Amyotrophic Lateral Sclerosis

Editorial office (to which all correspondence concerning manuscripts and editorial matters should be addressed):

Amyotrophic Lateral Sclerosis
Informa Healthcare
PO Box 3255
SE-103 65 Stockholm, Sweden
E-mail: als@informa.com

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Aims and Scope

Amyotrophic Lateral Sclerosis provides outstanding coverage of research in a wide range of issues related to motor neuron diseases, especially ALS (Lou Gehrig's disease) and spinal muscular atrophies. The journal also covers related disorders of the motor system, when relevant to these core diseases. Amyotrophic Lateral Sclerosis aims to disseminate information on new developments in the pathogenesis and management of motor neuron disease, and enhance awareness of these devastating and often under-recognised disorders.

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23rd international symposium on ALS/MND

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# AMYOTROPHIC LATERAL SCLEROSIS

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Introduction

The Motor Neurone Disease Association, in collaboration with the International Alliance of ALS/MND Associations, welcomes you to Chicago for this year's International Symposium on ALS/MND. We are warmly welcomed by our hosts at the Les Turner Foundation as the symposium returns to Chicago for the first time in 16 years.

This year the programme offers plenty of new perspectives and insights into our understanding of the disease, including the C9ORF72 gene and frontotemporal dementia. The Programme Committee, chaired by Prof Wim Robberecht, has compiled a thought-provoking and varied platform programme reflecting some of these exciting new developments.

Joint opening and closing plenary sessions reflect on the risk factors of the disease and the challenges of translating knowledge to treatment. Parallel scientific and clinical sessions will run for the remainder of the symposium exploring a wide variety of topical themes in more detail, from target pathways, disease models and biomarkers, through to cognitive changes, multidisciplinary management and clinical trials.

This year, once again, we have a large number of high quality poster presentations, discussing novel ideas that promise to give us two sessions of riveting and exciting debate, along with furthering the international exchange of knowledge.

Research Development Team
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1  Session 1  Joint Opening Session C1
2  Session 2A  RNA & Protein Dysregulation C2–C8
6  Session 2B  Cognitive Change C9–C14
10  Session 3A  Cell Stress Mechanisms C15–C19
13  Session 3B  Autonomy and Decision Making C20–C24
16  Session 4A  Genetics & Genomics C25–C30
20  Session 4B  Carer & Family Support C31–C35
23  Session 7A  Modelling ALS C36–C42
26  Session 7B  Clinical Trials & Trial Design C43–C49
30  Session 8A  Cellular Diversity and Selective Vulnerability C50–C54
33  Session 8B  Clinical Registers and Epidemiology C55–C59
36  Session 9A  Phenotypic Change/Modification C60–C65
40  Session 9B  Multidisciplinary Management C66–C71
44  Session 10A  Roles of Non-neuronal Cells C72–C76
47  Session 10B  Respiratory Support C77–C81
50  Session 11A  Murine Models C82–C88
54  Session 11B  Surrogate Markers C89–C96

Poster Communications

Poster Communications are available online via http://www.mndassociation.org/symposium and http://informahealthcare.com/aml
Discussion and conclusions: If clinicians are to make medical treatment decisions that are consistent with patient wishes, they must have a good working knowledge of patients' values, goals and preferences, and the confidence to make the right choices. Use of a computer-based decision aid by patients can not only help the patients become better informed about ACP but can also improve the likelihood that the clinical team is knowledgeable about patient wishes, and confident in their ability to translate this into a medical plan. Clinicians caring for patients with ALS should consider integrating such decision support tools into their practice.

