Abstracts from Themes BW and CW

Biomedical work in progress

Clinical work in progress

Glasgow, Scotland, UK

7-9 December 2018

Table of Contents

Biomedical work in progress

BW-01 The Dominant Inherited ALS (DIALS) Network: Methods For a Work in Progress

Katharine Nicholson[1], Katherine Burke[1], Diane Lucente[1], Sara Thrower[1], James Chan[1], Tania Gendron[2], Mercedes Prudencio[2], Leonard Petrucelli[2], James D Berry[1], Timothy Miller[3]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Mayo Clinic, Jacksonville, FL, USA, [3]Washington University, St. Louis, MO, USA

Email address for correspondence: knicholson@partners.org

Keywords: pre-symptomatic, gene carrier

Background: The pre-symptomatic period has not been defined for ALS and markers of clinical conversion have yet to be discovered. Identifying biomarkers in asymptomatic ALS gene carriers would shed light on inciting disease pathology and allow us to move up the diagnostic horizon. The validation of sensitive biological markers and outcomes to follow the earliest signs of disease will set the stage to conduct successful trials aimed at disease prevention in populations of asymptomatic gene carriers, such as the DIALS Network cohort.

Objectives: To identify the earliest biological and clinical markers of disease in people at high risk for developing ALS, such as asymptomatic carriers of ALS causative genes.

Methods: The DIALS network consists of a multicenter infrastructure (Massachusetts General Hospital and Washington University) with a streamlined protocol for CLIA genetic testing of asymptomatic potential ALS gene carriers through the New York Genome Center (NYGC). CLIA-genetic testing includes assessment for the *C9ORF72* repeat expansion and whole genome sequencing. Over 30 known ALS-causative mutations are checked for return of results. Participants have the option of genetic disclosure at 3 months. They are otherwise evaluated every 6 months with a neurological exam, biofluid collection (plasma, serum, whole blood, CSF, PBMCs, urine, skin biopsy) and outcomes (e.g. functional, respiratory, strength, cognitive, speech, and mood). Clinical data is collected using NeuroBANK. Biomarker analysis thus far has included assessment of neurofilament heavy (pNFH) and dipeptide repeat proteins in collaboration with the Petrucelli Lab at the Mayo Clinic Jacksonville, where samples are being evaluated alongside those from other collections involving ALS gene carriers.

Results: Thus far, 36 participants have enrolled in the DIALS Network, with an interval analysis performed on 30 of these individuals. Approximately half of these individuals harbor an ALS causative mutation (10 *C9ORF72*, 3 *SOD1*, one *SOD1* and *SQSTM1*). Three *C9ORF72* carriers have developed symptoms (2 ALS, 1 FTD) and one *SOD1* carrier was determined pauci-symptomatic at baseline; twenty-six remain asymptomatic. Enrollment and follow-up and biomarker and outcome data analyses are underway. We hope to expand to additional sites to increase sample size.

Discussion and conclusions: The DIALS Network is building a rich dataset in asymptomatic gene carriers. We have already characterized several symptom converters. Increased sample size and continued longitudinal follow-up will help define the fundamental components of the conversion period in familial ALS, and support the design of prevention trials in familial ALS.

Acknowledgements: ALS Finding a Cure, Target ALS, and Muscular Dystrophy Association have provided funding support for this project.

BW-02 Kinesin heavy chain (KIF5A) mutations in amyotrophic lateral sclerosis: A follow up study

Yevgeniya Abramzon[1,2], Adriano Chiò[3,4],

Bryan J Traynor[1,5]

[1]National Institutes of Health, Bethesda, Maryland, USA, [2]University College London, London, United Kingdom, [3]University of Torino, Torino, Italy, [4]AOU San Giovanni Battista Torino, Torino, Italy, [5]Johns Hopkins University, Baltimore, Maryland, USA

Email address for correspondence: yevgeniya.abramzon@nih.gov

Keywords: KIF5A, linkage disequilibrium

Background: Earlier this year *KIF5A* was identified as a cause of ALS (Nicolas et al., 2018). To date, ALS-associated mutations are mainly found at the C-terminal, the cargo-binding tail domain of the protein. In addition, the study determined that patients with loss-of-function mutations in C-terminal had an earlier disease onset but longer survival than typical ALS cases.

Objectives: The aim of this project is to sequence a large number of ALS patients coding for other mutations in *KIF5A*. We also wished to investigate if there are other variants within *KIF5A* gene in linkage disequilibrium with earlier described Pro986Leu variant that we identified as associated with the disease.

Methods: Written consent was obtained from all patients. This work was approved by Institutional Review Board at the National Institutes of Health.

DNA from 800 individuals affected by ALS were used for targeted gene resequencing on a MiSeq system (Illumina Inc.). The entire 35kb region of *KIF5A* on chromosome 12q13.3, including UTRs, exons and introns, was captured using target resequence capture (Illumina). The collected data was analyzed on Truseq Amplicon Basespace program for the presence of mutations associated with ALS. Human genome control databases were used for case/control analysis.

Results: Results describing mutation frequency and associate phenotypes will be presented at the symposium.

Discussion and conclusions: Understanding genetics of ALS is important to understanding the origin of the disease. Initial paper was important to identify the gene, but additional research is required to more fully elucidate the importance of this gene as a cause of ALS and to determine the full genotypic and phenotypic spectrum.

Acknowledgements: We would like to thank the patients and research participants who contributed samples for this study. Funding for this study was provided by Intramural Research Programs of the NIH, National Institute on Aging (Z01-AG000949-02). The authors declare no conflicts of interest.

References

Nicolas A, Kenna KP, Renton AE, et al. Neuron 2018;97:1268-83 e6.

BW-03 The potential role of a polymorphic VNTR in the aetiology of Motor Neurone Disease

Jack N Marshall[1], Ben A Middlehurst[1], Abigail L Savage[1], Richard J Mead[2], Pamela J Shaw[2], Vivien J Bubb[1], John P Quinn[1]

[1]University of Liverpool, Liverpool, United Kingdom, [2]University of Sheffield, Sheffield, United Kingdom

Email address for correspondence: j.marshall6@liverpool.ac.uk

Keywords: C21orf2, VNTR

Background: There have been a number of genes associated with familial and sporadic Motor Neurone Disease (MND) including the C21orf2 gene. Genetic variation in the exon of this gene could affect protein function and therefore be mechanistically associated with progression of MND. However the inappropriate regulation of the expression of C21orf2 could also modify the signalling pathways in which it is involved and offer another route to progression of MND; such as the

interaction with another MND gene, NEK1. Our analysis of this locus identified a Variable Number Tandem Repeat (VNTR) within intron 1 of this gene which we confirmed was polymorphic in copy number of the repeat element. Previous studies have demonstrated polymorphic VNTRs can be associated with predisposition to disease and this is often correlated with the differential transcriptional regulatory properties of the VNTR based upon the copy number of the repeat element. We will present data on the potential role of this VNTR in the pathogenesis of MND by addressing i) the frequency of the different alleles for the VNTR present within patients with MND in comparison with a matched control cohort, ii) functionality of the VNTR as a regulatory element in a reporter gene assay, iii) the potential for the variation present in this element to generate differential gene expression.

BW-04 The role of non-LTR retrotransposons in the increased genetic burden to MND at the NEK1 gene

Jack N Marshall[1], Ben A Middlehurst[1], Gerald G Schumann[2], Abigail L Savage[1], Richard J Mead[3], Pamela J Shaw[3], Vivien J Bubb[1], John P Quinn[1]

[1]University of Liverpool, Liverpool, United Kingdom, [2]Paul-Ehrlich-Institut, Langen, Germany, [3]University of Sheffield, Sheffield, United Kingdom

Email address for correspondence: j.marshall6@liverpool.ac.uk

Keywords: NEK1, SVA

Background: Genome-wide association studies (GWAS) and functional data has shown that there is a genetic basis contributing to sporadic and familial forms of MND. We have focused on the non-LTR (non-Long Terminal Repeat) retrotransposons, representing transposable elements in the human genome known to be currently mobilised in the brain and central nervous system (CNS) as genetic elements affecting the risk to MND. This subclass is divided into three families: Long Interspersed Elements-1 (LINE-1, L1), *Alu* elements and SVA (SINE-VNTR-Alu) elements. Using whole genome sequencing (WGS) data and retrotransposon capture sequencing (RC-Seq) it has been possible to detect non-LTR retrotransposon presence or absence insertion polymorphisms which previously had not been identified. Non-LTR retrotransposon can affect gene expression by two distinct mechanisms; as regulatory elements in the germline (found in the reference genome sequence) and as source elements for insertional somatic mutation via their mobilisation. We have focused on defining the non-LTR retrotransposon genetic variation generated by 1) presence or absence polymorphism of these elements and 2) polymorphism within the non-LTR retrotransposon itself, to determine the increased genetic burden at the NEK1 locus. We will present data on the frequency of such elements in MND cohort and how these domains may modify NEK1 gene expression.

BW-05 Regulation of Ubiquilin 2 dependent protein clearance

Matthew J Keuss, Roland Hjerpe, John S Bett, Thimo Kurz

University of Glasgow, Glasgow, United Kingdom

Email address for correspondence: matthew.keuss@glasgow.ac.uk

Keywords: Ubqln2, ubiquitin, proteasome

Background: Dysregulation of the ubiquitin proteasome system (UPS) is a common characteristic among neurodegenerative disorders. Aggregates in post mortem tissue from ALS patients are often immunoreactive to ubiquitin, which suggests that the targeting of ubiquitylated proteins for degradation is impaired in neurodegeneration. Ubiquilin 2 (Ubqln2) is one component of the UPS

that shuttles ubiquitylated proteins to the proteasome, and mutations in Ubqln2 cause ALS/FTD (1,2). Ubqln2 is unique among the Ubiquilin family members in that it contains a PxxP domain of unknown function. The importance of the PxxP domain is underscored as this domain is the main site where ALS/FTD linked mutations have been identified.

We previously showed that UBQLN2 is involved in autophagy independent protein aggregate clearance via interactions with HSP70 (3). A P506T mutation within the Ubqln2 PxxP domain reduces Ubqln2's ability to bind HSP70, which impairs aggregate clearance and contributes to neurodegeneration in a mouse knock-in model of the Ubqln2 P506T mutation (3).

Objectives: To better understand the role of Ubqln2 in aggregate clearance and how mutations negatively impact its function, we sought to identify novel binding partners of Ubqln2 that are involved in the UPS/protein quality control pathway. Further to this, we characterise how these binding partners promote Ubqln2 function.

Methods: Flp-In T-Rex 293 cell lines with Flag-Ubqln2 WT and Flag-Ubqln2 P506T were used in SILAC experiments to identify interactors whose binding was differentially regulated by Ubqln2 mutation. Identified partners were confirmed by *in vitro* binding assays and immunoprecipitation assays from cell lysates. Knockout/knockdown approaches were used to determine how identified interactors regulate Ubqln2 ability to clear proteins during proteotoxic stress.

Results: Several interactors of Ubqln2 have been identified with known roles in protein quality control/UPS function. The interactors with increased/decreased binding to the P506T mutant compared to WT were characterised for their ability to regulate Ubqln2's role in shuttling ubiquitylated proteins to the UPS.

Discussion and conclusions: Ubqln2 is a component of the UPS and regulates the clearance of aggregated and misfolded proteins to maintain protein homeostasis. The mechanism by which ubiquitylated proteins are targeted by Ubqln2 and chaperoned to the proteasome has not been fully characterized.

Acknowledgements: Funding for this study was provided by Motor Neurone Disease Scotland and the British Council BIRAX initiative.

References

1. Deng H X, Chen W, Hong S T *et al* Nature 2011; 477:211-215
2. Williams K L, Warraich S T, Yang S *et al* Neurobiol Aging 2012; 33:2527.e3-2527.e10
3. Hjerpe R, Bett J S, Keuss M J *et al* Cell 2016; 166:935-949

BW-06 Variability in the level of a motor neurone disease-relevant protein: survival motor neurone (SMN) in individual cells and associated vulnerability to hypoxic damage

Elena Hernandez Gerez[1,2], Ian N Fleming[2], Simon H Parson[2,1]

[1]Euan MacDonald Centre for MND Research, Edinburgh, United Kingdom, [2]University of Aberdeen, Aberdeen, United Kingdom

Email address for correspondence: r02eh16@abdn.ac.uk

Keywords: SMN, NSC-34, hypoxia

Background: In recent years there has been an increase in research correlating motor neurone disease with vascular abnormalities. In the inherited, predominately childhood form of motor neurone disease: spinal muscular atrophy (SMA), mouse models have shown disease-relevant hypoxia, with spinal cord tissue in pre- symptomatic animals showing clear hypoxia labelling, particularly in grey matter neurones.

This is correlated with a decrease in microvasculature density, which likely contributes to motor neurone loss (1). It is now becoming clear that there is more overlap between the predominately adult onset ALS and childhood onset SMA, including a role for SMN protein in ALS. This is particularly seen when single cells are studied. It also suggests that research in an SMA model is also relevant to ALS. SMA is caused by a mutation in a single gene, SMN1, which codes for SMN (Survival Neuron Neuron) protein. This has made it relatively straightforward to develop in-vivo and in vitro models to study the disease at a cellular level. Here, we use a cell culture model to study changes in hypoxia-pathway proteins and cell survival related factors in diseased motor neurones.

An SMA in-vitro model was developed by knocking-down SMN protein by siRNA transfection in NSC-34 cells. NSC-34 is an immortal cell line, produced by fusion of embryonic mouse spinal cord motor neurons with mouse neuroblastoma cells, and as such retains most characteristics of mice motor neurones. Initially we were interested in examining variations in SMN protein levels using western blot, immunofluorescence and flow cytometry. Western blot provides data on mean protein levels, while flow cytometry allows estimation of the SMN levels in individual cells. Preliminary data has shown that SMN levels vary considerably between individual cells, even in these clonal cell lines. Further, it was clear that SMN levels overlapped considerably between control and SMN-depleted (SMA disease model) cells. Together with recent data showing considerable spatial and temporal variations in SMN levels (2), this suggests that considerable care must be taken when aiming to understand SMN levels in tissues and organs, where multiple cell types are present. Further analysis is considering survival, apoptosis induction and metabolic rate, in addition to HIF1, VEGFR1 and 2 levels under control and hypoxic conditions. Metabolic rate is estimated by 18F-FDG,a radioactive glucose analog, uptake. Additional parameters are estimated by combinations of western blotting, immunofluorescence and flow cytometry, depending on their characteristics.

Together this work is providing key insights into the association between SMN protein and motor neurone vulnerability to cellular stressors.

References

1. Somers E, Lees RD, Hoban K *et al* Annals of neurology 2016; *79*(2): 217-230.
2. Rodriguez-Muela N, Litterman NK, Norabuena EM, *et al* Cell reports 2017; *18*(6): 1484-1498

BW-07 ARF GTP'ases control motor neuron death in models of fALS

Lei Zhang[1], Jelena Mojsilovic-Petrovic[1,2], Robert Kalb[1,2]

[1]Children's Hospital of Philadelphia, Philadelphia, PA, USA, [2]Northwestern University, Chicago, IL, USA

Email address for correspondence: robert.kalb1@northwestern.edu

Keywords: membrane traffic

Background: Intracellular trafficking defects are well described in ALS and many other neurodegenerative diseases and are likely to be important pathophysiological contributors. These abnormalities may be tied to coat protein assembly since this drives vesicle formation and cargo selection. COPI and clathrin coated vesicles are regulated by GTP-binding proteins called ADP ribosylation factors (ARFs). Rodents have 6 ARF genes; humans have 5. ARFs control critical trafficking events such as*trans*-Golgi to ER and *trans*-Golgi to endosome movement. ARFs are activated by guanine nucleotide exchange factors (e.g. GEFs) such as the BRAG/IQSec and Cytohesin protein families.

In heterologous expression systems, multiple cytohesins physically associate

with wild type and mutant SOD. The same is true of spinal cord tissue lysates from the G93A mutant mouse. These observations suggest that altered cytohesin, and by implication ARF GTP'ase function, contribute to ALS. In support of this, inhibition of cytohesin function (either pharmacologically or by RNAi-mediated knockdown) protects motor neurons from the noxious effects of G85R mutant SOD or A315T mutant TDP-43 expression *in vitro*. These actions are associated with reduced ER stress, enhanced autophagy and a reduced burden of misfolded SOD (*1*).

We hypothesize that reduced activity of some or all ARF GTP'ases can protect against insults relevant to familial ALS (fALS). To test this, we developed miRNAs that are capable of knockdown of each individual rat ARF specifically. We also developed a miRNA that knocks down all ARFs ("pan"). We then expressed these miRNAs in primary rat spinal cord cultures along with mutant SOD or mutant TDP-43 and assessed the effects on motor neuron survival. Knock down of ARF2, ARF3 and ARF5 (but not ARF1, ARF4 or ARF6) protected motor neurons from the toxicity of mutant SOD. Knock down of ARF2, ARF4 or ARF5 (but not ARF1, ARF3 or ARF6) protected motor neurons from the toxicity of mutant TDP-43. Reducing the abundance of all ARFs using a pan-ARF miRNA was noxious under all conditions. Thus, an overlapping set of ARFs, when knocked down, confer protection against the toxicity of mutant SOD and mutant TDP-43. This raises the possibility that both mutant SOD and mutant TDP-43 converge on a common pathophysiological pathway that can be modified by knockdown of either ARF2 or ARF5. These observations can be leveraged to: 1) understand the molecular mechanism by ALS causing mutant genes corrupt intracellular trafficking, and 2) guide the generation of therapeutics, such an antisense oligonucleotides, that target ARF2 or ARF 5.

