0.001$). In all 3 groups, MEG time frequency analysis revealed functional cortical oscillatory activity, most notably a lateralized beta-band desynchronization during movement preparation, and rebound synchronization after movement termination. Group comparisons revealed delayed contralateral beta-band desynchronization and rebound. Source reconstruction to a standard MRI template mapped these abnormalities to the precentral gyrus. Qualitatively similar, but quantitatively smaller effects were seen in the pre-symptomatic group.

**Discussion and conclusion:** These pilot findings suggest that beta-band activity is a candidate MEG-based biomarker for motor system dysfunction in ALS. It may shed light on both pathological and compensatory cortical processes, including those occurring before the development of symptoms. Functional neurophysiology might also be expected to respond more readily to pharmacological intervention and, with continued development; MEG will merit consideration as a source of pharmacodynamic biomarkers for CNS drug activity.

DOI: 10.3109/21678421.2014.960174/008

## P9 PROGNOSTIC FACTORS ON THE COURSE OF FUNCTIONAL STATUS OF PATIENTS WITH ALS; A SYSTEMATIC REVIEW

CREEMERS H[1], GRUPSTRA H[1], NOLLET F[1], VAN DEN BERG LH[2], BEELEN A[1]

[1]*Department of Rehabilitation, Academic Medical Center, Netherlands ALS Center, Amsterdam, The Netherlands,* [2]*Department of Neurology, Rudolf Magnus Institute of Neuroscience, Netherlands ALS Center, Utrecht, The Netherlands*

*Email address for correspondence: h.w.creemers@amc.uva.nl*

*Keywords: patient counselling, prognosis, disease progression*

**Background:** The progressive course of ALS results in a broad and ever-changing spectrum of the care needs of patients with ALS. The timing of appropriate interventions requires accurate prediction of the individual course of the disease. In clinical practice individual prognosis is largely based on the clinician's cumulated experience. Clinical prognostic tools for the functional course are lacking. Knowledge of prognostic factors for the functional course of ALS may enhance clinical prediction.

**Objectives:** To review the evidence regarding prognostic factors for the rate of decline in functional status of patients with ALS.

**Methods:** We searched the electronic databases Medline, EMBASE, CINAHL, PsycINFO, and Web of Science for longitudinal cohort studies reporting on prognostic factors for the course of the functional status, assessed with versions of the ALS Functional Rating Scale.

Two reviewers independently assessed the methodological quality of the included studies using the QUIPS tool. The overall quality of evidence for each prognostic factor was assessed using the GRADE approach, considering risk of bias, imprecision, inconsistency, in directness and publication bias.

**Results:** We included 9 prospective and 4 retrospective cohort studies with sample sizes ranging from 31 to 2452 patients, examining a wide variety of prognostic factors for a decline in ALSFRS(-R) total score (13 studies) or domain scores (one study). Five studies included an inception cohort, one study presented data of a population based ALS register. Thirteen potential prognostic factors for a decline in ALSFRS(-R) total score were studied in more than one cohort study. Based on the GRADE approach, the quality of evidence for the prognostic value of age at onset, site of onset, time from symptom onset to diagnosis, and ALSFRS-R baseline score was low, mainly due to the limited data and inconsistency of results in the small number of studies included. The prognostic value of age at diagnosis, forced vital capacity, frontotemporal dementia, body mass index and comorbidity remains unclear due to the limited number of studies and small sample sizes.

**Discussion and conclusion**: The low level of evidence for factors that are predictive for a decline in ALSFRS(-R) may

be due to the lack of unidimensionality of the scale and the heterogeneity of the ALS syndrome. Progress in understanding the genetics of the disease is needed to identify subtypes of ALS that allow for better prognosis.

The current evidence on prognostic factors for functional decline in ALS is insufficient to allow the development of a prediction tool that can support clinical decisions. Given the limited data, future prognostic studies may need to focus on factors that have a predictive value for a decline in ALSFRS(-R) domain scores, preferably based on internationally collected and shared data.

DOI: 10.3109/21678421.2014.960174/009

## P10 HYPONATREMIA IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: AN INDICATOR OF RESPIRATORY FAILURE?

ABSTRACT WITHDRAWN

## P11 ALS ONSET AND PROPAGATION: INSIGHT FROM RESPIRATORY FUNCTION TEST

SOHN S-Y[2], KIM D-G[1], HONG Y-H[3], PARK K-H[2], SUNG J-J[2], LEE K-W[2], PARK K-S[1]

[1]*Seoul National University Bundang hospital, Seongnam, Gyeonggi-do, Republic of Korea,* [2]*Seoul National University Hospital, Seoul, Republic of Korea,* [3]*Boramae Hospital, Seoul, Republic of Korea*

*Email address for correspondence: chungmoon@hanmail.net*

*Keywords: respiratory function test, respiratory muscle strength test, disease progression*

**Background:** Amyotrophic lateral sclerosis (ALS) develops clinical manifestations at a focal body and spreads to other regions. There is controversy surrounding the onset of neuronal change (focal, multifocal or ubiquitous) and propagation mechanism (contiguous or non-contiguous). Maximal inspiratory pressure (MIP) reflects the strength of the diaphragm, main inspiratory muscle, and other inspiratory muscles that are innervated by cervical spinal roots (C3, C4, C5) and thoracic roots (T1–12). Maximal expiratory pressure reflects the strength of expiratory muscles which is innervated by thoracic roots (T1–12).