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C69 ALS PARTNER - INTERNET PLATFORM FOR COMPREHENSIVE ALS CARE

MEYER T1, GREHL T2, WALTER B1, WAGNER R1, BUHL H1, NAUMANN V3, MUNCH C1

1Charité, ALS Center, Berlin, Germany, 2Ruhr University, ALS Center, Bochum, Germany, 3AmbulanzPartner GmbH, Berlin, Germany

Email address for correspondence: thomas.meyer@charite.de

Keywords: internet, home care, devices, aids

Background: People with ALS are dependent on provision of comprehensive care including assistive devices (mobility, transfer and advanced communication aids, orthotics) as well as physiotherapy, occupational therapy and speech therapy. Due to the severity and the progressive character of ALS there is an immense need for coordination.

Method: ALSPartner (AP) is a combined concept that unites social-medical service provision (case management), web-based technologies (www.ambulanzpartner.de) and an open network of ALS-trained home care providers. AP manages demanding organizational and care-related tasks liaising between outpatient departments, specialist medical practices, and specialized service providers that are coordinated, documented and visualized on a secure internet platform. The portal comprises a “secure personal care account” featuring all assistive devices and physical therapies, a status report on care provision processes and the option of rating all products and medical services.

Results: Between April 2011 and March 2012, 1040 patients were included - based at the ALS clinics at the Charité University Hospital in Berlin and of Ruhr University in Bochum. 3400 assistive devices and 620 physical therapies were coordinated. The pilot phase stretching a period of 12 months showed high acceptance of AP with a patient participation rate of 78% and a drop-out rate of less than 1%. Data on patient satisfaction are being captured from the perspective of different user groups. We demonstrate the meaningful use of electronic health record (EHR) in the user scenario of ALS.

Discussion: It is AP's prime intention and mission to bridge gaps and overcome barriers between professional groups, individuals playing different roles and separate care provision modules. The portal and the healthcare service provision structure enhance communication and cooperation between doctors, therapists and healthcare providers pertaining to various expert groups all acting in the ALS paradigm.

Acknowledgment: The project was supported by Stiftung Georgsmarienhütte Foundation, the Initiative 'Hilfe für ALS-kranke Menschen', the Air Berlin Fund for ALS Therapy Research, and funding of the German Ministry for Education and Research (BMBF) for the projects 'ServCare_ALS', and 'Innovationsdramaturgie nach dem Heldenprinzip'. TM and CM are founders of the internet platform AmbulanzPartner.

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C70 BULBAR MOTOR DETERIORATION IN ALS

GREEN J1, YUNUSOVA YA2, PATTEE G3, WANG J1, FALIKOWSKI M2, ZINMAN L2,3

1University of Nebraska-Lincoln, Lincoln, NE, USA, 2University of Toronto, Toronto, Canada, 3Sunnybrook Research Institute, Toronto, Canada, 4University of Nebraska Medical Center, Omaha, NE, USA

Email address for correspondence: jgreen4@gmail.com

Keywords: bulbar deterioration, speech production, bulbar assessment

Background: Bulbar symptoms associated with ALS have a devastating effect on quality of life and significantly shorten survival. To date, surprisingly few programmatic research efforts have been directed toward understanding the natural history of bulbar symptoms. Major obstacles have been the inaccessibility and complexity of the speech apparatus. This investigation responds to this need by studying bulbar decline longitudinally and comprehensively using instrument-based analysis of speech behaviors. Longitudinal patterns of decline were investigated to identify sensitive quantitative indicators of the rate of bulbar deterioration, and to determine which speech subsystem measures accurately predict the onset of speech decline and the subsequent loss of oral communication.

Objectives: To determine (1) the sensitivity of multiple measures of bulbar function to disease progression, (2) the relations between speech system and subsystem measures, and (3) the degree of individual variation in speech subsystem impairment.