Acknowledgements: This work was funded by National Institutes of Health Grants, NS087077 and NS05225 to R.G.K.

References

J. Zhai *et al.*, *J. Neurosci.*35, 9088–9105 (2015).

BW-08 The clinical effects of chlorovirus ATCV-1 on SOD1G93A transgenic ALS mice and identification of ANTI-ATCV-1 IG isotypes subclasses associated with ALS

Gary L Pattee[1,2], Thomas M Petro[3], David D Dunnigan[4], Zack Guinn[3], Irina Agarkova[4], James Van Etten[4]

[1]Neurology Associates, Lincoln, Nebraska, USA, [2]University of Nebraska Medical Center, Dept of Neurosciences, Omaha, Nebraska, USA, [3]University of Nebraska Medical Center, Dept of Microbiology and Immunology, Lincoln, Nebraska, USA, [4]University of Nebraska-Lincoln, Dept of Plant Pathology, Nebraska Center for Virology, Lincoln, Nebraska, USA

Email address for correspondence: glpattee@gmail.com

Keywords: chlorovirus, transgenic mice, IgG isotypes

Background: Environmental and infectious exposures have long been postulated as contributors to the initiation or propagation of MND. Documented infectious agents associated with MND include WNV, poliovirus, HIV, and cyanobacteria [1]. Recently, preliminary serological data has shown that sera from ALS patients have significantly elevated IgG antibody levels to Chlorovirus ATCV-1 compared with healthy subjects, suggesting a potential exposure related disease effect. Chloroviruses (CV), which naturally infect chlorella-like green algae, have been shown to infect mammalian macrophages, inducing inflammatory mediators and apoptosis [2]. ATCV-1, which is one of more than 30 chlorovirus types, encodes a Cu/Zn

SOD1, which if expressed in mammalian cells, may contribute to the clinical manifestations of ALS.

Objectives: To confirm the anti-ATCV-1 Ig isotype/subclasses associated with ALS patients and to determine if intracranial ATCV-1 injection into SOD1G93A-transgenic mice hastens the onset or development of ALS symptoms.

Methods: Serum samples were randomly collected from 17 patients with ALS and 13 age matched controls. These samples were evaluated for IgG1, IgG2, IgG3, IgG4, IgA, and IgM antibodies directed against ATCV-1 using ELISA techniques. As a control, IgG antibody to tetanus toxoid was also evaluated. Additionally, 10 SOD1G93A-transgenic and 10 C57Bl/6 wild type mice will be injected intracranially at 4 weeks of age with 10^6 infectious ATCV-1 virus particles or injected with an equal volume of saline. The mice will be closely monitored daily for development of motor dysfunction, which will include the time of onset of tail paralysis, hindlimb tucking and decreased righting reflex. Following euthanization, serum will be analyzed for ATCV-1 isotypes and inflammatory cytokines.

Results: Research will be presented examining an expanded range of human Ig isotypes/subclasses of anti-ATCV-1 in ALS patients. It is expected that one of the human Ig isotypes/subclasses will dominate anti-ATCV-1 in ALS patients. The time frame for onset of motor dysfunction in ATCV-1 infected SOD1G93A-transgenic mice will also be measured, identifying variations of phenotypic expression and disease onset when compared to uninfected transgenics.

Discussion and conclusions: Analysis of disease manifestations in ATCV-1 treated vs untreated SOD1 mice is currently underway, and study data will be reviewed at the time of presentation. Data on anti-ATCV-1 Ig isotype/subclasses associated with ALS will also be presented. This research will help identify if chloroviruses, which are ubiquitous in fresh water aquatic environments throughout the world, could be environmental triggers of ALS.

Acknowledgements: Funding was generously provided by the Stuart Nichols ALS Research Foundation.

References

1. Torbick, C., Ziniti, B., Stommel, E., et al. Neurotoxicity Research. 2017; 3:1-14.
2. Petro, T.M., Agarkova, I.V., Zhou, Y., et al. J. Virol. 2015; 89:12096-12107.

BW-09 Knock in mouse models to understand ALS pathomechanisms

Abraham Acevedo Arozena[1], Thomas J Cunningham[2], Anny Devoy[3], Adrian M Isaacs[3,4], Linda Greensmith[3], Pietro Fratta[3], Elizabeth M Fisher[3]

[1]Hospital Universitario de Canarias, Fundación Canaria de Investigación Sanitaria, La Laguna, Spain, [2]MRC Mammalian Genetics Unit, Harwell, United Kingdom, [3]UCL Institute of Neurology, London, United Kingdom, [4]UK Dementia Research Institute at UCL, London, United Kingdom

Email address for correspondence: aacevedo@ull.edu.es

Keywords: mouse models, Knock In, TDP-43

Background: Mouse models are critical to further our understanding of disease processes. To try to faithfully recapitulate disease pathogenesis, we have a long-term interest in creating knock in (KI) mouse models of ALS.

Here, together with information on other models that we are currently producing and characterising, we present data from KI models of three key ALS genes (*Sod1*, *Tardbp* and *Fus*) developed by us over the last few years: the *Sod1*^{D83G} mouse (1); the FUS Delta14 mouse (2) and an allelic set of *Tardbp* (TDP-43) mutants, including a new strain with spinal cord motor neuron degeneration

and novel splicing changes also found in human mutant *TARDBP*-ALS cells (3). Our methods of creating KI mice range from chemical mutagenesis through to CRISPR/Cas9 and sophisticated humanised targeting constructs for homologous recombination in embryonic stem cells. We employ a longitudinal panel of tests including behaviour, physiology, histology and transcriptomics – which are then validated in human tissue/cell lines. In our experience, KI models tend to produce mice with milder phenotypes and slower disease course than transgenic models, enabling us to particularly focus on early stage disease whilst distinguishing between gain and loss of function phenotypes.

Acknowledgements: This research is supported in part by funding from the Medical Research Council, the UK Motor Neurone Disease Association, the American Amyotrophic Lateral Sclerosis Association, the Brain Research Trust, the UK Dementia Research Institute, the Thierry Latran Foundation and the Instituto de Salud Carlos III.

References

1. Joyce P, McGoldrick P, Saccon R *et al*.Hum Mol Genet. 2015. 1; 24:1883-97
2. Devoy A, Kalmar B, Stewart M *et al***.** Brain. 2017. 1; 140:2797-2805
3. Fratta P, Sivakumar P, Humphrey J *et al*. EMBO J. 2018. 37:e98684

BW-10 Repeated concussions lead to CSMN degeneration with neuroinflammation.

Amiko K Lagrimas[1], Eric J McLaren[2], Eileen H Bigio[3], P. Hande Ozdinler[1], Javier H Jara[1]

[1]Dept. Neurology, Northwestern University, Chicago, IL, USA, [2]Davidson College, Davidson, NC, USA, [3]Cognitive Neurology and Alzheimer's Disease Center,, Chicago, IL, USA

Email address for correspondence: j-jara@northwestern.edu

Keywords: upper motor neurons, concussion, neuroinflammation

Background: Repeated concussions and traumatic brain injury (TBI) lead to development of neurodegenerative diseases including chronic traumatic encephalopathy (CTE) and ALS. Development of ALS after TBI remains controversial. However, several studies have revealed an association between development of ALS in professional athletes with concussion history, military veterans, and 4%-6% of patients with CTE [1]. Corticospinal motor neurons (CSMN) located in the cerebral cortex progressively degenerate in ALS and they might be more susceptible to damage after repeated concussions and TBI. Neurodegeneration is also accompanied by neuroinflammation in the cerebral cortex of ALS and TBI models and it is characterized by mainly by microgliosis. In fact, microglia activation is widely present the cerebral cortex in direct connection with clinical CSMN deficits in ALS patients and is present in the vicinity of diseased CSMN [2].

Objectives: To understand the mechanisms that lead to CSMN degeneration and neuroinflammation after repeated concussions, and to develop a novel model system that mimics TBI that occurs in human patients.

Methods: We use three repeated concussions performed at 72hrs intervals using a close-skull controlled cortical impact on UCHL1-eGFP (U-eGFP) transgenic line in which CSMN are genetically labeled with eGFP. Apical dendrite pattern, CSMN body size, and markers of apoptosis serve as a read-out to determine CSMN degeneration. To study neuroinflammation we use cellular markers of microglia activation in combination with morphological analysis. To further investigate the correlation between TBI and ALS, we use human motor cortices from ALS patients with and without trauma history.

Results: Our preliminary results show that a closed-skull TBI approach leads to CSMN degeneration with vacuolated apical dendrites and microgliosis. These results correlate with the observed CSMN degeneration in ALS mouse models. Microgliosis was gradually increased after each concussion and it was observer throughout the motor cortex. Analysis of Betz cells and microgliosis in ALS with or without trauma history reveals the presence of activated microglia and abnormal rod microglia, and Betz cells with different degrees of degeneration surrounded by microglia and as we have previously shown to be the case in ALS [3].

Discussion and conclusions: We find that CSMN have a degeneration pattern after repeated concussions that is similar to that of observed in ALS mouse models with CSMN degeneration. Moreover, the fact that microgliosis and Betz cells degeneration is present in ALS patients with previous history of trauma reinforces the importance of further studies to investigate the link between TBI and ALS.

Acknowledgements: Funding was provided by ALS Association (JHJ).

References

1. Moszczynski, A.J., Strong W., Xu, K. *et al*. Neurology. 2018; 90:e380-e387.
2. Brettschneider J, Toledo JB, Van Deerlin VM, *et al*. PLoS One. 2012;7:e39216. Epub 2012/06/22.
3. Jara J.H., Genç B., Stanford M.J., *et al*. J Neuroinflamm 2017;14:129.

BW-11 Humanised mouse models of ALS.

Remya R Nair[1], Anny Devoy[2], Samanta Gasco[1], Charlotte Tibbit[1], Asif Nakhuda[1], Carmelo Milioto[2,3], Abraham Acevedo-Arozena[4], Pietro Fratta[2], Adrian M Isaacs[2,3], Thomas J Cunningham[1], Elizabeth M Fisher[2,1]

[1]MRC Harwell Institute, Mammalian Genetics Unit, Harwell, United Kingdom, [2]UCL Institute of Neurology, London, United Kingdom, [3]UK Dementia Research Institute at UCL, London, United Kingdom, [4]Unidad de Investigación, Hospital Universitario de Canarias, La Laguna, Spain

Email address for correspondence: t.cunningham@har.mrc.ac.uk

Keywords: mouse model, C9orf72, FUS

Background: Modelling late onset neurodegenerative disease is challenging, and improved models are needed to more faithfully recapitulate human pathology. Our Mouse Models of Neurodegeneration Lab at MRC Harwell, in close collaboration with neurodegeneration experts and clinicians at the UCL Institute of Neurology, has a key focus to genetically engineer and phenotype new models of neurodegeneration via genomic humanisation of the mouse, to answer key questions surrounding mechanisms of action and to provide physiologically relevant models to test future therapeutics.

Here we present ongoing work on humanising two genes, C9ORF72 and FUS, including introduction of mutations that cause ALS. A hexanucleotide repeat expansion in the C9ORF72 gene represents the most common genetic cause of ALS and frontotemporal dementia. Our project to humanise this gene at the endogenous locus, with and without a large number of repeats, is in the initial phase, and we outline our BAC recombineering progress here.

We also present data on new humanised FUS-ALS mouse models generated by our UCL colleagues Anny Devoy and Elizabeth Fisher. FUS-delta14 mice harbour a partially humanised FUS gene plus human pathogenic splice site mutation causative for ALS, leading to progressive lower motor neuron loss in mice starting mid-life (1). In addition, we introduce mice harbouring a fully humanised FUS gene, in both the wild type state and with additional ALS-associated mutations introduced via CRISPR/Cas9 editing in zygotes, which

are in the very early stages of characterisation.

Acknowledgements: We would like to thank the MRC, the MND Association, and the American ALS Association for their generous funding.

References

1. Devoy A, Kalmar B, Stewart M *et al*. Brain. 2017. 1; 140:2797-2805

BW-12 Extramotor involvement differs with severity of bulbar ALS: post-mortem neuropathological findings

Sanjana Shellikeri[1], Julia Keith[2,1], Sandra E Black[2,1], Lorne Zinman[2,1], Yana Yunusova[2,1]

[1]University of Toronto, Toronto, ON, Canada, [2]Sunnybrook Health Sciences Center, Toronto, ON, Canada

Email address for correspondence: sanjana.shellikeri@mail.utoronto.ca

Keywords: bulbar, neuropathology, frontotemporal degeneration

Background: Bulbar onset or bulbar symptoms have been associated with an increased presence of extramotor deficits in ALS (1, 2). The link between motor and extramotor deficits can be explained by recent reports of a network breakdown in neurodegeneration, attributed to disease propagation through the axonal wiring system (3). As such, involvement of motor and extramotor regions part of a single network (4) may be related to the severity of motor dysfunction. This hypothesis has not yet been investigated in the context of bulbar ALS and the speech network.

Objectives: To conduct post-mortem neuropathological analysis of motor and extramotor speech network regions in cases with and without antemortem bulbar ALS.

Methods: Neuropathological examination of post-mortem brain tissue was conducted on 3 bulbar-onset cases (bALS), 3 spinal-onset cases with antemortem bulbar symptoms (ALSwB), and 3 spinal-onset cases without antemortem bulbar symptoms (ALSnoB). Cortical regions-of-interest included bulbar and limb regions of the primary motor cortex, and extramotor regions associated with the speech network including inferior frontal (Broca area), posterior superior temporal (Wernicke area), superior frontal (supplementary motor area, SMA), middle frontal (premotor area), and transverse temporal gyri (primary acoustic cortex, PAC). Brainstem regions included trigeminal, facial, and hypoglossal motor nuclei. Following blocking and slicing, regions were stained for neuronal loss, gliosis, and proteinopathy (i.e. TDP-43, tau). Tissue samples were semi-quantitatively rated by two observers, one of who was an experienced neuropathologist blinded to the diagnosis.

Results: Extramotor pathology in Broca's, Wernicke's, SMA, premotor area, and PAC were found only in cases with antemortem bulbar disease (i.e. bALS and ALSwB). Further, the severity and anatomic distribution of pathology was related to the degree of antemortem bulbar dysfunction with bALS presenting with the most severe and widespread pathology, followed by ALSwB and then by ALSnoB. Lastly, bALS cases presented with unique atypical pathological features (i.e. NFTs in superficial layers, and dot-like TDP-43 inclusions), not seen in any of the ALSwB or ALSnoB cases.

Discussion and conclusions: Findings suggest that regions of the speech network may be uniquely implicated in cases with bulbar ALS. Further, the degree of extramotor involvement may be related to the degree of bulbar symptoms. Together, the data supports the notion of the propagation of bulbar pathology through the structural connectome of the speech network.

Acknowledgements: We would like to thank the donors and families. Funding

was provided by NIH (R01 DC009890) and the Bernice Ramsay Discovery Grant. The authors declare no conflicts of interest.

References

1. Massman PJ, Sims J, Cooke N, *et al* J Neurol, Neurosurg and Psychiatry 1996;61:450-5.
2. Sterling LE, Jawaid A, Salamone AR, *et al* ALS 2010; 11:46-51.
3. Seeley WW, Crawford RK, Zhou J, *et al* Neuron 2009; 62:42-52.
4. Peeva MG, Guenther FH, Tourville JA, *et* al Neuroimage. 2010; 50:626-38.

BW-13 Mutations in *TARDBP* show axonal transport defects in induced pluripotent stem cell-derived motor neurons

Raheem Fazal

KULeuven - VIB - VRC, Leuven, Belgium

Email address for correspondence: raheem.fazal@kuleuven.vib.be

Keywords: TARDBP, hiPSCs, axonal transport

Background: TAR DNA binding protein 43 kDa (TDP-43) is a major component of pathological inclusions in sporadic and familial amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U). ALS patients suffer from progressive degeneration of motor neurons, while FTLD is characterised by the progressive degeneration of cortical neurons in the frontal and temporal lobe.

Moreover, mutations in the gene encoding TDP-43 have been directly linked to ALS. The aim of this study was to investigate whether mutant TDP-43 affects transport processes along the axons, which is important for the normal function of motor neurons.

We generated and characterized human induced pluripotent stem cells (hiPSCs) from ALS patients with different *TARDBP* mutations, as well as from healthy controls. The hiPSC lines were subsequently differentiated into motor neurons in order to study axonal transport. Therefore, we labelled mitochondria in motor neurons with MitoTracker-RED. Subsequently, mitochondrial movement along the processes of the motor neurons was registered by live cell imaging, and the number of stationary and moving mitochondria was determined. Compared to control lines, the average number of moving mitochondria was significantly lower in motor neurons derived from patients with a *TARDBP* mutations. Furthermore, pharmacological inhibition of histone deacetylase 6 (HDAC6) increases α-tubulin acetylation, and restores the axonal transport defects in patient-derived MNs.