**Objectives:** We hypothesized that the MIP and MEP ratio will be bigger in caudal region onset patients compared to rostral region onset patients, at the early stage of ALS, without severe respiratory dysfunction according to the focal onset, contiguous propagation theory. We performed a retrospective study to compare parameters of respiratory muscle strength tests between ALS patients with different regions of onset.

**Methods:** A retrospective study was performed in 114 ALS patients who clinically and electro-physiologically fulfill El Escorial criteria of definite and probable ALS. Patients carried out a battery of respiratory tests: spirometry, forced vital capacity (FVC), forced expiratory volume in one second (FEV1), MIP, MEP and stiff nasal inspiratory pressure (SNIP). MIP, MEP, SNIP, MIP per MEP ratio and SNIP per MEP ratio was compared between the patients with different regions of onset. The muscle strength and spirometry profile among patients who did not show severe respiratory dysfunction (FVC > 50%) was also determined.

**Results:** In this study 25 bulbar onset (male 14, female 11), 65 cervical onset (male 42, female 23), and 23 lumbosacral onset (male 17, female 6) ALS patients were analysed. The mean time from symptom onset to clinical examination was 20.6 months (2–74 months). 74 patients showed FVC > 50%: 14pts from the bulbar onset group (14/26), 40 from cervical region onset group (40/65), 20 from lumbosacral region onset group (20/23) ($p = 0.013$).

We compared respiratory muscle strength and spirometry profiles among patients with FVC > 50%. There was no difference in FVC between groups with FVC over 50% ($p = 0.22$). MIP and MIP/MEP ratio was lower in bulbar onset patients compared with cervical and lumbosacral onset patients ($p = 0.01$, $p = 0.017$). But SNIP and SNIP/MEP ratio showed no difference between groups ($p = 0.742$, $p = 0.292$).

**Discussion and conclusion:** There is a difference in FVC between ALS patients with different regions of onset. MIP and MIP/MEP were lower in bulbar onset compared with limb onset ALS. MIP might be influenced with bulbar dysfunction because there was no difference in MEP, SNIP, and SNIP/MEP ratio between ALS patients. These clinical findings cannot be explained by focal onset and propagation hypothesis.

DOI: 10.3109/21678421.2014.960174/011

## P12 THE RELATIONSHIP BETWEEN VOLUNTARY COUGH PRODUCTION AND SWALLOW SAFETY IN INDIVIDUALS WITH AMYOTROPHIC LATERAL SCLEROSIS

PLOWMAN EK, WATTS S, DOMER A, GAZIANO J, TABOR L

*University of South Florida, Tampa, Florida, USA*

*Email address for correspondence: plowman@usf.edu*

*Keywords: aspiration, cough, dysphagia*

**Background:** Cough is an essential airway protective mechanism and is particularly important for those with disordered swallowing. With the necessity for fine-tuned laryngeal and respiratory coordination for both cough and swallow, we hypothesize that dystussia (disorder of cough) may be predictive of swallowing dysfunction in individuals with Amyotrophic Lateral Sclerosis (ALS).

**Objectives:** To examine the relationship between voluntary cough productions and swallow safety in individuals with ALS.

**Methods:** 27 patients with ALS (El-Escorial criteria) underwent a standardized video fluoroscopic evaluation of swallowing and completed voluntary cough spirometry testing. Physiologic measures of voluntary cough production from 16 individuals with ALS showing no video fluoroscopic evidence of penetration/aspiration were examined and compared to 11 ALS participants with evidence of penetration/aspiration. Group differences were assessed using a one-way ANOVA and a series of Spearman's Rho correlations performed to assess the degree of relationship between voluntary cough measures and airway safety during swallowing. Alpha was set at 0.05.

**Discussion and conclusion:** The penetrator/aspirator group presented with significantly lower cough volume acceleration ($F(1,26) = 4.77$, $p < 0.05$). Mean cough volume acceleration was 76.38 (SEM = 13.59) for ALS non-penetrator/aspirators

vs. 40.01 (SEM = 6.62) for ALS penetrator/aspirators. In addition, a significant negative correlation was revealed between PAS score and cough volume acceleration ($r = 0.48$, $p < 0.05$) indicating that the higher degree of airway invasion of material during swallowing (PAS score), the lower the cough volume acceleration observed. Compression phase duration of voluntary cough was significantly longer for ALS patients who penetrated/aspirated, ($F(1,26) = 3.93$, $p < 0.05$) indicating increased time to glottic closure during voluntary cough production.