Methods: Fifty people with ALS were studied every three months for two years. Quantitative indices of motor deterioration were obtained for multiple speech subsystems including respiratory, phonatory, resonatory, and articulatory. To date, nine of the participants were diagnosed as bulbar-onset and eighteen as spinal-onset, four were diagnosed as both bulbar and spinal, and six were not specified. To ensure that the data sample included individuals who were experiencing bulbar decline, all participants will exhibit at least a 10% drop in speech intelligibility and/or a 20% drop in speaking rate. Recently developed three-dimensional motion-capture technologies were used to quantify longitudinal changes in lip, jaw, and tongue movements; aerodynamics were used to quantify declines in respiratory drive and resonatory function; and acoustics analyses were used to quantify declines phonatory function. Latent growth modeling was used to characterize individual and group patterns of deterioration in speech performance, and to establish associations between speech subsystem decline and speech loss.

Results: Of the speech subsystem measures, the velopharyngeal and oral articulatory measures exhibited a much faster rate of decline than did speech intelligibility. Despite differing levels of severity, participants showed a similar pattern in the speech subsystems that were most affected. Speech intelligibility was not correlated with speech subsystem measures.

Discussion: Findings to date suggest that speech subsystem measures decline more rapidly than speech system variables.
C67 CASE MANAGEMENT AS AN ADJUNCT TO MULTIDISCIPLINARY CARE FOR ALS PATIENTS AND THEIR PRIMARY CAREGIVERS IN THE NETHERLANDS; NO EFFECT ON QUALITY OF LIFE OR CAREGIVER STRAIN

CREEMERS H1, VELDINK J2, GRUPSTRA H1, NOLLET F1, BEELEN A1, VAN DEN BERG LH1
1Academic Medical Center of the University of Amsterdam, Netherlands ALS Center, Amsterdam, The Netherlands, 2Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Netherlands ALS Center, Utrecht, The Netherlands

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

Keywords: quality of life, quality of care, case management

Background: About 80% of the Dutch ALS patients and their primary caregivers are supported by one of the 43 multidisciplinary ALS care teams. From clinical practice we know that complex ALS care not always meets the needs of ALS patients and caregivers. Case management (CM) has been suggested as an innovative strategy to optimize care. Nevertheless, there is no evidence about the effectiveness of CM as an adjunct to usual care in ALS patients and their caregivers.

Objectives: The purpose of our study was to answer the following question: Does CM improve ALS patient’s quality of life, caregiver’s burden and perceived quality of care (QoC) of ALS patients and their caregivers?

Methods: We performed a cluster randomized controlled trial, with the ALS team as the unit of randomization. Participating ALS patients and caregivers received CM plus usual care or usual care only, conditional upon their team. Throughout 12 months, two occupational therapists provided CM and visited participants at home at study entry and every three months. Primary outcome measure was the ALS Assessment Questionnaire-40 items, domain Emotional Functioning (ALSAQ-40 EF). Secondary outcome measures were the Caregiver Strain Index (CSI) and QoC (rating score, range 0 to 10 = best possible). We performed assessments at baseline, four, eight and 12 months. We analysed change in emotional functioning and caregiver strain using a multilevel analysis. We used area under the curve analysis for the effect on perceived QoC.

Results: Thirty one teams recruited 71 patients and 66 caregivers for the intervention group and 61 patients and 60 caregivers for the control group. The extent to which participants relied on CM varied widely. Actions of the case manager were mostly in the area of emotional well-being, practical support and providing information. At baseline ALSAQ-40 EF was 19.6 (standard error (SE) 2.0) in both groups and did not change over time (0.56 (SE 0.57) /4 months; p = 0.331). In both groups, CSI scores increased from 5.3 (SE 0.4) at baseline with 0.7 (SE 0.1) points/4 months (p < 0.0001). We found no effect of CM on changes in emotional functioning or caregiver strain from baseline to 12 months. ALS patients from both groups rated their perceived QoC at baseline with a median score of 8 and caregivers with a median score for patient care of 8 and for caregiver care of 7.5. During follow-up, perceived QoC did not change and we found no significant effect of CM.

Discussion and conclusions: Our case management model as adjunct to multidisciplinary care had no effect on emotional functioning, caregiver strain and perceived QoC. One possible explanation is that multidisciplinary care in the Netherlands, which was high-ranked by the participants, leads to a high level of emotional functioning of ALS patients.