Taken all together, our results clearly show that mutations in *TARDBP* cause impairments in axonal mitochondrial transport in hiPSC-derived motor neurons and inhibition of HDAC6 results in axonal transport restoration.

BW-14 Molecular mechanisms underlying TDP-43 regulation on the Stress Granule assembly factor G3BP1

Hadjara S Sidibé[1], Geneviève Di Tomasso[2], Anais Aulas[1], Jade-Emmanuelle Deshaies[1], Laurie Destroismaisons[1], Alex J Parker[1], Pascale Legault[2], Christine Vande Velde[1]

[1]Université de Montréal - CRCHUM, Montréal, Canada, [2]Université de Montréal, Montréal, Canada

Email address for correspondence: hsidibe6@gmail.com

Keywords: TDP43, RNA metabolism, Stress Granules

Background: Amyotrophic lateral sclerosis is a neurodegenerative disease characterized by the progressive loss of motor neurons. The interplay between genetics and environment, particularly stress by toxins exposure, is suspected

to play a major role in the development of the sporadic form of the disease, which constitutes 90% of all cases. The disease main molecular feature is the presence of large cytoplasmic inclusions, primarily composed of the mislocalized nuclear protein TAR-DNA binding protein 43, an essential regulator of the RNA metabolism. We have previously reported that TDP-43-mediated regulation of G3BP1 is critical for proper Stress Granule (SGs) dynamics. The formation of these small cytoplasmic structures is a mechanism known to protect cells from stress.

Objectives: The goal of this project is to characterize the physiological mechanism by which TDP-43 regulates SGs via G3BP1 and determine the effect of TDP-43 mislocalization. Our hypothesis is that TDP-43 mislocalization alters SGs regulation via the impairment in G3BP1 mRNA metabolism, which contributes to neuronal vulnerability and loss in ALS.

Methods: This project involves bioinformatics, animal models, cellular and *in vitro* techniques.

Results: In this project, we characterized the physiological mechanism underlying G3BP1 regulation by TDP-43 and show that G3BP1 levels are also impaired with TDP-43 is mislocalization, suggesting an impairment of the regulation in ALS.

Discussion and conclusions: Understanding the mechanisms impaired in ALS is essential in order to discover biomarkers and therapeutic targets for this fatal disease still difficult to diagnostise

Acknowledgements: Project funded by ALS Canada/Brain Canada and FRQS

BW-15 Utilizing network medicine approaches to explore the role of muscle in ALS

Stephen Morgan, Stephanie Duguez, William Duddy

Ulster University, Derry/Londonderry, United Kingdom

Email address for correspondence: morgan-s20@ulster.ac.uk

Keywords: muscle, networks, pathways

Background: Amyotrophic Lateral Sclerosis (ALS), is a progressive and fatal neuromuscular disorder and the most common form of motor neuron disease (MND). The pathology is complex and multifactorial with many dysregulated physiological processes being identified to contribute. Recent evidence suggests that muscle could play an important role in disease pathology, and muscle is implicated in the neuronal dying back hypothesis. With this in mind, we will incorporate network medicine approaches to explore the role of muscle in ALS. We hypothesise that a mechanistic pathway in muscle cells is shared by ALS-associated genes. Furthermore, that these functional effects of ALS pathology, in muscle cells, can be understood in terms of changes to the behaviour of molecular interaction networks. To test this hypothesis, we will construct molecular interaction networks relevant to muscle tissue, and attempt to discover one or more functional modules linked to ALS-dysregulated or associated genes or genes carrying common genetic variants observed in sporadic patients.

Muscle specific networks have been constructed using the MyoMiner muscle gene co-expression database (http://sys-myo.com/myominer/), while tissue-type-generic networks have been obtained from the STRING protein database for protein-protein interactions, and the GTEx Portal for gene co-expression. We are investigating the ability of each network to form disease modules or links between differentially expressed genes (DEGs) from ALS myotubes, known MND associated genes and muscle specific disease gene lists. To test network suitability, the Disease Module Detection Algorithm (DIAMOnD) will be used to help identify the network or combination

of networks having the best linkage between these disease genes for each condition. Disease modules associated to ALS may suggest novel genes and pathways as biomarker and therapeutic candidates in ALS pathology.

Acknowledgements: This work was financed by TARGET-ALS (ViTAL consortium, PI: S Duguez), ARsLA (TEAM consortium, PI: Duguez). This work was also supported by £11.5M grant awarded to Professor Tony Bjourson from European Union Regional Development Fund (ERDF) EU Sustainable Competitiveness Programme for N. Ireland; Northern Ireland Public Health Agency (HSC R&D) & Ulster University.

BW-16 Gene expression biomarkers: a longitudinal study in ALS and FTD patients

Gabriel G Garcia Salamero[1], Gabriela G Atencia Cibreiro[1], Adrián A Martinez Cortes[1], Clara C Muñoz Pancorbo[1], Naiara N Carrillo Lucas[1], Ana Cristina A Calvo Royo[2,3], Daniel D Borrego Hernandez[1], Alexandra A Juarez Rufian[1], Miguel Angel M Martin Casanueva[1,4], Alberto A Villarejo Galende[1,5], Alejandro A Herrero San Martin[1], Sara S Llamas Velasco[1,5], Marta M Gonzalez Sanchez[1], Jesús J Esteban Perez[1,4], Rosario R Osta Pinzolas[2,3], Alberto A Garcia Redondo[4,1]

[1]12 de Octubre Hospital Health Research Institute, Madrid, Spain, [2]University of Zaragoza, Zaragoza, Spain, [3]Aragonese Institute of Health Sciences (IACS), Zaragoza, Spain, [4]CIBERER, Madrid, Spain, [5]CIBERNED, Madrid, Spain

Email address for correspondence: mito@h12o.es

Keywords: biomarker, GSR, SOD1

Background: Previous studies performed on muscle biopsies from mice SOD1G93A suggested that this animal model presents an alteration in the expression of five genes (*Mef2c, Gsr, Col19a, Calm1 and Snx10*). On the other hand, it is known that oxidative metabolism is one of the causes of neurodegenerative diseases, among which is the ALS [1]. In this point, two of the previous genes (*Gsr* and *Sod1*) are involved as an important part of defense against that stress [2].

Therefore, with these previous results, the expression of those genes could behave like potential prognostic biomarkers of longevity [3] and/or diagnostic biomarkers too. Despite the search for biomarkers in ALS being carried out in a wide variety of patients' samples, growing tendency relies on the study of new and less invasive tissues [4, 5].

Objectives: Our aim is to study the level expression of *GSR* and *SOD1* in lymphocytes (and its corresponding rates) to obtain a relation with disease progression and their diagnostic capacity.

Methods: cDNA serial samples from lymphocytes of 45 patients with ALS (27 males and 18 females) and 58 patients of FTD (33 males and 25 females) were subjected to qPCR in order to study expression levels of *GSR and SOD1.* The levels found in every sample were related to the main clinical parameters like days since onset of symptoms, clinical variant and others parameters. Statistical analysis and ROC curves were made with GraphPad Prism software support.

Results: In both genes significant differences were found between ALS and control groups, not so between FTD and control groups. A split in GSR expression level of the ALS group was found, but the reason of that is still unclear.

R^2 of ROC curves of ALS's GSR expression and ALS's SOD1 expression were respectively: 0,5704 (ALS1), 0,9872 (ALS2) and 0,7492.

The correlation inverse of days since onset of symptoms in ALS and FTD of GSR and SOD1 weren't significant.

Discussion and conclusions: Expression levels of GSR and SOD1 and

their corresponding rates seem as good diagnostic biomarkers of ALS. Unfortunately, the progression study does not yield concordant data based on the prognostic capacity of genes as prognostic biomarkers.

Acknowledgements: This work was supported by grants PI14/00088 and PI17/00491from the Instituto de Salud Carlos III (ISCIII) and the support of the Spanish Foundation for the development of ALS research (FUNDELA).

References

1. Radi E, Formichi P, Battisti C, Federico A. J Alzheimers Dis. 2014; 42 Suppl 3:S125-52.
2. Aleksandra Nikolic-Kokic, Zorica Stevic et al. Clin Chem Lab Med 2006; 44: 589–593
3. Calvo AC, Manzano R, Atencia-Cibreiro G *et al* PLoS One 2012; 7:e32632.
4. Nachmany H, Wald S, Abekasis M *et al*. Disease Markers 2012; 32: 211-220.
5. Pradat PF, Bruneteau G, González de Aguilar JL, *et al*. Ann. Neurol. 2007; 62: 15-20.

BW-17 Exosomes a Window into ALS

Sandra Banack, Paul Cox, Rachael Dunlop

Brain Chemistry Labs, Jackson, WY, USA

Email address for correspondence: sandra@ethnomedicine.org

Keywords: exosome, biomarkers

Background: Exosomes are small multivesicular bodies of endosomal origin, 30-100 nm in size. They carry messages between cells including proteins, RNA, DNA, and lipids. Since exosomes can be extracted from blood plasma they represent a non-invasive way to examine what is changing in the brain over time.

Objectives: To compare RNA and proteins released from neurally-derived exosomes extracted from blood plasma of ALS patients and examine changes due to disease process and possible therapy.

Methods: Neuronal surface markers were used to isolate neural-derived exosomes from other exosomes present in blood plasma. Using L1CAM immunoprecipitation, we isolated sub-populations of exosomes to examine enclosed RNA and proteins.

Results: Variation in RNA and proteins present in exosomes may be useful markers for disease progression and potential therapy.

Discussion and conclusions: Neurally-derived exosomes represent a non-invasive view of changes with the brain useful for understanding ALS disease progression and the effectiveness of therapy.

Acknowledgements: The authors thank the John and Josephine Louis Foundation for funding.

BW-18 Biomarkers for disease progression and potential therapeutic targets in Amyotrophic Lateral Sclerosis

Ozlem Yildiz[1], Gary Warnes[1], Valentina Pucino[2], Vittoria Lombardi[1], Fabiola Puentes[1], Jesmond Dalli[2], Claudio Mauro[3], Klaus Schmierer[1], Andrea Malaspina[1]

[1]Blizard Institute, Queen Mary University London, London, United Kingdom, [2]William Harvey Research Institute, Queen Mary University London, London, United Kingdom, [3]Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom

Email address for correspondence: o.yildiz@qmul.ac.uk

Keywords: biomarker; resolvins; lactate receptors

Background: An important aspect of

the inflammatory response linked to neurodegeneration is that it can co-exist with an altered metabolic state. Lactate is increasingly recognised as one of the mediators of chronic inflammation. In the context of rheumatological conditions, it has been shown that extracellular lactate causes T cell entrapment in sites of inflammation, by inhibition of CD4+ and CD8+ T cells motility, inducing a switch of CD4+ T helper cells towards Th17 phenotypes which is linked to production of pro-inflammatory cytokines and to the maintenance of chronic inflammation (*1*). These effects are mediated by lactate interaction with its transporter SLC5A12 / SLC16A1 and provide the rationale to target this metabolic signalling pathway to modulate inflammatory responses.

Another important clue on the close interplay between neuroinflammation and metabolism is the report that lipid mediators termed resolvins modulate adaptive immune responses downplaying progression to chronic inflammation. Recently published in vivo and in vitro data showed that resolvins reduce cytokine production by activating CD8 (+) T cells, CD4(+) T helper 1 (TH1) and TH17 cells and preventing naïve CD4(+) T cell differentiation into TH1 and TH17 by down-regulating their signature transcription factors in a mechanism mediated by GPR32 and ALX/FPR2 receptors (*2*).

Objectives: The project aims are whether the lactate and/or resolvins metabolic signalling-pathways can be harnessed to modulate inflammatory immune responses in amyotrophic lateral sclerosis (ALS) and whether it has a role in their phenotypic variability (slow vs fast progressing).

Methods: PBMCs were collected as part of ongoing recruitment into a national biomarker study (ALS Biomarker study), where ALS patients underwent serial blood sampling along with samples from age-matched disease controls (progressive multiple sclerosis) and healthy controls.

We studied expression and regulation of lactate and resolvins receptors, along with immune-phenotyping including monocytes, T and B cell subpopulations and cytokines using flow cytometry.

Results: Work is ongoing and results will be presented at the symposium.

Discussion and conclusions: The effects of resolvins and the lactate-mediated inhibition of lymphocytes migratory properties may represent different facets of the regulation of the immune response with the development of neurodegenerative conditions like ALS. Awareness and comprehension about these molecular pathways will provide 1) useful biomarkers to monitor disease progression and for prognostication and 2) clues for new therapeutic interventions.

Acknowledgements: We would like to thank patients for taking part in the study. This investigation is supported by local LCRN funding and by MND Association for the purpose of biological samples collection and biomarkers development (Turner/Oct15/972-797). The authors declare no conflicts of interest.

References

1. Haas R, Smith J, Rocher-Ros V, et al PLoS Biol. 2015 Jul 16;13(7):e1002202.
2. Chiurchiù V, Leuti A, Dalli J, et al Sci Transl Med. 2016 Aug 24;8(353):353ra111.

BW-19 An AI Drug Discovery Case Study Establishing New Neuroprotective Compounds for Treating ALS

Matthew Stopford[1], Nora Markus[1], Monika Myszczynska[1], Richard Mead[1], Laura Ferraiuolo[1], Dave Sheppard[2,3], Peter Richardson[2], Mark Rackham[2]

[1]Sheffield Institute of Translational Neuroscience, Sheffield, United Kingdom, [2]BenevolentAI, London, United Kingdom, [3]DW Sheppard Consultancy,

Cambridge, United Kingdom

Email address for correspondence: mark.rackham@benevolent.ai

Keywords: AI, polypharmacology, novel targets

Background: Artificial Intelligence enables meaningful inferences to be made from huge bodies of data, and therefore has the potential to transform many aspects of drug discovery. Due to the extremely complex and heterogeneous nature of ALS, this disease is an ideal area for AI-augmented drug discovery to make a significant impact.

Objectives: BenevolentAI has created the world's largest biomedical knowledge graph by ingesting publically available literature and databases. This data was used to discover novel drug targets which synergistically protect motor neurons, and can be modulated with a single drug.

Methods: Compounds identified from mining the knowledge graph were tested in an assay which measured the survival of (murine) induced motor neurons in the presence of astrocytes induced from the fibroblasts of ALS patients (1). Compounds which demonstrated robust protection of motor neurons were tested in the G93A SOD1 mouse model (2).

Results: A manual query of the knowledge graph returned multiple targets which are implicated in the biology of ALS, astrocytes and motor neurons, and drugs which could modulate these targets. From the initial query, five compounds were tested in the motor neuron in vitro assay; of these five, one compound was inactive, three showed weak rescue effects and one compound, Gefitinib, showed robust and dose dependent rescue of motor neurons. Gefitinib was then tested in the G93A SOD1 mouse model and showed a significant delay in symptom onset.

Although this result provided validation of the strategy, Gefitinib is not a suitable drug candidate for ALS due to extremely low CNS exposure. We captured the logic of the manual validation in an algorithm which was able to automatically query on a much higher throughput than a scientist, and uncovered multiple additional hits. A subset of these were tested in the in vitro motor neuron rescue experiment, and one compound showed 10-fold higher activity than Gefitinib, as well as activity in more diverse patient samples.

Discussion and conclusions: The strategy described above has proven highly effective in discovering compound which are novel in the context of ALS, provide significant neuroprotection to motor neurons in vitro, and delay symptom onset in the G93A SOD1 model. It was initially thought to use this strategy to identify drug repurposing opportunities, however relatively few marketed drugs have the properties required for sufficient CNS exposure. Lead optimisation is underway to further improve the pharmacokinetics of our most active hits, with the aim of entering clinical trials in 2020.

Acknowledgements: Funding for this study was provided by BenevolentAI. Multiple authors are employees of BenevolentAI.

References

1. Meyer, K., et al. Proceedings of the National Academy of Sciences, 2014, 111:829–832.
2. Zhang, B., et al. Journal of Cell Biology, 1997, 139:1307–1315.

BW-20 All-Optical Electrophysiology for High-Throughput Drug Screens and Functional Characterization of Human iPSC-Derived Motor Neurons from ALS patients

Sandy Hinckley[1], Hongkang Zhang[2], Luis Williams[2], Graham Dempsey[2], Daniel Elbaum[1], Adam Cohen[3,4], Kevin Eggan[3], Kasper C Roet[1,5]

[1]QurAlis Corporation, Cambridge, MA, USA, [2]Q-State Biosciences, Cambridge, MA, USA, [3]Harvard University,

Cambridge, MA, USA, [4]Howard Hughes Medical Institute, Chevy Chase, MD, USA, [5]Boston Children's Hospital, Boston, MA, USA

Email address for correspondence: kasper.roet@quralis.com

Keywords: stem cell, excitability, high throughput

Background: Threshold tracking and Transcranial Magnetic Stimulation (TMS) biomarker studies in ALS patients have revealed that the motor system of a significant number of patients exhibits abnormal excitability which is associated with poor disease prognosis [1,2]. Traditional patch clamp and multi-electrode array studies of ALS motor neurons derived from human induced pluripotent stem cells (iPSC) have revealed similar differences in intrinsic excitation properties [3,4]. The Woolf and Eggan labs previously identified decreased Kv7.2/7.3 activity as a main driver of excitability induced excitotoxicity in ALS patient derived motor neurons [3,5].