In this study, a relationship was observed between voluntary cough production and airway safety/protection during swallowing. ALS patients who penetrated/aspirated demonstrated weaker and less efficient voluntary cough production as evidenced by lower cough volume acceleration and increased time to glottic closure during cough (longer compression phase durations). Measures of voluntary cough may be useful predictors of penetration and aspiration in individuals with ALS. Voluntary cough could prove a useful screening tool to aide in the evaluation of airway protection in individuals with ALS, however further investigation is warranted to validate these initial findings.

DOI: 10.3109/21678421.2014.960174/012

## P13 CLINICAL CORRELATION OF THE YAWNING REFLEX IN ALS PATIENTS

KWAN J, DIAZ M, ALTEMEMI N, ZILLIOX L, EMPENO R, RUSSELL J

*University of Maryland, Baltimore, MD, USA*

*Email address for correspondence: jkwan@som.umaryland.edu*

*Keywords: yawn, sleep disorder, upper motor neuron dysfunction*

**Background:** Severe and excessive yawning is a symptom that has been observed and described in ALS patients (1, 2). Frequent yawning can also be present in several neurological disorders but the cause for this symptom is poorly understood (3). In ALS, patients who have bulbar onset symptoms, more frequently report excessive yawning (2), in addition, the yawning reflex has been suggested to be a sign of upper motor neuron dysfunction (4).

**Objectives:** The aim of this study is to determine the frequency of excessive yawning in ALS patients and to examine the clinical correlate for this symptom.

**Methods:** A prospective study was conducted to determine the frequency of yawning in consecutive ALS patients evaluated at University of Maryland ALS Clinic. A patient self-reported yawning scale was administered and the severity of yawning was determine as none/normal, moderately excessive, and severely excessive. Additional clinical parameters collected from each patient include: date of symptom onset; date of diagnosis; site of symptom onset; clinical rating of cortical motor neuron dysfunction; ALSFRS-R; forced vital capacity; arterial blood gas (in patients whose FVC was less than 70% of predicted); Epworth Sleepiness Scale; CNS lability scale for pseudobulbar affect; and ALS depression inventory scale.

**Results:** 30 consecutive ALS patients were evaluated for this study. Four patients reported severely excessive yawning, nine patients reported moderately excessive yawning, and 16 patients reported no increase in yawning. Excessive yawning was significantly correlated to excessive sleepiness as determined by the Epworth Sleepiness Scale. ALS patients who had excessive yawning were more likely to have excessive sleepiness. In patients with excessive yawning, there was a trend towards greater clinical findings of upper motor neuron impairment, shorter duration until onset of bulbar symptoms, and shorter disease duration. There was no association between excessive yawning and respiratory parameters or severity of bulbar dysfunction.

**Discussion and conclusion:** Excessive yawning is a frequent symptom in ALS patients. In this study, excessive yawning is associated with excessive daytime sleepiness.

**References:**

1. Louwerse, E. J Neurosci Res. 1998 supplement: 392.
2. Wicks P. Acta Psychiatr Scand. 2007; 116(1): 76.
3. Thompson SB. Med Hypotheses. 2010; 75(6): 630–3.
4. Williams, DR. Neurology 2000; 55, 1592–1593.

DOI: 10.3109/21678421.2014.960174/013

## P14 AMYOTROPHIC LATERAL SCLEROSIS AND OXIDATIVE STRESS BIOMARKERS IN RELATION TO PHYSICAL EXERCISE

CHICO L, LOGERFO A, CALDARAZZO EI, PETROZZI L, ROCCHI A, CARLESI C, ORSUCCI D, SCHIRINZI E, SIMONCINI C, MANCUSO M, SICILIANO G

*University of Pisa, Pisa, Toscana, Italy*

*Email address for correspondence: lucia.chico@katamail.com*

*Keywords: oxidative stress, biomarkers, exercise*

**Background:** Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease for which there is no cure. Among the assumptions made regarding the pathogenesis of ALS, the most reliable, call into question the oxidative stress, as well as the excitotoxic theory and alterations of mitochondria (1).

Oxidative stress describes a condition in which the antioxidant defences are unable to maintain cellular ROS levels below the toxicity threshold. This could be the result of an excessive ROS production, or a loss of the natural antioxidant defences, or of both factors. There is a general misunderstanding among healthcare professionals of the proper use and potential benefits of physical therapy to treat the symptoms and resulting loss of independence. Physical activity leads to a temporary imbalance between the ROS production and their disposal and, therefore, could be the primary cause of oxidative stress, however, there are currently major limitations of the knowledge of the relationship between oxidative stress and performance (2).