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C68 USE OF A COMPUTER-BASED DECISION AID CAN IMPROVE CLINICIAN UNDERSTANDING OF TREATMENT WISHES OF PATIENTS WITH ALS

SIMMONS Z, LEVI B, BROTHERS A, WHITEHEAD M, FARACE E, SCHUBART J, LEHMAN E, GREEN M
Penn State College of Medicine, Hershey, PA, USA

Email address for correspondence: ssimmons@psu.edu

Keywords: advance directives, advance care planning, quality of life

Background: Patients with amyotrophic lateral sclerosis (ALS) face inevitable physical decline, necessitating reflection about, and decisions regarding, advance care planning (ACP).

Objectives: To determine whether a computer-based decision aid for ACP can help improve communication about end-of-life issues between patients with ALS and the clinicians who treat them.

Methods: Patients in an ALS multidisciplinary clinic were invited to use a computer-based decision aid to help them think about and document treatment preferences if they are unable to speak for themselves. Before patients used the decision aid, the ALS clinic team was presented with 3 hypothetical vignettes, and asked which particular treatments they would provide the patient in each scenario (ventilator, cardiopulmonary resuscitation, dialysis, feeding tube, etc.). The team also was asked how confident they were that they could "appropriately translate the patient's goals and values into clinical decisions that accurately reflect his or her wishes" (1 = not at all; 10 = extremely). Patients then used the decision aid, and generated an advance directive. The clinic team met three months later, reviewed the advance directive, and the vignette-based treatment decision process was repeated. Patients were then interviewed by telephone and asked which treatments they actually would want for each scenario. For each decision, concordance was determined between the patient's wishes and the ALS team's treatment plan. Summary scores were expressed as percent agreement, and pre-post comparisons were made using paired t-tests. Patient knowledge, anxiety, and self-determination were also compared pre and post intervention. The study was approved by Penn State's IRB.

Results: 44 patients participated (66% male, 77% married, mean age 58 years). At the time of enrollment, 50% had completed an advance directive. Prior to the intervention, concordance between patient wishes and the clinic team decisions was low (mean = 54.3%, SD 54.3). Following the intervention, concordance was dramatically higher (mean = 92.8%, SD 10.3; p < 0.001). ALS team member mean confidence increased significantly pre-post intervention (from 3.3 to 6.4; p < 0.001). Additionally, patient knowledge of advance care planning increased significantly after the intervention (from 47.8% correct responses to 66.3%; p < 0.001), without any adverse effect on patient anxiety or sense of self-determination.
The surprising lack of association between speech subsystem decline and speech intelligibility may be explained by prior reports suggesting that subsystem decline predates changes in speech intelligibility.

**Conclusions:** These findings suggest that speech subsystem measures of bulbar function can be identified prior to commonly used clinical measures of bulbar involvement such as speech intelligibility and speaking rate, and that these subsystem measures may provide sensitive outcome measures of bulbar involvement for clinical trials.

**DOI:** 10.3109/17482968.2012.721231/070

**C71 ALS MANAGEMENT AND SURVIVAL IN MODENA, ITALY: A STUDY ON A TEN-YEAR PROSPECTIVE POPULATION-BASED COHORT**

GEORGIOULOPOULOU E1, FINI N2, MONELLI M3, PINELLI G3, VACONDIO P3, SOLA P3, NICHELLI P1, MANDRIOLI J2

1Department of Neuroscience, University of Modena and Reggio Emilia, Modena, Italy, 2Department of Neuroscience, S. Agostino-Estense Hospital, Modena, Italy, 3Department of Emergency Medicine, S. Agostino-Estense Hospital, Modena, Italy, 4Department of Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy, 5Department of Palliative Care, Modena Health District, Modena, Italy

Email address for correspondence: j.mandrioli@ausl.mo.it

Keywords: survival, prognostic factors, therapeutic intervention

**Objective:** A number of clinical factors have been reported to predict ALS survival: age and site of onset, the severity and the rate of disease progression, the degree of diagnostic certainty, and the presence of dementia. Riluzole, enteral nutrition, non-invasive ventilation (NIV) and interdisciplinary care are also accompanied by a higher survival rate. We performed a study focused on ALS survival based on a population-based series, with particular attention to respiratory management and therapeutic intervention.