Objectives: We aimed at developing the transformative Optopatch technology into a high-throughput functional characterization pipeline that can: i) Rapidly analyze the excitability profile of ALS motor neurons with low variability, ii) provide ongoing medicinal chemistry support and iii) qualify the translational potential of molecules for treatment of abnormal excitability and excitotoxicity in ALS patients.

Methods: QurAlis and Q-State use all optical electrophysiology "Optopatch" to both stimulate neurons and record their electrical behavior with light. In this system, each neuron emits a brief flash every time it sends an electrical signal. The custom developed microscopes record from more than 100 neurons in parallel, a recording platform that is highly scalable compared to manual patch clamp [6]. The Optopatch technology is used together with iPSC derived motor neurons.

Results: iPSC derived motor neurons with an ALS-causing mutation (SOD1 A4V) were compared to isogenic corrected control motor neurons and showed an increase in spike rates with no or weak optogenetic stimulation. Strong stimulation increased the probability of entering a depolarization block [7].
We have successfully developed the Optopatch platform to run in a 96-well plate format and implemented multiparametric analysis to identify both "on target" and "off target" Kv7.2/7.3 compound properties in high-throughput in ALS motor neurons.

Discussion and conclusions: The Optopatch technology is a powerful new method that can be used for ALS drug discovery and development. The technology enables: i) excitability profiling of patient specific motor neurons, ii) drug target and drug identification and iii) medicinal chemistry support in a translational human stem cell system.

Acknowledgements: We would like to thank Evangelos Kiskinis for developing the first ALS motor neuron Optopatch assay. Both QurAlis Corporation and Q-State Biosciences are for-profit organizations

References

1. Kanai K, Shibuya K, Sato Y, et al; J Neurol Neurosurgy Psychiatry. 2012; 83:734-8
2. Shibuya K, Park SB, Geevasinga N, et al; Neurology. 2016. 87:513-20.
3. Wainger BJ, Kiskinis E, Mellin C, et al; Cell Rep. 2014. 7:1-11.
4. Devlin AC, Burr K, Borooah S, et al; Nat Commun. 2015. 12;6:5999.
5. Kiskinis E, Sandoe J, Williams LA, et al; Cell Stem Cell. 2014. 14:781-95.
6. Werley CA, Brookings T, Upadhyay H, et al; Curr Protoc Pharmacol. 2017. 11;78:11.20.1-11.20.24.
7. Kiskinis E, Kralj JM, Zou P, et al; Stem Cell Reports. 2018. 10:1991-2004.

BW-21 Patient Blood Derived Cell Lines Provide Unlimited Supply of DNA

Debbie Blick, Clare Wilson, Ayuen Lual, Sharon Bahia, Edward Burnett, Bryan Bolton, Julie E Russell

The European Collection of Authenticated Cell Cultures, Salisbury, United Kingdom

Email address for correspondence: sharon.bahia@phe.gov.uk

Keywords: genetics, risk factor, C9orf72

Background: Advances in genomic profiling techniques have enabled researchers to identify risk factor genes that can contribute towards an individual's susceptibility to particular diseases. The validity and reproducibility of research relies on access to ethically sourced, authenticated and quality controlled samples. To ensure results are statistically significant, gene profiling studies often need to utilise large sample sizes. In 2003, the MND Association, with funding from the Wellcome Trust, established the UK MND DNA Bank as a worldwide, accessible resource for the collation of patient and control DNA samples for MND research (1). In 2016, the UK MND DNA Bank was renamed the UK MND Collections comprising the DNA bank based at the Centre for Integrated Genomic Medical Research (CIGMR), the Cell bank based at the European Collection of Authenticated Cell Cultures (ECACC) and the Epidemiological data, curated by the MND Association.

Objectives: The objectives were to collect cohorts of patients, their parents/siblings and control samples, and associated clinical data, to represent cases of sporadic and familial MND. The resulting samples and data were to be made accessible to the international research community for research into the genetic risk factors for MND.

Methods: To form the collection, over 3,000 patient and control blood samples were collected between 2003 and 2012. These samples were sent to CIGMR for extraction of DNA and to ECACC for storage and Epstein-Barr virus (EBV) transformation into lymphoblastoid cell lines (LCL). DNA extracted from blood is a finite resource, once it has been utilised additional patient blood samples are required to produce more. EBV transformation of peripheral blood lymphocytes had previously been demonstrated by ECACC to be an efficient and cost effective method for immortalising valuable patient samples, allowing for a potentially unlimited supply of patient DNA (2). The LCL underwent authentication testing using short tandem repeat profiling to ensure that they matched the original patient blood sample and the respective DNA.

Results: LCL were generated from most blood samples in the collection, approximately 2,700 samples. In 2015, the MND Association selected a sub-set of 193 samples (familial and control) to undergo extra quality control, which are now available to researchers. Gene mutations present in the collection of cell lines include C9orf72, SOD1, FUS and TARDBP.

Discussion and conclusions: To support MND research the cell lines are available from ECACC free of charge (plus admin and shipping costs; commercial and for-profit organisations incur an additional fee). On completion of an application form, and approval from the MND Association for access, UK based researchers receive the lines within 3 working days.

Acknowledgements: We would like to thank the MND Association for curating the samples and the Wellcome Trust for additional funding, for the formation of the cell line collection.

References

1. Smith L, Cupid B C, Dickie B G M *et al* BCM Genetics 2015; 16:84
2. Blick D, Cooper J, Baker N *et al*, Nature Methods Application Notes 2011; https://www.nature.com/app_notes/nmeth/2011/111312/pdf/an8194.pdf

BW-22 Alterations of lipid metabolism define potential circulating biomarkers of amyotrophic lateral sclerosis

Gorka Fernández Eulate[1,2], José Ignacio Ruiz-Sanz[3], Javier Riancho[4,5,6], Mónica Zufiria[2,6], Roberto Fernandez-Torrón[7,2,6], Juan José Poza-Aldea[1,6], Juan Bautista Espinal[1,6], Gonzalo González-Chinchón[8], Miren Zulaica[2,6], M Begoña Ruiz-Larrea[3], Francisco Gil-Bea[2,6], Adolfo López de Munain[1,2,6,9]

[1]Donostia Universitary Hospital, San Sebastian, Spain, [2]Biodonostia Research Institute, San Sebastian, Spain, [3]UPV/EHU, Leioa, Spain, [4]Sierrallana Hospital, Torrelavega, Spain, [5]University of Cantabria, Santander, Spain, [6]CIBERNED, Madrid, Spain, [7]Donostia Universitary Hospital, San Sebastián, Spain, [8]Araba Universitary Hospital, Vitoria, Spain, [9]UPV/EHU, San Sebastian, Spain

Email address for correspondence: gorkaeulate@gmail.com

Keywords: metabolomics, lipidomics, biomarker

Background: A priority issue in amyotrophic lateral sclerosis is to find biomarkers to accelerate drug discovery. Accumulating evidence suggests an imbalance of energy homeostasis in people with ALS, leading to decreased fat depots. By analizing blood lipid metabolites we could increase our understanding of the metabolic abnormalities in ALS, and provide novel biomarkers of diagnosis and prognosis.

Objectives: To perform a comprehensive scan of blood lipid metabolites in ALS patients and correlate these alterations with prognosis and survival.

Methods: We have performed a comprehensive analysis of the metabolomic profile in serum from a multicenter open label, non-randomized cohort of 71 fasting subjects (39 ALS patients and 32 healthy controls) using different chromatography techniques. Univariate (T-student and Wilcoxon test) and multivariate (principal components) analysis was performed to compare the metabolic profile in cases vs controls. To quantify differences in survival between patients, we used univariate and multivariate Cox proportional hazard regression models. Subjects were paired by dietary intake, and so most controls were the patient's partner. Significant differences in gender were observed between groups so we adjusted for gender in all the multivariate analyses statistical analysis. Follow-up was 2.5 years from onset of symptoms.

Results: In a first untargeted metabolomic approach, a total of 30 out of 446 metabolites detected were altered in ALS patients. Further study of metabolites of interest showed higher levels of very long chain fatty acids (VLCFA) ω-3 and ω-9 and lower levels of ω-6. There were also decreased levels of C:14 and C:16 long chain fatty acids (LCFA). A combination of high levels of palmitoleic acid (C16:1, ω-7) and myristic acid (C14:0) was related to a decreased odds of mortality (HR 0.148 95% CI= 0.003-0.292, $p<0.01$), of future percutaneous endoscopic gastrostomy feeding (HR 0.193 95% CI= 0.011-0.374, $p<0.01$) and noninvasive mechanical ventilation (HR 0.401 95% CI= 0.079-0.722, $p<0.05$) at 2.5 years.

Discussion and conclusions: No specific class of lipid metabolite is altered in the serum of people with ALS, however there is a trend towards higher levels ofω-9 and ω-3, and lower levels of ω-6 VLCFAs. In addition, LCFAs containing 14 and 16 carbons are decreased in patients with ALS and this in combination is an independent predictor of survival and disease progression of ALS.

Acknowledgements: This work was supported by grants from CIBERNED (2016/04), ISCII (PI17/01841 and PI14/00436), and the Basque Government (2015/11038, RIS3 2017222021 and BIO16/ER/022). M. Z. and G. G. received a studentship from the Department of Education, University and Research of the Basque Government, (PRE_2017_2_0291) and (POS_2015_1_0028), respectively.

References

1. Zufiria M, Gil-Bea FJ, Fernández-Torrón R et al. Prog Neurobiol. 2016 Jul;142:104-29

2. Blasco H, Veyrat-Duberex C, Bocca C et al. *Scientific Reports. 2017 Dec;7:*17652

3. Dodge JC, Treleaven CM, Pacheco J et al. Glycosphingolipids are modulators of disease pathogenesis in amyotrophic lateral sclerosis. 2015 112(26):8100-05

BW-23 Investigating metabolic dysfunction in a yeast model of Sod1-associated ALS

Kevin M Doyle

University of Kent, Canterbury, United Kingdom

Email address for correspondence: kmd25@kent.ac.uk

Keywords: metabolic dysfunction, Saccharomyces cerevisiae, vacuole

Background: Amyotrophic lateral sclerosis is a motor neuron disease characterised by progressive degeneration of motor neurons in the brain and spinal cord. Mutations in the gene *SOD1* that encodes the Cu/Zn binding enzyme superoxide dismutase are associated with 20% of familial ALS cases. Aggregation of mutated, unstable Sod1 gives rises to fALS through a toxic gain-of function. Research suggests a role for soluble mutated or misfolded Sod1 proteins in addition to larger insoluble aggregates that are often reported.

Previous work from a *Saccharomyces cerevisiae* model of ALS established in our lab showed toxic effects of ALS-linked Sod1 mutations in yeast that were linked with metabolic dysfunction. This appeared to correlate with an inability to regulate amino acid levels coupled with a vacuole acidification defect. The yeast Vacuole is functionally comparable to the mammalian lysosome and lysosomal dysfunction has been associated with neurodegeneration due to the high metabolic demand of neurons.

In this work, we demonstrate a novel interaction between Sod1 and four subunits of the cytosolic V1 complex of the yeast V-ATPase pump using a protein complementation DHFR assay. This interaction can be modulated under environmental conditions that may be related to cellular stress, such as changes in pH or glucose availability. In addition expression of the Sod1A4V isoform appears to compete with Sod1 for vATPase interaction sites.

This work suggest a mechanism by which unstable forms of Sod1, or indeed the overexpression of SOD1, may lead to a failure to regulate vacuole function generating a cascade of metabolic defects that may underpin the recognised toxic gain of function.

Clinical work in progress

CW-01 Investigating bioenergetic dysfunction in motor neurone disease using 31 phosphorus magnetic resonance spectroscopy: a feasibility study

Matilde Sassani[1], Julia Bigley[2], James J Alix[1], Nigel Hoggard[2], Pamela J Shaw[1], Thomas M Jenkins[1], Iain D Wilkinson[2]

[1]Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, United Kingdom, [2]Academic Unit of Radiology, University of Sheffield, Sheffield, United Kingdom

Email address for correspondence: msassani1@sheffield.ac.uk

Keywords: energy metabolism, magnetic resonance spectroscopy, imaging

Background: An emerging role for the importance of bioenergetic dysfunction in the pathophysiology of MND is recognised and characterised by deficits in energy metabolites such as adenosine triphosphate (ATP) and phosphocreatine (PCr). Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) allows detection of ATP and PCr and represents a non-invasive tool to probe cellular bioenergetics *in vivo*. There are technical challenges and, although a few previous muscle studies exist, no ^{31}P-MRS brain study has yet been conducted in MND.

Objectives: The objective of this pilot study is to demonstrate feasibility of a ^{31}P-MRS protocol to study bioenergetics in both brain and muscle in patients with MND.

Methods: ^{31}P-MRS spectra were acquired from eight healthy volunteers, each scanned three times, from a coronal acquisition centred on motor tracts. Quality of spectra was evaluated using signal to noise ratios. Repeatability and reproducibility were assessed using coefficients of repeatability (CR), coefficients of variability (CV), and Bland-Altman upper and lower limits of agreement (ULOA and LLOA); measurement bias was evaluated; and feasibility in terms of participants' tolerance was assessed. In muscle, a dynamic protocol to measure changes in PCr during contraction of lower leg muscles was developed and tested in four healthy volunteers. Pilot brain and muscle ^{31}P-MRS spectra have been acquired employing the developed protocol from four MND patients, to date.

Results: Signal to noise ratios for brain PCr and γATP were 134.5 and 31.6, respectively. In healthy volunteers, mean deep white matter PCr/γATP was 1.11 (±0.15) and was characterised by CR=0.40, CV=13.5%, ULOA=0.35, and LLOA= -0.30. No systematic bias was detected. Mean muscle PCr/total phosphorus signal was 0.51 (±0.02) at rest and 0.41 (±0.02) at the end of muscle contraction in healthy volunteers. In patients, deep white matter PCr/ γATP was 1.30 (±0.07) and mean muscle PCr/total phosphorus signal results were 0.45 (±0.16) at rest and 0.18 (±0.11) following exercise. Spectra acquisition was well tolerated by healthy participants and MND patients in all cases.

Discussion and conclusions: We have demonstrated feasibility of applying ^{31}P-MRS in healthy participants and people with MND in both brain and muscle. The technique yields good quality spectra (as shown by the relatively high signal to noise ratio), is repeatable and reproducible (as exemplified by low CR, CV, and relatively narrow limits of agreement), and was well tolerated by participants even in the presence of significant disability. The technique has potential to identify patients with abnormal bioenergetics, decipher mechanisms underpinning energy dysmetabolism, and merits further investigation as a biomarker for future clinical trials.

Acknowledgements: This work was supported by the NIHR Sheffield Biomedical Research Centre for Translational Neuroscience, by the British Medical Association Vera Down Grant, and by charitable funding from Neurocare/Ryder Briggs Trust.

CW-02 Exploring SICI using TMS-EEG: a potential diagnostic tool for MND

Vishal Rawji, Izabella Kaczmarczyk, Lorenzo Rocchi, John Rothwell, Nikhil Sharma

University College London, London, United Kingdom

Email address for correspondence: vishal.rawji.11@ucl.ac.uk

Keywords: TMS, biomarker, diagnosis

Background: A pathological hallmark of MND is the loss of cortical motor neurones (CMN), which is not present in mimics such as cervical spondylosis and multifocal motor neuropathy. Difficulty in establishing CMN loss clinically leads to diagnostic uncertainty and may contribute to late entry in clinical trials. One promising approach uses transcranial magnetic stimulation (TMS) to measure short interval intracortical inhibition (SICI). SICI is a measure of corticospinal inhibitory function and has been shown to be decreased in ALS (Menon *et al.*, 2015). The major limitation of TMS is the reliance on a motor evoked potential output in a peripheral muscle (often FDI) – this muscle is often wasted in ALS, limiting the clinical use of SICI. The ability to isolate and probe CMN function, independent of muscle wasting, would be a powerful diagnostic tool. Concurrent TMS-EEG is a novel technique that can exclusively isolate and probe cortical function. The EEG potential measured after TMS (TEP) is a measure of cortical dynamics, devoid of confounding from the peripheral motor system. This may, therefore, have diagnostic potential in MND.

Objectives: To develop an experimental pipeline to assay cortical excitability and inhibitory function in healthy humans, with the aim of employing this in a large MND and mimic patient cohort.