**Objectives:** To investigate, through the monitoring of certain biological markers, some alterations of the mechanisms that underlie the regulation of cellular response against oxidative stress in relation to the exercise, in order to verify a possible correlation between exercise and increases in these parameters.

**Methods:** The work was divided into two experimental phases: in the first phase markers of oxidative damage in 32 ALS patients (mean age $63.6 \pm 10.8$) at diagnosis and in 54 healthy volunteers (mean age $69.9 \pm 9.2$) were measured in order to check a possible alteration of the cellular state redox in patients compared to controls. Following discharge, 11

patients have conducted, for a period of 50 days, an aerobic workout of moderate intensity, while the remaining 21 have not been subjected to any training program.

**Results:** The results obtained, confirm the redox alteration in ALS patients with sporadic form of diagnosis. What emerged from the comparison of these parameters before and after the training period is that these values have remained constant over time, while there has been an increase of oxidative damage in patients who received no training ($p < 0.01$).

**Discussion and conclusion:** Despite the aggressive and rapid progression of the disease, a moderate-intensity exercise may be helpful to maintaining the welfare of the musculoskeletal system.

**References:**

1. van Groenestijn AC. BMC Neurol 2011; 11:70.
2. Kiernan MC. J Physiol. 2009; 587(Pt 15):3759–60.

DOI: 10.3109/21678421.2014.960174/014

## P15 SIT TO STAND (STS) RATING SCALE: CONSTRUCT VALIDITY OF A NOVEL MEASURE OF LOWER EXTREMITY (LE) FUNCTION IN ALS PATIENTS

SANJAK MS[1,2], OLDHAM J[2], BOYLES G[1], HOLSTEN SE[1,3], BOCKENEK W[1,3], STORY SJ[1,3], LINDBLOM SS[1,3], PACCICO T[1,3], BRAVVER E[1], RUSSO PC[1], BROOKS BR[1]

[1]*Carolinas Healthcare System, Carolinas Neuromuscular, ALS-MDA Center, Charlotte, NC, USA,* [2]*Department of Kinesiology, University of North Carolina, Charlotte, NC, USA,* [3]*Univ North Carolina Sch of Med, Charlotte, NC, USA*

*Email address for correspondence: Mohammed.Sanjak@carolinashealthcare.org*

*Keywords: sit to stand (STS), lower extremity strength, mobility*

**Background:** The STS manoeuvre is essential to everyday physical function and independent living. Loss of STS ability can be devastating for patients' quality of life, as it precedes loss of independence in other fundamental motor functions such as transfer and ambulation. LE muscle strength and power are the main determinants of the STS manoeuvre. A standardized, valid, quick, and easy-to-perform descriptive rating scale that reflects the clinical level of impairment of LE function in ALS patients is lacking.

**Objectives:** To establish a novel 5 point rating scale for the STS manoeuvre in individuals with ALS.

**Methods:** A five point scale ranging from 0–4 was developed to reflect patients' level of impairment during the STS manoeuvre. The scale was based on the level of assistance needed to complete the manoeuvre, and was graded as follows: 4 = no arm or compensation; 3 = use of one arm; 2 = use of two arms; 1 = minimal/moderate assistance of one person; 0 = cannot stand/requires lifting. The STS evaluation was performed on 69 individuals with ALS. Bilateral LE muscle strength was evaluated by measuring maximum voluntary isometric contractions (MVIC) of ankle dorsiflexors, knee extensors and flexors, and hip extensors and flexors using computerized fixed dynamometry. In addition, walking capacity was evaluated by the 6 minute walk test (6MW), gait speed by the 25 foot walk test (25 FWT), and mobility and balance by the timed up and go (TUG) test. Pearson correlation coefficients were calculated to identify linear relationships between the STS rating scale and the motor function outcome measures.

**Results:** Statistically significant correlations were observed between the STS scale and the motor function outcome measures. Patients with higher STS scores were stronger on MVIC ($r = 0.775$, $p = 0.001$), walk further in 6MW ($r = 0.803$, $p = 0.001$), faster in 25FWT ($r = -0.720$, $p = 0.001$), and TUG ($r = -0.759$, $p = 0.001$).

**Discussion and conclusion:** This STS grading scale is a valid measure of gross LE motor function in ALS patients, and scoring correlates with functional impairment in a linear fashion. The test is easily administered in the clinic and is clinically descriptive of a patient's level of impairment. STS scale could be used as an outcome measure for therapeutic efficacy and clinical decision-making.