**Methods:** We registered all patients diagnosed with ALS between 2000 and 2009 and resident in Modena (population: 694,580). From 2000 onwards, a Centre for MND has been active in our province as well as a prospective registry collecting all incident cases. Demographic and clinical details were collected together with information about nutrition and ventilation support.

**Results:** Among the collected 193 incident cases, 47.67% underwent NIV. Patients who underwent NIV were younger. Phenotype did not influence the likelihood to undergo NIV. Patients followed by ALS multidisciplinary centres, as well as patients who underwent enteral nutrition, had significantly higher probability to undergo NIV (OR 5.6 and 6.3 respectively). Forty-seven patients (24.35%) underwent tracheostomy (always after informed consent). Tracheostomised patients were younger (42.86% of patients < 55yrs, 29.63% of patients aged 55-74yrs, 10.29% of patients > 74yrs). There were no differences between genders and among phenotypes, except for bulbar ALS, who underwent tracheostomy significantly less frequent than other phenotypes. The presence of dementia or multidisciplinary approach did not influence the likelihood of being tracheostomised. The 49.22% of patients underwent to PEG. Patients who underwent to PEG presented more frequently with bulbar or classic phenotype, were younger and followed in multidisciplinary centre. The median survival time from onset to death was 41 months. The overall 3-year and 5-year survival rates were 54.36%, and 28.81%, respectively. At univariate analysis, factors related to survival (from onset to death, p < 0.05) were: age at diagnosis, sex, phenotype (classic vs bulbar vs UMN vs flail vs respiratory phenotype: 32, 26, 67, 67, 18 months respectively), riluzole treatment (yes vs no: 43 vs 31 months), tracheostomy. Factors not related to survival were presence or absence of dementia, follow-up at an ALS centre, PEG or NIV. In the Cox multivariable model, the factors independently related to a longer survival were age (p = 0.002) and riluzole treatment (p = 0.005).

**Discussion and conclusions:** Surprisingly in our observational study, some procedures like PEG and NIV did not influence ALS survival. Also surprising are data about riluzole treatment which determines a gain in ALS survival of 12 months. This observational study describes the effect of our management and therapeutic intervention on ALS in a setting which may approximate routine clinical practice more closely than RCT, but effects of uncontrolled potential confounders cannot be excluded.

**DOI:** 10.3109/17482968.2012.721231/071
SESSION 10A ROLES OF NON-NEURONAL CELLS

C72 NEURON-ASTROCYTE CROSSTALK IN ALS
PRDEZBORSKI S
Columbia University, New York, USA
Email address for correspondence: sp30@columbia.edu
DOI: 10.3109/17482968.2012.721231/072

C73 GENE EXPRESSION PROFILING OF ASTROCYTES FROM DIFFERENT DISEASE STAGES OF THE SOD1G93A MOUSE MODEL OF ALS REVEALS PERTURBATIONS IN LYPOSOMAL FUNCTION AND CHOLESTEROL METABOLISM
BLACKBURN D1, BAKER D1, FERRAIUOLO L2, HEATH PR1, KIRBY J1, SHAW P1
1The Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, UK; 2The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA
Email address for correspondence: d.blackburn@sheffield.ac.uk
Keywords: astrocytes, lysosomes, cholesterol

Background: Astrocytes play an important role in disease progression in the SOD1G93A transgenic mouse model(1) and show a selective toxicity to motor neurons(2, 3) but the toxic factor(s) have not been identified. Laser-capture microdissection (LCM) allows individual cells to be isolated. We have previously published analyses of LCM motor neurons (MN) from the SOD1G93A and the Vascular Endothelial Growth factor (VEGF) transgenic mouse models of ALS, which revealed altered carbohydrate and lipid metabolism in the SOD1G93A model(4) and a downregulation of cholesterol biosynthesis in the VEGF model(5). We have published data from LCM astrocytes from pre-symptomatic (60 day) SOD1G93A mice, which revealed perturbed lactate metabolism and pro-NGF -p75 receptor signalling (6).