Methods: The data presented will be performed in healthy, human subjects. In session one, single-pulse TMS and SICI are applied to the dominant motor cortex (M1) whilst subjects undergo concurrent EEG (TMS-EEG). We measure TEPs and motor evoked potentials (MEPs) from the FDI and ABP hand muscles. As indices of cortical excitability, specific peak amplitude analysis, global and local mean field power are calculated between single pulse and SICI conditions. To test functional connectivity, we use a time-frequency analysis approach (coherence and synchronisation). This is repeated for the non-dominant hemisphere to compare the effect of hand dominance on cortical dynamics (this will be important when comparing affected vs non-affected limbs in MND). We also perform a repeat study the day after to assess whether the cortical signatures of excitation and inhibition are reproducible. SICI is known to resist change during use-dependent plasticity protocols.

Summary: To this end, we aim to test whether SICI TEPs are also unmodulated during a task of use dependent plasticity, to ascertain whether the TEP measure of SICI is valid. Finally, we propose a protocol to longitudinally track cortical excitability and connectivity changes in MND, with a view to aiding in diagnosis.

Acknowledgements: Reta Lila Weston Trust

References:

Menon, P. *et al* Lancet Neurology 2015; 14(5):478-484

CW-03 Investigating selective vulnerability to denervation in MND using whole-body muscle MR measures

Taniya Esmail[1], Jacob Fingret[1], James J Alix[1,2], Nigel Hoggard[3], Julia Bigley[3], Christopher J McDermott[1,4], Pamela J Shaw[1,4], Iain D Wilkinson[3], Thomas M Jenkins[1,4]

[1]Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, United Kingdom, [2]Neurophysiology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [3]Academic Unit of Radiology, University of Sheffield, Sheffield, United Kingdom, [4] Department of Neurology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

Email address for correspondence: t.m.jenkins@sheffield.ac.uk

Keywords: muscle, MRI, MUNIX

Background: Previously, we showed that MR-derived semi-quantitative relative T2 signal estimates in muscle were higher in MND patients than healthy controls in the tongue, biceps, thoracic paraspinals and tibialis anterior. Associations with clinical weakness and neurophysiological loss of motor units suggested that higher relative T2 signal reflects greater denervation [1].

Objectives: In the present study, we extend the analysis to a wider selection of muscles with the aim of deriving an MND muscle vulnerability index to identify targets on which to focus future fully quantitative T2 relaxometry studies. The overall objective is to develop a biomarker to facilitate future clinical trials in MND.

Methods: A prospective longitudinal observational cohort study. Twenty-nine patients with MND and 22 age- and sex-matched healthy controls were assessed with clinical measures, electrophysiological motor unit index (MUNIX), and whole-body muscle MR at baseline, 4 and 12 months (3 Tesla, T2-weighted fast spin-echo, TR-1107ms, effective TE-80ms, interpolated voxel size-0.78x0.78x5mm^3). Relative T2 signal estimates were derived from regions-of-interest including the following muscles: tongue, sternocleidomastoids, splenius capitis, trapezius, deltoids, biceps, forearm compartment including brachioradialis, thenar and hypothenar eminences, first dorsal interossei, thoracic paraspinals, psoas, gluteus maximus, quadriceps, hamstrings, anterior lower leg compartment encompassing tibialis anterior, and posterior lower leg compartment including gastrocnemius and soleus. For each region-of-interest, an MND vulnerability index was calculated, defined as the percentage increase in relative T2 signal in MND patients relative to healthy controls at baseline, and muscles ranked accordingly, assigning higher vulnerability indices to muscles with greater relative T2 differences. Statistical significance of between-group differences, clinical and electrophysiological associations and longitudinal change were assessed using multivariable linear regression models, adjusted for age, gender and multiple comparisons. Associations between baseline vulnerability index and subsequent clinical, electrophysiological and radiological progression were investigated.

Results: Analysis is ongoing and results will be presented in full at the conference.

Acknowledgements: This work was supported by charitable funding from a British Medical Association Vera Down Grant Award, Neurocare and the Ryder-Briggs Trust. This work was supported by the NIHR Sheffield Biomedical Research Centre.

References

1. Jenkins TM, Alix JJP, David C, et al. J Neurol Neurosurg Psychiatry 2018; 89: 248-55.

CW-04 Are there acoustic markers of LMN versus UMN involvement in motor neuron diseases?

Nathalie Leveque[1,2], François Salachas[1], Timothée Lenglet[1], Maria Del Mar Amador[1], Rabab Debs[1], Nadine Le Forestier[1], Pierre-François Pradat[1], Cécile Fougeron[2], Gaëlle Bruneteau[1]

[1]APHP, Salpêtrière Hospital, Neurology Department, Paris ALS Center, Paris,

France, [2]Laboratoire de Phonétique et Phonologie, UMR 7018, CNRS/Sorbonne-Nouvelle, Paris, France

Email address for correspondence: naleveque@yahoo.fr

Keywords: acoustic markers, dysarthria

Background: The dysarthria classification system developed by the Mayo Clinic [1,2] is based on site of lesion and common speech perceptual characteristics. According to the Mayo system, the dysarthria in amyotrophic lateral sclerosis (ALS) is commonly described as a mixed spastic-flaccid type with the spastic component reflecting upper motor neuron (UMN) involvement and the flaccid component reflecting lower motor neuron (LMN) involvement. However, LMN signs and UMN signs vary within and across individuals contributing to phenotypic heterogeneity. In this study we aim to identify acoustic markers reflecting LMN and UMN involvement based on EMG and clinical signs. For this purpose, the dysarthria profiles of ALS patients will be compared to the dysarthria profiles of patients with exclusive UMN involvement (primary lateral sclerosis, PLS) and exclusive LMN involvement (Kennedy's disease, KD). Identification of such markers could improve diagnostic procedures for assessing bulbar dysfunction in early-stage ALS and could provide directions for speech therapy.

Objectives: The primary objective of this study is to identify dysarthria profiles in patients with ALS, PLS and KD. Our secondary objectives are to correlate the dysarthria profiles with clinical and electrophysiological parameters.

Methods: This study will include 40 patients with ALS, 20 patients with PLS and 20 KD patients. Data from normal control patients will be used to establish the standards of a multidimensional and quantified assessment of voice and speech. We will record the patients' speech with the MonPaGe computerized tool [3].

Bulbar function will be evaluated using the Norris score and the ALS functional rating scale-R (ALS FRS-R). Routine clinical examination of the bulbar site will be used to assess UMN and LMN involvement. The severity of the dysarthria will be evaluated with the Perceptual Score of the Batterie d'Evaluation Clinique de la Dysarthrie (BECD) [4].

Results: With this study, we expect to identify a set of acoustic markers that will discriminate central versus peripheral involvement in bulbar ALS. These acoustic markers will help guiding speech therapy and will also be useful to differentiate ALS from other motor neuron disorders at early stage.

References

1. Darley FL, Aronson AE, Brown JR. J Speech Hear Res 1969; 12:462-496.
2. Darley FL, Aronson AE, Brown JR. Motor speech disorders.1975 Philadelphia: WB Saunders.
3. Fougeron C, Delvaux V, Pernon M et al. Chapitre 14. MonPaGe : un protocole informatisé d'évaluation de la parole pathologique en langue française. 2016.In Actes du colloque UNADREO « Orthophonie et technologies innovantes » (Joyeux N. & Topouzkhanian S., eds)
4. Auzou P, Rolland-Monnoury V. Batterie d'Evaluation Clinique de la Dysarthrie (BECD). 2006 Isbergues, France : Ortho Edition

CW-05 Case of Motor Neuron Disease in patient with Human Immunodeficiency Virus: association or coincidence?

Aram Aslanyan, David McKee

Salford Royal Foundation Trust, Manchester, United Kingdom

Email address for correspondence: aram.aslanyan@doctors.org.uk

Keywords: HIV, ART

Background: Incidence of amyotrophic lateral sclerosis (ALS) is described to be

between 0.4 to 2 per 100,000 (1,2). Occurrence of central nervous system complications of Human Immunodeficiency Virus (HIV) infection is rare but it is described to be 27-fold more than expected (2).

Literature showed mixed opinion regarding Motor Neuron Disease (MND) with background of HIV. Some articles described cases of MND in HIV infected patients, where the antiretroviral therapy (ART) improved the HIV infection but unfortunately did not improve the MND (3,4).

However it has been also described that ART has had some positive response on patients with MND with background of HIV (1). Different response to ART raises a question of whether MND occurring in patients with background of HIV is secondary to HIV or is a coincidence.

We describe a case of 44 year old male who presented with 2-month history of increased weakness of left arm and leg. He had a background of well-controlled HIV (undetectable viral load, good CD4 count), previously treated syphilis. He also had ongoing neck pain for 15 years due to paragliding accident. Further examination and nerve conduction studies resulted in diagnosis of MND. Despite good multidisciplinary team approach the patient's symptoms sadly deteriorated significantly and the patient passed away in just over a year after the diagnosis.

Discussion and conclusions: The patient developed MND and rapidly deteriorated despite the fact that HIV was well controlled. The question still remains on whether MND in patients with HIV is a coincidence or is secondary to HIV.

Humoral endogenous retrovirus K (HERV-K) seems to play a role in development of some neurological diseases including ALS. Possibly more research is needed to find out whether the increased level of HERV-K could potentially serve as an early biomarker in ALS, predict the prognosis and maybe differentiate subtypes of ALS, which could explain varied ART response (5).

References

1. Alfahad T, Nath, A. 2013. Antiviral Res, 99:180-7.
2. Jubelt B, Berger JR. 2001. Neurology, 57:945-946.
3. Lorenzoni PJ, Ducci RD, Dalledone GO *et al*. 2018. Clinical Neurology and Neurosurgery, 171:139-142.
4. Orsini M, de Freitas MR, Silva JG *et al*. 2012. Current HIV Research, 10:694-9.
5. Arru G, Mameli G, Deiana GA *et al*. 2018. European Journal of Neurology, 25:1076-84.

CW-06 People living with ALS and their caregivers' input into drug development in Europe

Miriam Galvin[1], Orla Hardiman[2,1], Christopher McDemott (on behalf of Impact European Survey Advisory Group)[3], Amy Laverdiere[4], Bonnie Charpentier[4], Jennifer Petrillo[5], Kristina Bowyer[6], Lucie Bruijn[7]

[1]Academic Unit of Neurology, Trinity College Dublin, Dublin, Dublin, Ireland, [2]Beaumont Hospital Dublin, Dublin, Ireland, [3]Sheffield Institute for Translational Neuroscience, Sheffield, Sheffield, United Kingdom, [4]Cytokinetics, San Francisco, CA, USA, [5]Biogen, Cambridge, MA, USA, [6]Ionis, Carlsbad, CA, USA, [7]ALS Association, Washington, District of Columbia, USA

Email address for correspondence: galvinmi@tcd.ie

Keywords: patient-focused drug development

Background: There is a growing call for rigorous patient input into key areas of drug development, regulatory consideration, clinically meaningful outcomes, and benefit/risk calculations. There is also an emerging focus on patient engagement in determinations of value for health system utilization and payment. These developments offer a critical opportunity to use established

methods to ensure that patient input is appropriately integrated into drug development. Through a survey of ALS patients and caregivers in Europe, this initiative aims to gather perspectives of the burden of disease of amyotrophic lateral sclerosis (ALS) with emphasis on the loss of function over the course of the disease. Although some medical groups have published information on the burden of ALS, these studies are small or geographically limited, which limits their interpretability and generalizability. The European Medicines Agency (EMA) is considering methods to better incorporate patient and caregiver input into regulatory review processes. Given the potential for EMA review of several new ALS therapies over the coming years, it is important for the community to develop this type of information.

Objectives: To conduct an on-line survey of European ALS patients and in-home caregivers to capture the burden of ALS. The survey will generate information on patient burden across approximately 10 countries. Anecdotal information and observations indicate that patients and their primary caregivers have different perceptions and concerns regarding the burden of disease. The survey will allow for comparisons of perspectives, and to capture how these perspectives change during ALS progression for patient demographics and subpopulations. Finally this survey allows a comparison with results from a 2017 US survey.

Methods: A steering committee was established, consisting of industry partners, clinical and methodological experts, with input from patients and caregivers. Recruitment of patients and caregivers will be carried out with the partnership of European Network for the Cure of ALS (ENCALS) and advocacy groups in each country. A representative sample of patients and caregivers across disease severity, demographics and regional areas will be targeted.

Results: Descriptive statistical analysis of European patient and caregiver data, and free text analysis of open ended responses. The survey results will also be analyzed in conjunction with the results of a similar survey carried out in the United States.

Discussion and conclusions: The ALS patient and caregiver survey in Europe will provide information on ALS disease burden from both perspectives and to provide guidance into drug development processes.

Acknowledgements: The IMPACT European Survey Advisory Group: Christopher McDermott, Steve Bell, Judith Newton, Leonard Van Den Berg, Garrit-Jan Blonk, Jesus Mora Pardina, Phillip Van Damme, Evy Reviers, Danny Reviers (patient), Mia Mahy(caregiver) Riviers, Dorothea Lule, Francois Salachas, Caroline Ingre, Lucie Bruijn. Cytokinetics, South San Francisco, USA; Biogen, Cambridge, MA, USA; Ionis, Carlsbad, CA, USA. The authors report no conflicts of interest.

CW-07 Analysing Inclusion Criteria in Surgical Trials in ALS/MND to Identify Differences in Long Term Results

Raymond Onders, MaryJo Elmo, Bashar Katirji, Robert Schilz

University Hospitals Cleveland Medical Center, Shaker, OH, USA

Email address for correspondence: raymond.onders@uhhospitals.org

Keywords: diaphragm pacing, inclusion criteria

Background: ALS/MND patients present to research centres along a broad disease course. Effectiveness of interventions are significantly different based on the stage of the disease. This is critical when only one muscle system is addressed by the therapy. Diaphragm Pacing (DP) was designed for a select group of ALS/MND patients who had intact lower motor units with loss of control of UMN where stimulation can improve ventilation. Since the initial FDA trial in the US, two additional trials,

in Europe, have reported negative results.

Objectives: To analyze four separate diaphragm studies based on inclusion criteria: US FDA IDE, US Post-Approval, UK DiPALS and French RespiStim study.

Methods: All reports and databases were reviewed. The inclusion criteria that specifically involved the single muscle being studied – the diaphragm- was evaluated. Inclusion criteria to identify chronic hypoventilation which helps in staging the function of the diaphragm was evaluated 6 ways in these studies: FVC, SVC, MIP, SNIP, pCO2 and Nocturnal O2. Minimum Inclusion criteria included 3 points: FVC, SNIP and NIV use. Key inclusion of identifying phrenic function was studied 7 ways: Bilateral Function, PNCS, Fluoroscopy, Ultrasound, Magnetic stimulation, physical exam alone, and surgical evaluation. In total for this report there were 16 separate inclusion criteria.

Results: The US FDA IDE study led to the US indications for use and thus the US FDA Post- Approval study overlapped 100% with the FDA approved inclusion criteria with similar survival results. The FDA study that lead to approval in the United States in comparison to the UK DiPALS study only had 2 out 16 inclusion criteria focusing on the diaphragm that were the same. (12.5%) The US compared to the French RespiStim had 5 out of the 16 inclusion criteria that were the same (31%). More importantly 7 of the RespiStim inclusion criteria were directly opposite to the US trial such as elevated vs low FVC.

Discussion and conclusions: All of these reports helped identify in separate ways the correct patients that diaphragm pacing should be offered. Patients should be later in their disease to not put at risk phrenic LMNs that may be destined to deteriorate. Patients need intact motor units to stimulate with an understanding that patient may go to surgery and not be implanted. If patients are unable to contract their intact diaphragm motor units but DP can, it will improve ventilation. With the non-homogeneity of ALS/MND, no therapy is universal. However in a specific subgroup DP can improve ventilation. Unfortunately negative studies in a different patient population can decrease patient's use of therapy for the correct indication.

References

1. FDA: HDEH100006. http://www.accessdata.fda.gov/cdrh_docs/pdf10/H100006b.pdf.
2. Onders et al Am Surgery 2014;207:393-397
3. DiPALS Writing Committee. Lancet Neurol 2015;14:883-92
4. Gonzalez-Bermejo et al Lancet Neurol 2016;15:1217-27.

CW-08 Rationale and methods of EMERALD: A randomised, double-blind, single-centre, placebo-controlled phase II trial evaluating the safety, tolerability, and efficacy of Cannabis based medicine extract (CBME) in patients with Amyotrophic Lateral Sclerosis (pALS)

Arman Sabet[1], Berzenn Urbi[1], Richard Bedlack[2], Ethan Russo[3], Simon Broadley[4]

[1]Gold Coast University Hospital, Gold Coast, QLD, Australia, [2]Duke Institute for Brain Sciences, Durham, NC, USA, [3]International Cannabis and Cannabinoids Institute, Czechia, Czech Republic, [4]Griffith University, Gold Coast, QLD, Australia

Email address for correspondence: berzenn.urbi@health.qld.gov.au

Keywords: cannabinoid, ALS, MND, efficacy, cannabis

Background: ALS is a neurodegenerative disorder with no known cure and a life expectancy of 2.5 years post diagnosis [1]. It is unsurprising that most patients with ALS (pALS) attempt to use complementary and alternative medicine such as medicinal cannabis in search for a

potential treatment or cure [1]. Despite anecdotal reports and pre-clinical studies demonstrating efficacy of cannabinoid in extending survival and slowing ALS progression [2], a clinical trial in pALS with these objectives has not been conducted. EMERALD trial is designed to fill this research gap.