DOI: 10.3109/21678421.2014.960174/015

## P16 A DESCRIPTION OF PHYSICIAN PAIN MANAGEMENT PRACTICE IN ALS

SIMMONS Z[1], WALSH S[2], STEPHENS H[1]

[1]*Penn State Hershey Medical Center, Hershey, PA, USA,* [2]*ALS Association, Greater Philadelphia Chapter, Harrisburg, PA, USA*

*Email address for correspondence: hstephens1@psu.edu*

*Keywords: pain, symptom management, physician practice*

**Background:** Pain in ALS occurs in up to 70% of patients at some time during their course of the disease. The under-recognition of pain in ALS has been the subject of a recent editorial. Research on pain in ALS and guidelines for its treatment are needed.

**Objectives:** To describe North American physicians' practices of, and perspectives on, pain management in ALS.

**Methods:** A self-reported and descriptive survey of pain management was designed and e-mailed to physician members of the Northeast ALS Consortium (NEALS) with a link to the anonymous survey.

**Results:** A 33% response rate was obtained. All 37 respondents were Neurologists who routinely assessed for pain in ALS Clinics. Pain assessments were performed by the Neurologist (92%), Nurse (58%), PT/OT (54%), and Medical Assistant (15%). Most commonly, open-ended questions were utilized to assess for pain (88.5%). Less commonly used was numeric rating scales (15%), visual analog scales (8%), and standardized questionnaires (4%). Management of pain was most frequently under the domain of the Neurologist (96%) and less frequently by palliative care (27%), pain management clinics (27%), and primary care providers (20%). Close to half of the sample indicated that ALS pain was of sufficient severity to impair quality of life. Most common types of pain seen in ALS patients were musculoskeletal (100%), muscle cramps and spasms (96%), generalized/poorly defined (61%), and radicular (34%). Pharmacologic pain management included use of anti-spasticity medications (100%), agents for neuropathic pain (100%), non-narcotic analgesics (96%), narcotic analgesics (75%) and trigger point injections (21%). Non-pharmacologic pain management therapies included PT (100%), complementary/alternative management (50%), biofeedback (8%) and cognitive behavioural and mindfulness therapies (each 4%). Top perceived barriers to effective management of

pain in ALS were lack of effective medications (70%), limited information regarding best practices for pain management in ALS (57%) and physician training and experiences in pain management (40%).

**Discussion and conclusion:** Similar to perceptions of patients with ALS, their professional care providers found pain to be a significant component of the disease. As expected, musculoskeletal pain and muscle cramps were common, but the frequent perception by physicians that pain often is generalized and poorly defined points to a need to better understand patients' perception of such pain, and to a need for physicians to understand the overlap with suffering, depression, hopelessness, and other psychological pain. The perceived lack of effective medications may relate to a poor understanding of the aetiopathogenesis of this type of generalized pain. Many physicians are seeking best practices for pain management, and better training to accomplish this. A more complete knowledge of physical pain and psychological pain and suffering in patients with ALS should be considered as important steps toward addressing these needs.

DOI: 10.3109/21678421.2014.960174/016

## P17 SELF-REPORTED MEASURES PREDICT SURVIVAL IN ALS

THAKORE N, PIORO E

*Cleveland Clinic, Cleveland, Ohio, USA*

*Email address for correspondence: thakorn@ccf.org*

*Keywords: survival, DeltaFS (ΔFS), ALSFRS-R*

**Objective:** To explore the effect of self-reported measures on survival in ALS.

**Methods**: ALSFRS-R and other self-reported measures were prospectively collected on tablet devices in outpatient waiting rooms using software developed in-house (Knowledge Program). Cox proportional hazard models identified predictors of survival.

**Results:** Of 931 patients with ALS seen over a 7-year period, 256 died with a median survival of 726 days (about 2 years). Rate of decline of ALSFRS-R (ΔFS) was computed from 2 ALSFRS-R measures at least 45 days apart in 297 patients. Median ΔFS was 0.59 points/month. Higher ΔFS was strongly predictive of poorer survival, with a hazard ratio of 2.02 per point (CI 1.70–2.41). On univariate analyses, additional predictors were increasing age (HR 1.04 per year, CI 1.03–1.06); lower initial ALSFRS-R (HR 1.03 per point, CI 1.01–1.05); lower initial bulbar and respiratory ALSFRS-R subscores (HR 1.1 and 1.09 respectively per point); predominant bulbar/respiratory dysfunction (HR 1.79, CI 1.21–2.64); lower initial EQ-5D (HR 1.16 per 0.1 change, CI 1.10–1.22); higher initial PHQ9 (HR 1.07 per point, CI 1.05–1.10); and lower initial body weight and BMI (HR 1.03 per kg and 1.1 per unit respectively). ΔFS, age, PHQ9, predominant bulbar/respiratory dysfunction, and weight/BMI emerged as significant independent predictors of survival in stepwise regression. A predictive survival model is presented.

**Discussion and conclusion:** Self-reported measures have utility in predicting outcomes and for stratification of ALS patients into clinical trials.