Methods: Astrocytes were isolated by LCM from spinal cord of symptomatic (90 day) and late-stage (120 day) time-points from SOD1G93A mice and non-transgenic littermates. cRNA was hybridised onto the Affymetrix Mouse Genome 430_2 GeneChip and microarray analysis performed using Genespring GX (Agilent Technologies Inc) software with the probe logarithmic intensity error (PLIER) algorithm.

Results: 269 and 1834 genes were differentially expressed at the symptomatic and late disease stage. Annotation clustering analysis showed an upregulation of many genes in inflammatory pathways but also an upregulation of lysosomal genes (DAVID enrichment score 2.44) such as Cathepsin D (+2.32 and +3.28 fold at 90 & 120 days) and Laptm5 (+2.81 & +5.7 at 90 & 120 days). In late-stage astrocytes there is a downregulation of multiple genes in cholesterol and steroid biosynthesis (hydroxysteroid 11-beta dehydrogenase 1 -2.32 & 5.05; hydroxysteroid (17-beta) dehydrogenase 7 -2.05 & 2.88) storage and excretion of cholesterol (24-dehydrocholesterol reductase -2.10 at 60 & -2.66 at 120 days) and uptake of cholesterol (low density lipoprotein receptor & lipoprotein lipase -3.39 and -11.21 respectively). We are currently conducting further validation and functional assays.

Conclusions: We have found evidence for altered lysosomal function in SOD1G93A astrocytes at symptomatic and late-stage disease. Cathepsin D is upregulated in SOD1G93A mice spinal cord (7) but decreased in human mutant SOD1 MN(8), whilst the cathepsin inhibitor Cystatin C is decreased in CSF of ALS patients (9, 10). Furthermore, overexpression of Laptm5 increases lysosomal membrane permeabilisation, Cathepsin D leakage and non-caspase dependent cell death. Cholesterol levels are increased in the spinal cord of SOD1G93A mouse model at pre-symptomatic and endstage as well as in spinal cord of patients with ALS (11). Excess cholesterol is toxic to MN(12) and altered cholesterol metabolism is seen in MN at end stage from the SOD1G93A and the VEGF mice (4, 5). We believe that, like several other late onset neurodegenerative diseases, cholesterol transport abnormalities may contribute to motor neuron injury in ALS and that astrocytes play a key part in this process.

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C74 ASTROCYTES FROM FAMILIAL AND SPORADIC ALS PATIENTS ARE TOXIC TO MOTOR NEURONS
MEYER K1, HAIDET-PHILLIPS A1, HESTER M1, MIRANDA C1, BRAUN L1, MENDELL J1,2, BURGHESS A1,2, KASPAR B1,2
1The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA, 2The Ohio State University, Columbus, OH, USA
Email address for correspondence: Kathrin.Meyer@nationwidechildrens.org
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Background: Amyotrophic Lateral Sclerosis (ALS) is a fatal motor neuron (MN) disease with astrocytes implicated as a significant contributor to MN death in familial ALS (fALS). However, these conclusions, in part, derive from rodent models of fALS based upon dominant mutations within the superoxide dismutase 1 (SOD1) gene which account for less than 2% of all ALS cases. Studies performed in fALS mouse models have implicated non-neuronal cells such as microglia and astrocytes in the progression phase of fALS. In particular, in vitro co-culture systems have shown that MNs perish in the presence of astrocytes harboring SOD1 mutations. However, all of these in vitro and in vivo studies have been conducted...