Objectives: To discuss the rationale and methods of EMERALD trial

Methods: EMERALD trial is a randomised, placebo-controlled cannabis trial in pALS at Gold Coast University Hospital (GCUH). A medicinal cannabis extract with high CBD and low THC concentration will be used as a study medication. High CBD concentration was chosen as it protects against proposed mechanisms of ALS pathogenesis such as glutamate-excitotoxicity, inflammation and oxidative stress [3]. A minimum of 30 pALS with probable or definite ALS diagnosis based on El Escorial criteria, age between 25-75 years old and with at least 75% FVC will be recruited. They will be treated with either CBME or placebo for over 6 months. The primary objective of the study is to evaluate the safety, tolerability and efficacy of CBME compared to placebo in slowing the disease progression measured by differences in mean ALSFRS-R and FVC score between groups at end of treatment (EOT). The secondary objectives are to evaluate the effects of CBME on spasticity, pain, weight loss and quality of life assessed by differences in mean Numeric Rating Scale in spasticity and pain, percentage of total weight loss and ALSQOL-R, respectively at EOT. Study outcomes will be analysed by comparing the differences in mean scores from baseline to the end of treatment using linear regression.

Results: EMERALD trial will commence recruitment in June 2018. A safety update of the trial, if available, will be provided during the conference.

Discussion and conclusions: This paper describes the rationale and methods in evaluating the effects of CBME in ALS both as a disease modifying and symptomatic treatment.

Acknowledgements: Funding was provided by Gold Coast Health and Gold Coast Health Foundation. Study drugs are being provided by CannTrust Inc.

References

1. Bedlack, R., Joyce, N., Carter, G. et al. Neurologic Clinics. 2015; 33, 909-909.
2. Carter, G. T., Abood, M. E., Aggarwal, S. K. et al. American Journal of Hospice and Palliative Medicine. 2010; 27, 347-356.
3. Carter, G. T., and Rosen, B. S. American Journal of Hospice and Palliative Medicine. 2001;18, 264-270.

CW-09 Observational Quantitative Data in Adult Patients with SMA Dosed with Nusinersen

Cosette M Burian, Senda Ajroud Driss, Ashley Bozeman

Northwestern Neurology Feinberg School of Medicine Division of Neuromuscular Medicine, Chicago, IL, USA

Email address for correspondence: cosette.burian@nm.org

Keywords: nusinersen

Background: Nusinersen is a novel antisense oligonucleotide that is FDA approved for the treatment of all patients with SMA. This approval was based on functional benefit found in larger-scale, longer-term studies in the pediatric population, with more limited data available in adults. Functional benefit or possible risks of dosing this medication in the adult patient with SMA is not well-defined. Lab monitoring parameters recommended based on these studies include random urine protein and platelet count. Long term safety of nusinersen in adults in unknown. Objective strength and function measurements used to track outcomes in the pediatric studies often

pertain to motor milestones and infantile activities and are not applicable or validated in the adult patient.

Objectives: In this report, our large center of >20 adult patients dosed with nusinersen seeks to present lab, strength and functional objective measurements collected from our adult SMA population dosed with nusinersen since 6/17.

Methods: Data to be collected from our patient cohort of >20 adults receiving nusinersen from 2016 to approximately date of symposium. Parameters including, serially and as applicable,: 24 hour and random urine protein, serum studies, cystatin C, platelet count, RULM score, dynamometer testing, 6 minute walk test, spirometry. Information from patient histories and clinic experience in administrating nusinersen program also to be presented.

Results: Work in progress, results to be presented at the symposium.

Discussion and conclusions: We are presenting our experience with nusinersen in adults and sharing the unique challenges of the adult population, as regards management of nusinersen program, lab, objective strength and function measurements, and long term safety. Conclusions in progress, to be presented at the symposium.

References

Bastings E. US Food and Drug Administration Drug Approvals and Databases 2016; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000SumR.pdf

CW-10 Design and status of the ongoing Phase II, randomized, placebo-controlled trial of AMX0035 in Amyotrophic Lateral Sclerosis (CENTAUR)

Joshua Cohen[1], Kent Leslie[1], Justin Klee[1], Patricia Andres[2], Merit Cudkowicz[2], Nazem Atassi[2], Sabrina Paganoni[2]

[1]Amylyx Pharmaceuticals, Cambridge, MA, USA, [2]Massachusetts General Hospital, Boston, MA, USA

Email address for correspondence: kent_leslie@amylyx.com

Keywords: trial, ATLIS, biomarkers

Background: Amylyx has developed a novel therapeutic, AMX0035, for the treatment of ALS. AMX0035 is a combination of two compounds, Sodium Phenylbutyrate (PB) and Tauroursodeoxycholic Acid (TUDCA). PB and TUDCA have been individually tested in early clinical trials of ALS and showed promising early results, yet there has been no follow-up. Preclinical models revealed a synergy between the two compounds when administered together in particular ratios. In these models, AMX0035 blocked neuronal death and neuroinflammation through simultaneous inhibition of ER and mitochondrial stress.

AMX0035 initiated the CENTAUR trial, a parallel-group, randomized, double-blind, placebo-controlled study in June 2017. Patients in the active group will receive 3g PB and 1g TUDCA b.i.d administered twice daily.

The CENTAUR trial is powered to detect change in the slope of ALSFRS-R over 6-months. Analysis of the PRO-ACT database found that patients less than 540 days since symptom onset with a diagnosis of Definite ALS by El Escorial Criteria experienced disease progression at a faster rate than did the overall ALS patient population. Applying these clinical criteria to an independent patient cohort (the Ceftriaxone clinical trial) provided the sample size calculation basis for the trial.

Participants are being evaluated for clinical measures, muscle strength testing and biomarkers. Muscle strength is being measuring using ATLIS – Accurate Test of Limb Isometric Strength –a device shown to be more sensitively track ALS disease progression than

ALSFRS-R. Blood and imaging-based biomarkers of ALS include levels of NfL, pNfH, and SUVR of the PET tracer [^{11}C]-PBR28.

In April 2018, Amylyx initiated an open-label extension study, CENTAUR-OLE. The 12-month extension trial will evaluate the long-term safety and tolerability of AMX0035, while assessing muscle strength and clinical measures.

Acknowledgements: Amylyx would like to thank Lucie Bruijn and the ALS Association and the ALS Finding a Cure foundation for their generous support of the CENTAUR trial as part of the ALS Accelerated Therapeutics (ACT) initiative. Furthermore, Amylyx would like to thank the incredible staff at the NCRI for their tireless efforts making the trial a reality. Specifically, we would like to thank Michelle McGovern, Emily Engel, Elizabeth Simpson, Sara Thrower, Melissa Ricker, Lindsay Pothier, Nitzah Winter, Alexander Sherman, Mileena Torres, Jason Walker, Daniella Walker, Marianne Kearney, James Berry, Katy Nicholson, We would also like to thank the team at the Barrow Neurological Institute for providing clinical monitoring support, including Jeremy Shefner, Ashley Sconzo, and Meghan Hall. Our gratitude to our patient advocates, Stephen Winthrop and Steve Kolb for their invaluable insight. We would also like to thank all participating clinical trial sites and principal investigators for their commitment to this study.
Most importantly, we would like to thank the patients and their families for their sacrifice and generosity in participating in our study.

CW-11 Long-term Outcome of Filgrastim (G-CSF) in ALS Patients

Siw Johannesen[1], Bettina Budeus[2], Tim-Henrik Bruun[1], Sebastian Peters[1], Anne-Louise Meier[1], Sabrina Küspert[1], Ines Kobor[1], Ohnmar Hsam[1], Anna-Maria Wirth[1], Wilhelm Schulte-Mattler[1], Sabine Iberl[3], Armin Schneider[2], Winfried Koch[4], Ulrich Bogdahn[1]

[1]Department of Neurology, University of Regensburg, Regensburg, Germany, [2]Life.Data.Science, Heidelberg, Germany, [3]Department of Hematology, University of Regensburg, Regensburg, Germany, [4]BDS Koch, Schwetzingen, Germany

Email address for correspondence: siwwj@hotmail.com

Keywords: G-CSF, treatment, biomarker

Background: The role of G-CSF in ALS so far is unclear.

Objectives: To investigate long-term G-CSF treatment in ALS patients.

Methods: 36 definite ALS patients (mean age 52 yrs, 25m/11f) treated with informed written consent on a named outpatient basis from 2010 to 2017 (mean dose: 351 Mio IU G-CSF/month, median treatment duration 13.7 months). Survival, disease progression (ALS-FRS-R) and matching were compared to a defined entire PRO-ACT patient pool, and a best reference subgroup of riluzole + placebo - patients. A survival prediction model based upon PRO-ACT was established for biomarkers. Further modelling tried to investigate ALSFRS-R slopes during G-CSF treatment.

Results: Safety, feasibility and tolerance were excellent. Significant differences in ALSFRS-R slopes between G-CSF and PRO-ACT depended on time between 1st. symptom and treatment onset: in patients with less than 10 months disease duration G-CSF treated patients lost 3.73 ALS-FRS-R points less than PRO-ACT at 6 months (p=0,0006). Profiles of ALSFRS-R in the G-CSF group presented flattening compared to PRO-ACT over 36 months (niveau of 28). Non-adjusted and multi parameter adjusted survival analyses revealed significant superiority for G-CSF treatment, specifically to the best PRO-ACT- subgroup (Riluzole + Placebo). This could be confirmed for matched pairs also - revealing a benefit of approx. 50%: G-CSF versus PRO-ACT (373 versus 596 days, p< 0,001)) or G-CSF versus riluzole + placebo (596 versus

403 days, p< 0,0001). The G-CSF survival curve clearly separated after 365 days of treatment. Observed survival correlated significantly to estimated survival as assessed by the individual survival prediction modelling within PRO-ACT (p<0,0001). Differences between observed to PRO-ACT-predicted survival times were significantly in favor for G-CSF, but also revealed different subgroups within G-CSF. Median survival in the best responders was 1378 +/- 866 days (p<0,001). Biomarkers - monitored in individual patients - correlated with prognosis *and* with G-CSF response. Individual response was significantly associated with patients´ hematopoietic stem cell mobilization. With a significant benefit of G-CSF for all ALS patients, a highly responsive subgroup of ALS patients with a distinct biomarker profile could be delineated.

Discussion and conclusions: Long-time G-CSF therapy in ALS patients seems extremely encouraging. A survival prediction model indicated survival times significantly in favor for G-CSF compared to PRO-ACT. G-CSF treated patients presented a slower decline in ALSFRS-R already over the first 6 months of treatment compared to PRO-ACT-database. A further flattening of the ALSFRS-R slope was observed and present after 2 and 3 years. Biomarkers help to identify a highly responsive subpopulation, which has a substantial benefit from this safe outpatient therapy. As these are results of non-randomized comparisons, our findings require to be verified in a controlled clinical trial.

Acknowledgements: Supported in part by BMBF-GO-Bio Grant

CW-12 Novel drug RCH4 slows ALSFRS-R decline by 63.3%. (*n=51 p=0.0001. Treatment-years=54*). The presentation compares treatment outcomes between Radicava, generic Edaravone, RCH4, and addresses the question: "Do they work", not: "How do they work".

Michael Curan

RC Charity Research Group, London, United Kingdom

Email address for correspondence: wheurope@aol.com

Keywords: RCH4, RC Charity

Background:
Mode of action: RCH4 rationale is based on suppressing a previously unrecognised agent exclusively found (1) in MND, FTD, Alzheimer`s and Huntington`s. It evidences numerous effects including upregulating glutamate expression (2,3,4,5). The whole package was offered as a Humanitarian gift to the MND research community but declined.

RCH4 is now provided open label, free of charge, by a charity. Monthly self assessed monitoring reports, same as the Lunasin trial, provided by 51 subjects (*54 patient-treatment-years. 10,416 data points*) statistically evaluated.

The RCH4 evidence: Medicine is evidence based. The defining evidence are patients long term outcomes: ALSFRS-R progression slowed by average 63.3%, i.e. more effective than Riluzole or Radicava. It appears remarkably well tolerated. >5,000 doses. There are no reports of any notable related side effects (6).

Data source: Radicava: 34.5 treatment-years. (7) RCH4: 54.3 treatment-years. Monitoring reports (*n=629 p=0.0001*) deemed highly accurate (8).

Comparison: (9) Radicava: ALSFRS-R progression slowed 33.0%, non-responders excluded. (*n=68 p=0.0013. Starting score 41.9*). Infusion 12 days/month. RCH4: ALSFRS-R progression slowed 70.3%, non-responders excluded. (*n=51 p=0.0001. Starting score 33.9*). 8 intra-muscular injections/month. RCH4 ALSFRS-R slowed 63.3%, non-responders included: (*16% p=0.0001).*

Dropouts: 14%. RCH4 withdrawn from those discovered using counterfeit "Radicava" (10).

Riluzole concomitant: Radicava: >90%, RCH4: 72% (+Radicava concomitant 12%)
Radicava: 6-month trial. Effective in 7% of MND population. Trial criteria excluded the 93% non-efficacies of earlier trial. Ethnicity: Asian.
RCH4: 54.3 patient-treatment-years. Effective in 84%. No exclusion criteria, all accepted, i.e., Humanitarian undertaking. 4 Ethnicities.

Reversals: Radicava: No progression reversals, i.e., no ALSFRS-R score increase.
RCH4: Of particular interest, 8% have a score higher than when treatment started, i.e., ALSFRS-R score reversal/increase. (*Average 24.6 treatment-months)*. They each average 29 ALSFRS-R points higher than projected. Projected score extrapolated from date of formal diagnosis to start of RCH4 (*15.3 months*).

Controls: Radicava: Placebo arm. Monthly ALSFRS-R decline 1.125.
RCH4: Historic. Monthly ALSFRS-R decline 1.148 before RH4 start.
RCH4 historic control supported by the `PRO-ACT` database monthly decline of 1.028 ALSFRS-R points/month in placebo arms over all trials. Total 8,600 individuals (11).

Phase II Trial? Insufficient funds.

Patients: Perceived efficacy at 05/06/2018
Independently reported by those who registered their evaluations on the `Patients Like Me` forum:
Major efficacy: Riluzole 2%, Radicava 2%, RCH4 85%, Moderate: Riluzole 7%. Radicava 19%, RCH4 9%, Slight: Riluzole 8%, Radicava 12%, RCH4 2%, None/unknown: Riluzole 83%, Radicava 67%, RCH4 4% (12&13), (Evaluations: Riluzole *n=1084*, Radicava *n=54,* RCH4 *n=61)*.

Patient interest: ALS-UNTANGLED
Votes: (14)
Radicava ("Edaravone"): 531
RCH4: 1,353

Placebo/bias effect: Average treatment >1 year far exceeds normally expected placebo or bias time.

Acknowledgements: No conflicts.

References

1. www.als-new-drug.com
2.https://www.ncbi.nlm.nih.gov/pubmed/25245510
3.https://www.rarediseasesnetwork.org/cms/Portals/5/Article%20for%20patients-%20Frontotemporal%20Degeneration.pdf
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5791143/%20%20
5.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4679930/
6. www.als-new-drug.com/efficacy
7. https://www.radicava.com/hcp/efficacy-and-safety/
8. https://www.tandfonline.com/doi/abs/10.3109/17482968.2011.633268
9. www.als-new-drug.com/rch4-efficacy
10. www.als-new-drug.com/molecule
11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4239834/
12. https://www.patientslikeme.com/treatments/show/25456
13. https://www.patientslikeme.com/treatments/show/28469#overview
14. http://alsuntangled.com/open.php

CW-13 Edaravone as an antioxidant agent to treat amyotrophic lateral sclerosis: a longitudinal prospective study of a cohort of patients from Veneto area, Italy

Gianni Soraru[1], Andrea Fortuna[1], Ilaria Martinelli[1], Elena Pegoraro[1], Maurizio Corbetta[1], Giorgio Caneve[2], Nicoletta Freddi[3], Sandro Guzzon[4], Stefania Lelli[5], Alessandra Vidali[6], Marianna Fortunato[7], Franco Ferraci[8], Luigi Bartolomei[9], Francesco Perini[9], Flavio Sanson[10], Mauro Scarpelli[11], Silvia Romito[11], Ernesto Gastaldo[12], Roberto Lerario[13], Matteo Gizzi[1]

[1]Department of Neurosciences, University of Padova, Padova, Italy,

[2]Neurologia, Ospedale Cittadella, Cittadella (PD), Italy, [3]Neurologia, Ospedale S. Antonio, Padova, Italy, [4]Neurologia, Ospedali Riuniti Schiavonia, Schiavonia (PD), Italy, [5]Neurologia, Ospeldae Castelfranco V.to (TV), Castelfranco V.to (TV), Italy, [6]Neurologia, Ospedale di Treviso, Treviso, Italy, [7]Neurologia, Ospedale di Conegliano, Conegliano V.to (TV), Italy, [8]Neurologia, Ospedale di Belluno, Belluno, Italy, [9]Neurologia, Ospedale di Vicenza, Vicenza, Italy, [10]Neurologia Ospedale Alto Vicentino via Garziere n. 42 - Santorso (VI, Santorso (VI), Italy, [11]Neurologia, Ospeldae Borgo Trento, Verona, Italy, [12]Ospedale dell'Angelo di Mestre, Mestre (VE), Italy, [13]Neurologia, Ospedale di Rovigo, Rovigo, Italy

Email address for correspondence: gianni.soraru@unipd.it

Keywords: edaravone, ALSFRSr, trial

Background: Based on positive results of a recent clinical trial conducted in Japanese ALS patients [1], the Italian Medicines Agency (AIFA) has approved the use of edaravone in people with ALS who meet a selected set of inclusion criteria (age greater than 18 years; each ALSFRSr item score of at least 2 points; disease duration of 2 years or less; forced vital capacity of 80% or more).