DOI: 10.3109/21678421.2014.960174/017

## P18 BIOLOGICAL FOLLOW-UP IN AMYOTROPHIC LATERAL SCLEROSIS: CREATININE DECREASE AND FERRITIN INCREASE ARE PREDICTIVE OF A POOR PROGNOSIS

PATIN F[1,2], CORCIA P[1,3], MADJI HOUNOUM B[1], VEYRAT-DUREBEX C[1,2], RESPAUD E[1], PIVER E[4], BENZ DE BRETAGNE I[2], VOURC'H P[1,2], ANDRES CR[1,2], BLASCO H[1,2]

[1]*Unité mixte de recherche U930, Institut National de la Santé et de la Recherche Médicale, Université François-Rabelais, équipe "Neurogénétique et Neurométabolomique", Tours, France,* [2]*Laboratoire de Biochimie et de Biologie Moléculaire, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire de Tours, Tours, France,* [3]*Service de Neurologie, Centre Hospitalier Régional Universitaire de Lille, Lille, France,* [4]*Laboratoire de Biochimie, Hôpital Trousseau, Centre Hospitalier Régional Universitaire de Tours, Tours, France*

*Email address for correspondence: patin.franck@gmail.com*

*Keywords: biomarkers, creatinine, ferritin*

**Background:** Clinical parameters are insufficient to predict disease duration in ALS patients, and biological follow-up is often limited to monitoring hepatic toxicity of Riluzole.

**Objectives:** To determine the progression of 13 routine biochemical markers in ALS and their correlation with clinical parameters at diagnosis and during disease evolution.

**Methods:** We retrospectively collected biological data from systematic routine monitoring of 216 patients: creatinine; ASAT; ALAT; GGT; ALP; iron; ferritin; transferrin; total cholesterol; HDL-cholesterol; LDL-cholesterol; and triglycerides, both at diagnosis and every 3 months until 30 months. We also noted the following clinical data: site at onset; age at onset; ALSFRS; FVC at diagnosis. We chose the annual decline of ALSFRS-R and survival as markers of disease progression. Firstly the relationship between clinical parameters and biological parameters at diagnosis was evaluated using Student t-test and spearman rho correlation. Secondly, the evolution of the biological parameters levels (early and late variation was measured at 6th and 24th months respectively) was evaluated and the relationship between the evolution over 24 months of these biological parameters and the disease progression using ANOVA test on repeated measures was assessed. Finally, the relationship between biological parameters at the diagnosis and their early variation (over 6 months) on the disease progression was evaluated. Correlation test of Spearman was used to analyze the annual decline of ALSFRS-R and survival analysis was performed using a Cox multivariate analysis.

**Results:** First, we observed that, at diagnostic time, creatinine was correlated with ALSFRS-R ($p < 0.0001$) and ferritin was linked to FVC ($p = 0.0168$). We highlighted a significant variation of creatinine ($p = 0.0166$) and ferritin ($p = 0.0306$) over the 24 first months of disease. Interestingly, we showed that early and long-term creatinine decrease (ANOVA: $p < 0.002$ and Cox model: $p = 0.004$) and ferritin increase (ANOVA: $p < 0.002$ and Cox model: $p = 0.0101$) were linked to disease progression. Elevated LDL/HDL ratio at diagnosis was found to be predictive of a shorter survival time (Cox model: $p = 0.0028$). Final multivariate model for survival analysis, including age at disease onset, early variation of ferritin, Forced Vital Capacity at diagnosis and diagnostic delay, showed that early variation of ferritin was an independent factor to predict patients' survival ($p = 0.0047$). LDL/HDL

ratio was correlated with diagnostic delay, and data were insufficient for early variation of creatinine, so LDL/HDL and early variation of creatinine were not included in multivariate analysis.

**Discussion and conclusion:** Ferritin and creatinine seem to vary over time, and this variation was linked to disease progression. This study provides new evidences suggesting that these routine biological biomarkers could be evaluated in patient's follow-up. To our knowledge, it is the first study describing the effect of time on these biomarkers and the relation between their evolution and disease progression

DOI: 10.3109/21678421.2014.960174/018

## P19 WHAT DO ALS PATIENTS DIE OF? – AN AUTOPSY STUDY OF 70 ALS PATIENTS

BURKHARDT C[1], NEURWIRTH C[1], SOMMACAL A[2], ANDERSEN P[3], WEBER M[1]

[1]*ALS Clinic/Neuromuscular department Kantonsspital St. Gallen, St. Gallen, Switzerland,* [2]*Department of Pathology Kantonsspital St. Gallen, St. Gallen, Switzerland,* [3]*Institute of Pharmacology and Clinical Neuroscience, Umeå University, Umeå, Sweden*

*Email address for correspondence: christian.burkhardt@kssg.ch*

*Keywords: causes of death, autopsy, survival*

**Background:** Death is the definitive hallmark of amyotrophic lateral sclerosis and primary endpoint in most treatment studies. Despite its importance limited data are available about the definitive causes of death in ALS nowadays. Previous autopsy studies (1) pointed out that defining the cause of death based solely on a clinical examination is not a reliable method to reveal the true cause of death. Treatment of our patients was according to the EFNS guidelines for patient care from 2005 (2). It is unclear if treatments such as non-invasive ventilation (NIV) or percutaneous gastrostomy (PEG) have an impact on the cause of death.