Objectives: To further evaluate efficacy and safety of edaravone in ALS.

Methods: Since AIFA approval in July 2017, 44 ALS patients meeting the identified inclusion criteria have started the treatment with edaravone at 4 hospitals of the Italian Veneto region. According to the Japanese clinical trial protocol, patients are receiving 60 mg intravenous edaravone with a monthly dosing scheme including two weeks on and two weeks off. The following functional and bioumoral parameters are being monitored every 3 months: 1. ALSFRSr score; 2. forced vital capacity (FVC) %; ALSAQ-5; routine blood chemistry. To evaluate efficacy and safety of the drug, functional and bioumoral data will be compared with the same parameters collected in a retrospective cohort of ALS patients referred to the Motor Neuron Disease Clinic of the University of Padova (Italy), and matching for sex, age, disease duration and ALSFRSr scores.

Results: At the time of this abstract submission, 41 patients are regularly on edaravone treatment. One patient died after about two months of treatment for unknown reasons (sudden death), whereas two patients were asked to discontinue the drug after developing both a deep vein thrombosis. In the other patients, the drug is still well tolerated, being mild and transient dizziness the most common side effect. Eleven patients have completed the 6-monts assessment and 22 the 3-months assessment.

Discussion and conclusions: This study will provide novel data on the role of edaravone in Caucasian ALS patients.

Acknowledgements: We desire to acknowledge Registro Malattie Rare, Regione Veneto, Telethon BioBank (GTB12001D), the EuroBioBank network.

References

1. The Writing Group on behalf of the Edaravone (MCI-186)ALS19 Study Group. Lancet Neurol 2017;16:505

CW-14 Surveillance of using novel free radical scavenger, edaravone to investigate survival effect for ALS patients in Japan (SUNRISE Japan): Report for intermediate summary

Manabu Hirai[1], Satoshi Yuki[2], Kaoru Ishizaki[3], Hiroaki Matsuda[4], Gen Sobue[5]

[1]Clinical Research & Development I Department, [2]Medical Intelligence Department, [3]Pharmacovigilance Department, [4]Data Science Department; Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan, [5]Brain and Mind Research Center, Nagoya University Graduate School of Medicine, Nagoya, Japan

Email address for correspondence: hirai.manabu@mp.mt-pharma.co.jp

Keywords: edaravone, post-marketing surveillance

Background: Edaravone, a free radical scavenger developed as a neuroprotectant, was first approved in 2001 in Japan as the indication for acute ischemic stroke (AIS). Based on a series of clinical studies completed in Japan in patients suffering from amyotrophic lateral sclerosis (ALS), edaravone was approved in Japan in June 2015, in South Korea in December 2015 and in the United States in May 2017 for the treatment of ALS. The approval was based on the efficacy and safety data of patients with definite or probable ALS diagnosis. Edaravone demonstrated statistically significant efficacy in slowing the progression of ALS, as assessed based on the ALS Functional Rating Scale-Revised (ALSFRS-R) score, however, to date, other survival endpoints such as time to survival or time to tracheal intubation have not been assessed.

Objectives: We aimed to assess the long-term efficacy, including survival endpoints, and safety of edaravone in the post-marketing surveillance of patients with ALS for up to 5 years. Furthermore, we will compare the efficacy with appropriate external control data.

Methods: Overall, more than 800 ALS patients who are naive pertaining to edaravone treatment have been enrolled and will be followed up for 5 years. Observation of efficacy: 1) Duration of survival and duration until invasive tracheal intubation up to 5 years. 2) Clinical events such as introduction of tube feeding, gastrostomy, and intermittent non-invasive ventilator assistance up to 1.5 years. 3) ALSFRS-R score up to 1.5 years. Observation of safety: Adverse events up to 1 year. The survey conducted in accordance with ministerial ordinance on Good Postmarketing Study Practice in Japan.

Results: The enrollment ended in October 12, 2017. In this paper, we report the information on patient background and safety data collected on October 2018.

Discussion and conclusions: The survey is proceeding as planned. These data may be useful not only medical staff and ALS patients in Japan but also in Korea and the United States. This survey is expected to take a lead in the evaluation of drugs against neurological disorders.

Acknowledgements: We would like to thank patients and investigators for taking part in this post-marketing surveillance.

References

The writing group on behalf of the edaravone (MCI-186) ALS 19 study group. Lancet Neurol 2017; 16:505-512

CW-15 Protocol and Design of the Radicava® (edaravone) Biomarker Study for ALS Patients in the United States

Benjamin Brooks[1], James Berry[2], Angela Genge[3], Terry Heiman-Patterson[4], Stanley Appel[5], Michael Benatar[6], Robert Bowser[7], Merit Cudkowicz[8], Clifton Gooch[9], Jeremy Shefner[10], Jean Hubble[11], Steve Apple[11], Wendy Agnese[11], Charley Merrill[11], Sally Nelson[11]

[1]University of North Carolina School of Medicine, Chapel Hill, NC, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Montreal Neurological Institute and Hospital, Montreal, Canada, [4]Temple University, Philadelphia, PA, USA, [5]Houston Methodist, Houston, TX, USA, [6]University of Miami, Miami, FL, USA, [7]Dignity Health St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA, [8]Harvard Medical School, Boston, MA, USA, [9]University of South Florida, Tampa, FL, USA, [10]Barrow Neurological Institute, Phoenix, AZ, USA, [11]Mitsubishi Tanabe Pharma America, Inc., Jersey City, NJ, USA

Email address for correspondence: stephen_apple@mt-pharma-us.com

Keywords: edaravone, biomarker, prospective study

Background: Biomarkers have become an important tool in disease diagnosis, prognosis, and treatment assessment (1). In amyotrophic lateral sclerosis (ALS), various biomarker candidates have been identified, but not fully validated (1). Edaravone (Radicava®) is an FDA-approved treatment for ALS that has been demonstrated in a Phase 3 clinical trial to significantly slow functional loss and deterioration of quality of life (2). This study aims to investigate biomarkers for their capacity to demonstrate a treatment effect with edaravone.

Objectives: To assess a panel of putative biomarkers to serve as quantifiable biological non-clinical measure(s) of edaravone's effect in ALS.

Methods: This is a prospective, observational, longitudinal, multicenter US study. It is designed to enroll approximately 125 patients with ALS (male or female, age ≥18 years) who have been prescribed edaravone prior to study enrollment. Patients will receive edaravone for 24 weeks: 60 mg daily by intravenous infusion for 14 days for the initial treatment cycle, followed by daily dosing on 10 out of 14 days in subsequent treatment cycles (each treatment period is followed by a 14-day drug-free period). Biomarker testing and standard-of-care clinical assessments will be performed at enrollment, baseline (start of cycle 1) and at the end of cycle 6. Urine and serum samples will be collected at pre-specified timepoints within each treatment cycle to evaluate selected biomarkers for oxidative stress, inflammation, and neuronal injury and death. Biomarker results will be compared with available historical samples. Efficacy assessments include changes in ALSFRS-R scores, King's clinical staging, ALSAQ-40 score, respiratory function, and states of disease progression. A sub-study on the Appel ALS rating score will be conducted. Associations between biomarker levels and treatment outcomes will be investigated. Safety will be assessed, including adverse events, prospectively throughout the study. Disease progression models based on all data will be assessed.

Results: Interim data are expected in 2019.

Discussion and conclusions: The findings of this study will help to establish the feasibility of using biomarkers to assess the effect of edaravone in ALS. These biomarkers will comprise an important assessment tool for use in patient treatment plans and future clinical programs and may provide insights into the mechanism of action of edaravone. Such real-world data will also advance our understanding of the safety and efficacy of edaravone beyond the profile attained from clinical trials.

Acknowledgements: *p*-value communications provided editorial support. The study was funded and conducted by Mitsubishi Tanabe Pharma America (MTPA). JH, SA, WA, CM, and SN are employees of MTPA.

References

1. Benatar M, et al. *Muscle Nerve.* 2016;53:169-182.
2. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. *Lancet Neurol.* 2017;16:505-512.

CW-16 French securing of Edaravone distribution network: risk management linked to Japanese packaging and time consuming consequences

Emmeline L Lagrange[1], Audrey Lehman[2]

[1]Grenoble University Hospital, Grenoble, France, [2]Grenoble university Hospital, Grenoble, France

Email address for correspondence: elagrange@chu-grenoble.fr

Keywords: edaravone securing process

Background: Edaravone is an antioxidant free-radical scavenger approved by the FDA in 2017 for the treatment of ALS. A French patient had a first advice/medical prescription approved by the Boston team in May 2017. The French distribution network did not exist on that date. We had to identify with the European drug agency ANSM how to obtain, how to deliver and then, how to secure edaravone administration for this first French patient treated.

We had to translate all documents from English to French, and, as we received both Japanese and English drugs we had to manage the risk network, step by step for a safe administration and traceability. We noticed some severe dysfunctions.

This collaborative work was time consuming, took months, but is a success, as it permitted to create a real partnership with ANSM, for a safe and controlled distribution. The patient had a real benefit thanks to edaravone.

Objectives: Securing Edaravone network distribution and administration in France.

Methods: Risk analysis step by step thanks to a quality process and corrective action plan, from order to delivery, administration and follow up of Edaravone in France.

Results: From May 2017 to September 2017 we were in relation with ANSM and Health Ministry to obtain Edaravone access, with time spent in administrative strike. We received American drug explanations and leaflet. Edaravone was first delivered in a Japanese packaging, with all text written in gandji. All traceability was in gandji too. In a second time we received the two different packaging, American and Japanese in a context of tightness of supply of drug. In a third time we noticed a material dysfunction that we declare to ANSM. Temporary authorization of Edaravone was suspended for months and a fructuous collaboration with the ANSM permitted the upholding of Edaravone disposition for new and former patients. We secured all the process for this first French patient treated by edaravone. All the procedures were down with the ANSM for a large French distribution.

Discussion and conclusions: Cooperation within the healthcare community, clinicians, patients, European drug agency is necessary to advance ALS management and treatment, and to improve patient access for Edaravone. Some dysfunctions are still unresolved, like the limited patient access at home, as French hospital are no longer able to admit patients for intravenous recurrent drips.

Acknowledgements: Dr Philippe Vella ANSM, Dr Olivier Véran Grenoble University Hospital.

CW-17 What would a King's staging 2.0 look like? A retrospective review

Nathalie Magnan, Toni Vitale, Natalie Saunders, Angela Genge

Montreal Neurological Institute and Hospital, ALS Clinic, Montreal, QC, Canada

Email address for correspondence: natalie.saunders@mcgill.ca

Keywords: clinical trial, King's staging, disease presentation

Background: Since 2012, an emphasis on the creation of a staging system in patients with amyotrophic lateral sclerosis has been widely discussed in the literature (1). The benefits of a clinical staging have been cited to be the following: it is an easy tool that can be administered quickly, can assist in planning stage appropriate health care, and it can facilitate research in two ways: disease classification can be created with patients grouped along the continuum of early versus late disease stages and secondly clinical trials can be

designed to target specific stages (2). Therefore, it was proposed to integrate the King's staging system into the Montreal Neurological Hospital Multidisciplinary ALS clinic.

During this time, we observed some interesting findings with the application of the King's staging. The King's staging system is an excellent first step but does it unfairly bias some patients towards a worse stage? In a chart review, we aim to describe these findings and highlight any potential clinical and research implications.

Objectives: A retrospective chart review of 10-15 cases will be presented supporting the hypothesis that based on the criteria of the King's staging, some patients may score at a higher level than expected because of their disease presentation.

Methods: A retrospective chart review from May 2017 to May 2018 for patients followed at the Montreal Neurological Hospital Multidisciplinary ALS clinic. The following data will be collected from the chart: age, sex, date of diagnosis, site of symptom onset, King's stage scoring, ALSFRS-R scoring, pulmonary function measure (forced vital capacity, snip), weight, driving status, working status, clinical trial participation and insertion of PEG.

Results: The results presented will highlight data from the retrospective review and elaborate on the clinical implications of these results.

Discussion and conclusions: This is a work in progress, therefore conclusions will be made when chart reviews are complete.

References

1. Roche, J.C, Rojas-Garcia, R, Scott, K.M *et al* Brain 2012; 135:847-852
2. Balendra, R, Jones, A, Jivraj, N *et al* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2014; 15:279-284
3. Ferraro, D, Consonni, D, Fini, N *et al* European Journal of Neurology 2016; 0:1-7
4. Fang, T, Al Khleifat, A, Stahl, D.R *et al* Amyotrophic Lateral Sclerosis and Frontotemporal 2017; 18:227-232
5. Trojsi, F, Santangelo, G, Caiazzo, G *et al* Amyotrophic Lateral Sclerosis and Frontotemporal 2016; 17:228-235

CW-18 Development of improved single switch scanning for powered wheelchair control: the result of effective collaboration

Rosanne M Gibb

Calvary Health Care Bethlehem, Melbourne, Australia

Email address for correspondence: rosanne.gibb@calvarycare.org.au

Keywords: collaboration, scanning, independence

Background: With progression of Motor Neurone Disease (MND) leading to decreased ability to walk, powered wheelchairs (PWC) provide valuable independent mobility and control of position for comfort. If upper limb function also decreases, conventional joystick controls may become too difficult to use. In this case scanning controls may be useful, using a single switch operated by the part of the body with most reliable control.
In Victoria, Australia, people with MND are provided with equipment through MNDVic. This includes Frontier powered wheelchairs manufactured by the company Magic Mobility in Melbourne. Previously these wheelchairs had Dynamic controllers which were compatible with Click to Go scanners. These types of scanners offer 8 directions for driving. When Magic Mobility changed to Penny and Giles controls, the option for scanner controls became the Omni. The therapists at Calvary Health Care Bethlehem found that this did not provide such good control of the PWC for this population as the older Click to Go, as it only had 4 directions of driving.

A collaboration between the therapists at Calvary Health Care Bethlehem and Magic Mobility led to an engineer at Magic Mobility developing a new scanning box. This was added to the Omni to provide extra driving directions, resulting in much better control of driving for the PWC user. This new scanner has 6 directions of driving and is an easier system to set up and to control.

This successful collaboration between the therapy staff at Calvary Health Care Bethlehem, technical development from Magic Mobility and funding from MNDV has led to a much better outcome for people with MND needing alternative controls on their PWCs.

CW-19 MND Association wheelchair champions project

Jenny A Rolfe

Oxford MND Care Centre, Oxford, United Kingdom, MND Association, Northampton, United Kingdom

Email address for correspondence: jennifer.rolfe@ndcn.ox.ac.uk

Keywords: wheelchairs, education

Background: The MND Association has supported statutory services in England on the timely provision of appropriate wheelchairs by providing specialist therapists and funding to support people living with MND/ALS, working with NHS England, statutory service wheelchair providers (management and clinicians), manufacturers and other charities. Resource limitations challenge wheelchair provision in England and some service delivery models can be prohibitive to accessing equipment in a timely way (1). The latest MND Association wheelchair project is an education programme: "Wheelchair Champions".

Objectives: Roll out an education programme to providers of wheelchairs to people with MND/ ALS in England to enable them to become "MND/ALS Wheelchiar Champion' for their service.

Methods: The programme involves attendance at a specific training day with the participant completing pre and post-training evaluations of their own skills and their wheelchair service delivery models. The pre-training audit will give them a benchmark against which to measure changes they implement post-training aiming to improve service delivery to people living with MND/ALS.

Results: Two pilot training days have been completed and a further date is planned. There were 10 participants at the first event and 13 at the second. Post and pre-training audits and personal evaluations are being collected. Two clinicians out of 10 from the first cohort have been awarded Wheelchair Champion Status. Changes reported from the 2 Champions include: providing better information and contact details to users of the wheelchair service, improved knowledge and understanding of the postural limitations experienced; and improved multidisciplinary working. Post-training audits from 8 of the participants have not yet been returned. The three month re-audit period has not elapsed to collect data from the second cohort. It is hoped more results will be available and analysed to present.

Discussion and conclusions: The sharing of best practice is aimed to up-skill staff working in wheelchair provision for people with MND/ALS. A training programme specifically designed for wheelchair providers gives clinicians a sense of investment in them and aimed to facilitate service delivery changes to the benefit of MND/ALS patients. From the results of the limited data collected so far, this has been shown to be achievable. A limitation of the project is the post-training audits have not always been returned. This highlights that the method by which change in service delivery is demonstrated & reported (as a result of participation in the programme) is key to evaluating the success of the programme. A low return of post training audits has lead to exploring alternatives such as a written

summary and a poster presentation to demonstrate changes in practice.