**Objectives:** The aim of this study was to gain a better understanding of causes of death in ALS patients and to investigate how these supportive treatments have an impact on the survival and the causes of death in ALS patients.

**Methods:** Seventy ALS patients were followed in our outpatient clinic and autopsied including a complete macroscopic and microscopic post mortem analysis between 2003 and 2014. Viscera for the pathological causes of death and relevant concomitant diseases were also studied. Neural tissue and CSF was stored for upcoming projects. Median time from point of death to autopsy was 4 h.

**Results:** In this study, the main cause of death was respiratory failure (69/70 patients). In 39/70, aspiration pneumonia and broncho-pneumonia led to death. 22//70 died of hypoxia and 5 patients requested assisted suicide inducing respiratory failure. Pulmonary embolism alone or in combination with pneumonia was detected in six. Both bulbar ($n = 3$) and spinal onset patients ($N = 3$) had embolism without any clear correlation to mobility status. A single patient died from a complication after PEG insertion. Average survival in patients using NIV was 7 month longer than without NIV and even more distinct in the NIV group comparing only limb onset patients. Bronchopneumonia was more frequent in patients using NIV versus non-NIV patients (19/38 versus 5/26, $p < 0.003$). The proportion of aspiration pneumonia was significantly lower in patients with PEG (7/43 versus 7/26, $p < 0.003$). PEG had no effect on survival or BMI at death. Genetic testing could be performed in 32 patients prior to death. Disease-causing mutations (*SOD1* or *C9orf72*) were found in about 1/4 of this cohort.

**Discussion and conclusion:** In this first autopsy study after establishing of the EFNS guidelines, NIV has a positive effect on survival but may be a risk factor for bronchopneumonia. PEG insertion lowers the risk of aspiration pneumonia but has no effect on survival. No correlation was observed between pulmonary embolism and ambulatory disability or site of onset.

**References:**

1. Corcia *et al.* Amyotroph Lateral Scler. 2008; 9(1): 59–62.
2. Andersen *et al.* Eur J Neurol. 2005; 12(12): 921–38.

DOI: 10.3109/21678421.2014.960174/019

## P20 MUSCLE ARCHITECTURE BY MEANS OF ECHOMYOGRAPHY, MULTIFREQUENCY ELECTRICAL IMPEDANCE MYOGRAPHY (MEIM) AND FORCE-TIME CURVE (F-TC) ANALYSIS IN ALS PATIENTS AS BIOMARKERS FOR PREDICTING MUSCLE DISEASE PROGRESSION

CORBIANCO S[1,3], BONGIOANNI P[1,2], TOSI C[3], D'ERAMO M[3], ROSSI B[1], DINI M[3,2]

[1]*Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy,* [2]*NeuroCare onlus, Pisa, Italy,* [3]*HuMoRe Lab, Pisa, Italy*

*Email address for correspondence: bongioanni.paolo@gmail.com*

*Keywords: echomyography, MEIM, Force-time curve analysis*

**Background:** The typical ALS disease course is characterized by progressive irreversible muscle wasting of limbs, torso, abdomen, and oropharynx, in the absence of muscle markers of disease progression. The aim of this study was to clarify if EchoIntesity (EI), EchoMuscle Thickness (EMT) and Multifrequency Electrical Impedence Myography (MEIM) are correlated with muscle force and clinical disease progression in ALS patients, and whether such analyses can be used as clinical biomarkers.

**Methods:** Nine male patients (mean age ± SD: $57.3 \pm 9.5$ yrs) with defined ALS according to the El Escorial criteria (1) were enrolled in our study. All patients were stable in pharmacological medication (50 mg riluzole twice a day); none received any steroid drug treatment. Force was measured both for biceps brachialis and tibialis anterior by a strain gauge system (Loumas Load Cell - Modena, Italy), and results were expressed in relation to a force peak (F) and course in 30 sec-1 (F-TC). MEIM was performed by an impedenzometer (DSMedical - Milan, Italy) that was calibrated each morning before measurements were made. In MEIM analysis (0 to 300 kHz) two source electrodes and two detecting electrodes were used to determine the Nyquist plot (Xc, Rz) for both biceps and tibialis muscles (2). Muscle ultrasonography (EI and EMT) was performed in real time by a 7.5-MHz linear array; gain, time-gain compensation and compression were kept constant (3). All patients were tested every 4 months and analyzed across a 12-month period.

**Results:** F and F-TC significantly ($p < 0.05$) decreased in all patients along the disease progression. EMT decreased and

EI increased significantly ($p < 0.05$) at the month12, but not at months 4 and 8. MEIM analysis, in particular at 50 kHz, pointed out significantly ($p < 0.05$) enhanced Rz and decreased Xc values month 8, and even more significantly ($p < 0.01$) both ones at month 12 ($p < 0.01$).

**Discussion and conclusion:** Data analysis suggests a significant correlation among MEIM, EI, EMT and disease progression, especially when the disease worsens rapidly. The Nyquist plot components are the earliest biomarkers for muscle decline during disease progression. Such findings might be related to the likely initial re-innervation as a factor for maintenance of almost normal values for EI and EMT parameters, whereas the MEIM values that directly come from the muscle cell derangement (intramuscular fibrous and fatty tissue) alone, across the disease progression, precociously highlight pathophysiological condition.

**References:**

1. Brooks BR. ALS other MND. 1: 293–9 (2000).
2. Rutkove SB. Clin Neurophysiol. 116: 290–9 (2005).
3. Pillen S. Muscle Nerve. 27: 699–705 (2003).

DOI: 10.3109/21678421.2014.960174/020

## P21 VIBRATION-INDUCED INHIBITION OF H-REFLEX IN ALS – A BIOMARKER FOR UPPER MOTOR NEURON DYSFUNCTION AND PREDICTOR OF FUNCTIONAL IMPAIRMENT

LEE MI[1], LANCE J[3], BURKE D[3], FITZPATRICK R[1], SIMON N[2], KIERNAN M[2]

[1]*Neuroscience Research Australia, Sydney, Australia,* [2]*Brain and Mind Research Institute, The University of Sydney, Sydney, Australia,* [3]*Institute of Clinical Neurosciences, Royal Prince Alfred Hospital and The University of Sydney, Sydney, Australia*

*Email address for correspondence: m.lee@neura.edu.au*

*Keywords: H-reflex, vibration, upper motor neuron signs*

**Background:** The diagnosis of ALS relies on clinical detection of concomitant upper motor neuron (UMN) and lower motor neuron (LMN) dysfunctions in the same limb or bulbar region. However, UMN signs in the limbs of ALS patients are difficult to assess clinically particularly if there is prominent neurogenic weakness.

**Objectives:** To investigate vibration-induced inhibition of the soleus H-reflex in patients with ALS and the results correlated with clinical UMN score (1) and Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS).

**Methods:** Soleus H-reflex studies were undertaken using a threshold-tracking paradigm in 35 ALS patients and 21 healthy controls. The tibial nerve at the popliteal fossa was electrically stimulated to elicit H-reflex in the soleus muscle. The electrical current needed to produce a H-reflex amplitude of approximately 10% of the maximal direct motor response (Mmax) was tracked using a semi-automated computer program (Q-Trac) and used as a surrogate marker of motoneuronal excitability and will be referred to as H-Th from here on. Soleus H-Th was compared between groups and across 3 conditions: during focal vibration (50 Hz) of the Achilles' tendon (Ach) or tibialis anterior (TA) and no vibration (control condition).

**Results:** Soleus H-reflex was absent in 7 ALS patients (20%, present in all controls). H-Th was higher in ALS patients (14 mA; $n = 28$) compared to controls (8.5 mA; $p = 0.0031$). In all controls, vibration of Ach and TA immediately abolished the H-reflex and the H-Th was elevated (by 30.7% and 24.7% respectively) to compensate for the vibration-induced inhibition. In contrast, ALS patients ($n = 23$) showed much smaller threshold changes during Ach and TA vibration (3.1% and 5.5% respectively; $p < 0.0004$). This was a consistent feature in all ALS patients irrespective of UMN signs (mean UMN score = 8, range between 0–16). ALSFRS was positively correlated with Soleus H-Th change during vibration of Ach ($r = 0.478$, $p = 0.002$) and TA ($r = 0.466$, $p = 0.022$), with the association stronger for bulbar onset ($r = 0.63$, $n = 11$, $p = 0.04$) and upper limb onset ALS patients ($r = 0.93$, $n = 7$, $p = 0.003$).

**Discussion and conclusion:** Vibration-induced inhibition of H-reflex is suppressed in ALS patients with and without clinically detectable UMN signs and may assist in identifying UMN pathology in patients referred with the possible diagnosis of ALS. Furthermore, the magnitude of H-reflex inhibition correlates with the level of functional impairment, particularly for bulbar and upper limb onset ALS.

**Reference:**

1. Turner MR. *et al.* Neurobiol Dis. 2004; 15:601–609.

DOI: 10.3109/21678421.2014.960174/021