Acknowledgements: MND Association

References

Rolfe, J (2012) British Journal of Occupational Therapists. 75:1-6

CW-20 Outcome measures for the mobile arm support in individuals with Amyotrophic lateral sclerosis (ALS)

Joyce A Khowdee[1,2], Jeffrey Rosenfeld[1,3]

[1]Center for Restorative Neurology, Loma Linda University Health, Loma Linda, CA, USA, [2]Department of Occupational Therapy, Loma Linda University School of Allied Health, Loma Linda, CA, USA, [3]Department of Neurology Loma Linda University School of Medicine, Loma Linda, CA, USA

Email address for correspondence: jkhowdee@llu.edu

Keywords: mobile arm support, outcomes, quality–of-life

Background: The mobile arm support (MAS) is a readily available, but perhaps under-utilized resource to allow individuals with ALS significant improvement in upper extremity function. The device has been shown to markedly improve daily activities such as grooming, hygiene, feeding, writing, leisure activities as well as facilitating all gravity-eliminated exercise [1,2,3]. The use of a MAS offers occupational therapy practitioners a means to support the rehabilitation and treatment by offering immediate feedback, training, interventions, and adjustments in order to improve mobility and maximize independence with the upper extremity to participate in daily life [4].

Objectives: The purpose of this study is to examine, through a quantitative and qualitative study design, the impact of the mobile arm support on functional abilities and meaningful activities while understanding its significance on quality of life for individuals with ALS.

Methods: Twenty-four participants, (12 ALS patients and 12 caregivers) are being recruited for this study. Patient inclusion criteria include: age (27-88), ability to provide consent, availability of a primary caregiver, absence of significant pain (level 0-5/10), no increase in upper extremity muscle tone/spasticity, ability to sit upright and deltoid strength not < = 2/5 on manual muscle testing. Qualitative data will be collected through an audio recorded semi-structured interview yielding a second round of analyses on the subjective measures contributing to the efficacy of MAS.

Results: The final data analysis for this project will be presented. Results will indicate whether there are perceived functional changes in the ability to perform activities of daily living for 10 common tasks performed on the MAS. Changes in functional impairment and mobility will be reported using the Functional Independence Measure (FIM) scores. Comparing pre and post scores on the ALSSQOL-R we will better understand the change in quality of life with use of the MAS. Data derived from verbatim transcription and coding of all interviews, will be presented to quantitate categories and themes that emerge regarding the impact of the MAS on functional abilities and quality of life.

Discussion and conclusions: Identification of outcome measures in the use of the MAS for individuals with ALS will underscore the relative importance of this resource in the treatment protocols used by practitioners. This study will increase understanding of how to use the MAS to improve specific functional abilities and to more objectively document the benefits enabling a greater ease of access.

References

Atkins M et al The Journal of Spinal Cord Medicine 2008; 31(4): 388-393.

Yasuda Y, et al Archives of Physical Medicine and Rehabilitation 1986; 67(4): 253-256.
Van der Heide L et al Journal Of Rehabilitation Research & Development 2016; 53(6): 1139- 1150.
Nijenhuis S et al In The Eighth International Conference on eHealth, Telemedicine, and Social Medicine 2016; eTELEMED.

CW-21 Modifying Cervical Support to Allow Rotation with a 3-D Printed Attachment

Sara M Feldman[1], Mark Goren[1], Thinh Nguyen[2]

[1]Temple University, Philadelphia, PA, USA, [2]Drexel University, Philadelphia, PA, USA

Email address for correspondence: sarafeldmanpt@gmail.com

Keywords: cervical support, neck brace, 3D printing

Background: Individuals with amyotrophic lateral sclerosis (ALS) often present with neck weakness leading to the recommendation of a cervical support, or collar, to compensate for this weakness. Current cervical orthotics are designed to provide support and to restrict movement within the collar. Not all individuals with ALS need this level of confinement and would benefit from a collar that provides dynamic maneuverability, specifically rotation, while still limiting forward flexion.
Objectives: The goal of our project was to adapt a neck brace or support that was capable of establishing neutral head position for individuals with decreased neck muscle strength, especially extensors, limiting movement in the sagittal plane; while allowing rotational movement with minimal effort in the transverse plane. The design must be lightweight, easy to use, and affordable.

Methods: The initial stages of the project included input from people living with ALS (PALS), healthcare professionals (OT, PT, SLP) and designers (Biomedical Engineering student, 3D printer coordinator).

The strategy was to work with existing collars to design two separate components: 1) A rail piece to attach to the collar and 2) a chin piece with a roller attached.

Using a variety of materials, the design has been modified several times to reach the current prototype. The rail piece consists of a lightweight, flexible, nylon material with a curved groove. The chin piece has a supportive surface with a slot for a magnet and a concave space for a ball bearing. Both the rail piece and the chin piece have been 3D printed.

Results: We have designed a basic prototype and are in the next phase of the physical design process. We are undertaking an assessment of perceived comfort, movement effort and support comparing the new design to standard models of cervical collars. Though PALS were involved in the initial design, all of the users to date as we worked on the first models have been healthy controls. Our next step will be to undertake this assessment with PALS.

Discussion and conclusions: The objective of this project is to improve upon the current neck support systems by providing more dynamic maneuverability while continuing to provide the support needed. A cervical support that allows for rotation while providing support will fulfill this objective and our prototype is ready to move to the next step in development. We will report on the final design and our user assessments.

Acknowledgements: The PALS who volunteered to assist with this project; Patrick Lyons, Innovation Librarian at Temple University who assisted with the 3d printing

CW-22 The initiation of Dignity Therapy for people affected by Motor Neurone Disease in the West of Scotland.

Laura J Cunningham[1], Bridget Johnston[2]

[1]Department of Neurology NHS GGHBC, Glasgow, United Kingdom, [2]University of Glasgow and NHS GGHBC, Glasgow, United Kingdom

Email address for correspondence: laura.cunningham@ggc.scot.nhs.uk

Keywords: dignity, therapy, Scotland

Background: Dignity Therapy is a psycho- therapeutic intervention for individuals facing death or a life limiting illness, such as motor neurone disease. It is evidenced based and has been tested and evaluated in randomised controlled trials worldwide (1).

Objectives: The introduction of Dignity Therapy into the care of patients with Motor Neurone Disease in the West of Scotland

Methods: Funding for Dignity Therapy training was granted by charitable bodies (see acknowledgements). Study leave was also approved by NHS Greater Glasgow and Clyde. Dignity Therapy training took place in Winnipeg by Professor Harvey Chochinov a leading researcher and expert in Dignity(2,3) and colleagues, at Manitoba Palliative Care Research Unit. www.dignityincare.ca/en/ A new clinical intervention of Dignity Therapy-intervention for patients affected by Motor Neurone Disease in clinical practice was produced and presented to the Neurology Clinical Governance group within the Institute of Neurological Sciences. This was subsequently approved. Measures were taken to ensure confidentiality within the transcription process. Consent and documentation that the Dignity Therapy was undertaken were recorded within the clinical record.

Results: Dignity Therapy was initiated in March of 2018 and is now available to patients with motor neurone disease in the West of Scotland. At the current time one patient has successfully undertaken this therapy. The Dignity Therapy took just under an hour and the recording was transcribed and edited within a week. Subsequently at a return visit to the patient the transcript was read to the patient for reflection and adjustment. Once this took place a legacy document was produced. Four copies were then gifted to the patient May 2018. As of the time of writing a further two patients have shown interest.

Discussion and conclusions: Dignity Therapy is now available to patients with motor neurone disease in the West of Scotland. Over the coming twelve months audit of the new service is planned to support its ongoing use.

Acknowledgements: MND Scotland, Euan MacDonald Centre for Motor Neurone Disease Research. Graham Christie NHS Line Manager GGHBC. Judith Newton, National Nursing Lead/ Consultant Nurse Motor Neurone Disease. Dr George Gorrie Lead Neurolgist-MND -NHS GGHBC. Professor Bridget Johnston University of Glasgow and NHS Greater Glsgow and Clyde. MND Clinical Nurse Specialists Janice Hatrick, Ann Silver, Helen Lennox.

References

1. Chochinov HM, Kristjanson LJ, BereitbartW,et al (2011) Lancet Oncology 12:753-762
2. Chochinov HM, Hack T, McClement S, et al (2002). *Social Science and Medicine*, 54:433-443.
3. Chochinov HM (2002). *JAMA*, 287:2253-2260

CW-23 Mechanisms of psychosis and psychosis-risk in motor neurone disease and frontotemporal dementia with motor neurone disease

Alicia Wilcox, Rhys C Roberts, James B Rowe

Department of Clinical Neurosciences, Cambridge University, Cambridge, United Kingdom

Email address for correspondence:

aw644@medschl.cam.ac.uk

Keywords: psychosis, FTD-MND syndrome, neural mechanisms

Background: Although distinct in their classic forms, motor neurone disease (MND) and frontotemporal dementia (FTD) overlap in the syndrome of FTD-MND and are closely related by their common genetic association with the hexanucleotide repeat expansion of the C9orf72 gene. Psychosis is a challenging symptom associated with C9orf72, occurring overtly in a third of patients with the expansion. While research has focused on clinically evident psychotic features in the FTD-MND syndrome, milder, sub-threshold psychotic features are common.

Objectives: The overarching aim is to develop a comprehensive framework to understand psychotic and risk-states for psychosis in FTD-MND. Specifically, to establish the prevalence and severity of psychotic features in FTD-MND, including atypical and sub-clinical psychosis; investigate three key cognitive systems that predispose to psychosis, and the associated abnormalities in key neural pathways.

Methods: *N*=150 patient participants are screened in the NHS specialist MND and FTD clinics, using validated cognitive screening measures. *N*=50 patient participants are invited to participate in more in-depth neuropsychological testing, along with *N*=30 healthy control participants. Performance on neurocognitive paradigms of associative learning, aberrant reward processing and executive function are correlated with clinical rating scales of psychosis symptomatology and with magnetic resonance imaging.

Discussion and conclusions: We treat psychosis features as a continuum of severity, and not confined to the minority with overt clinical psychosis. This establishes a dimensional approach to the neural mechanisms of psychosis and psychosis-risk. The results will develop a clinically oriented framework to better identify and accelerate treatment of psychiatric dysfunction in the FTD-MND syndrome.

Acknowledgements: We would like to acknowledge Alzheimer's Research UK for funding the study, all the patients, their families and participants for being keen to participate in research, and the Arthur Rank Hospice and their volunteers for making the MND clinic a supportive and pleasant environment.

CW-24 Successful introduction of Alternative and Augmentative Communication for pALS: retrospective study of cases of 'Yay' and 'Nay'

Malin S Börjesson

Department of Neurologopedi, Sahlgrenska University Hospital, Göteborg, Sweden

Email address for correspondence: malin.sixt.borjesson@vgregion.se

Keywords: AAC acceptance

Background: Up to 80-95% of all persons with ALS will reach a point when they are no longer able to meet their communicative needs with natural speech [1]. The progress of the disease often makes the use of Alternative and Augmentative Communication (AAC) a question of *when* to begin using it, rather than *if* to begin. In the bulbar subgroup a communication device is sometimes the first medical aid that enters the home of the diseased.

Communicative participation has been defined as "taking part in life situations where knowledge, information, ideas, and feelings are exchanged" [2]. Communicative participation is not only related to speech but also to the use of AAC, e.g. a speech generating device, and to the attitude towards this device from the user and his/her communication partners. Literature suggests that around 4-25% of pALS do not accept AAC [3].

Objectives: The aim is to investigate successful/unsuccessful AAC interventions to inform future prescriptions. Specific points of interests: 1) Are there early indications that a communication intervention would/would not be successful? 2) Are there cases where an unsuccessful prescripted device was replaced and a second device was accepted and used? 3) Does there seem to be any specific traits (in user, carer, clinician) that would indicate acceptance and success?

Methods: This study will, mainly through medical journals, look retrospectively at 6-12 consecutive cases of AAC interventions where speech generating devices were prescribed. Success of the AAC intervention is defined as when patients and their carer(s) have reported that the prescribed communication devices were used on a daily basis and/or they were used in meetings with ALS team members, and this is noted in the medical journal.

Results: Data on factors that seem to be neutral, positive and/or negative to the AAC intervention will be presented (e.g. age, gender, earlier habit of keyboard usage, timing of introduction to AAC and of AAC intervention in relation to level of dysarthria, signs of cognitive decline).

Discussion and conclusions: The hypothesis is that timing and personal factors are important for successful interventions. An early indication for possible success seems to be when a person spontaneously or with only light prompting uses a device for communicative purposes at first introduction. Cognitive impairment seem in many cases to be a negative predictor.

References

1. Beukelman D, Fager S, & Nordness A. Neurology Research International, 2011(3):714693
2. Eadie T, Yorkston K, Klasner E *et al*. Am J Speech Lang Pathol. 2006; 15(4):307-20.
3. Ball L, Beukelman D, Pattee G. Augmentative and Alternative Communication, 2004; 20 (2), pp. 113–122

CW-25 An education program to support communication for people with ALS: checking discretion ability by a pre- and post-test evaluation.

Takemasa Ishikawa[1], Yugo Narita[1], Chihiro Mizumoto[1], Erisa Takahashi[1], Michiko Nakai[2], Keiko Fukuroku[1], Yuji Tanaka[3], Tamotsu Imura[4]

[1]Mie university, Tsu, Japan, [2]Suzuka University of Medical Science, Suzuka, Japan, [3]Aichi University of Education, Kariya, Japan, [4]Chubu Gakuin University, Seki, Japan

Email address for correspondence: 08801508@m.mie-u.ac.jp

Keywords: communication, AAC, education

Background: Many clinical professionals and families have tried to communicate by obtaining signals from severely disabled patients with amyotrophic lateral sclerosis (ALS) even when they are on a mechanical ventilator with a tracheostomy. Regardless of how subtle the signal is, if it is detectable, it can be connected to an augmentative and alternative communication (AAC) device. Healthcare professionals are often too busy to acquire this knowledge and become familiar with new skills. Although undergraduates in health-related disciplines are also likely to have access to full programs, they may also be more able to find time to develop communication skills than graduates. We plan to offer a half-day course on communication support for patients with ALS that includes a pre- and post-test. We consider this feasible given the advent of two important, related resources: 1) a trial focused on how to use letter boards conducted in the School of Nursing in 2016 and, 2) the

guidebook for the introduction of AAC for patients with neuromuscular disorders (1), which was published in August 2017. All topics in the pre- and post-test were extracted from the Guidebook.

Objectives: An education program on ALS communication support was planned for students. We aimed to investigate how the knowledge and skills acquired by the students in these short sessions would be maintained over time. The next step in the process was to check discretion ability using a pre- and post-test evaluation of the educational session.

Methods: Six students at the university (4 medical students and 2 nursing students, 4 males, and 2 females, aged 20-22 years old) participated in the first trial of the course on 22nd March, 2018.

Immediately before and after the half-day course, the participants took the same 10-minute test, which comprised 10 questions. Participants were asked to describe their burden using a visual analogue scale about their burden. We did this trial with the permission of the Mie University Faculty of Medicine IRB (No.3245, March, 2018).

Results: All participants completed the test within the time allotted. The average post-test score was 7.5 +/- 1.87, which was higher than the pre-test (5.0 +/- 2.45) score, with a p value <.0099 according to paired t-test (JMP 8.0, 2008). Participant's burden was remained the same in the pre-test (45 +/- 17.6 mm) and post-test (46 +/- 8 mm).

Discussion and conclusions: The test showed a significant difference in knowledge of AAC, even though the number of participants was small. Participants' burden was stable in pre- and post-tests. Our trial suggested the usefulness of an education program on communication support for people with ALS.

References

1. Imura T. The guidebook to assist introduction of AAC for patients with neuromuscular disorders. http://rel.chubu-gu.ac.jp/files/2016-rep/guidebook-all.pdf (accessed on 12th June, 2018)

CW-26 The Multidisciplinary Chest Management Programme for Patient's Living with Motor Neurone Disease: The benefits of joint Speech and Language Therapy and Physiotherapy working in the assessment and management of swallow and cough.

Jodi E Allen, Charlotte F Massey

The National Hospital for Neurology and Neurosurgery, University College London Hospitals, London, United Kingdom

Email address for correspondence: jodi.allen@nhs.net

Keywords: cough, swallow, multidisciplinary

Introduction: Assessment and management of cough for airway clearance typically falls within the remit of respiratory physiotherapy. A cough peak flow of <270l/min, difficulty clearing upper respiratory tract secretions and/or recurrent chest infections indicate the need for cough augmentation.

Joint working between Speech and Language Therapy (SLT) and Physiotherapy (PT) facilitates holisitic assessment of cough and airway clearance, permitting individualised airway management techniques, optimising patient comfort and clinical outcomes. This series of eight patients highlights the benefits of joint working and value of multidisciplinary airway management.

Case Studies: All patients were referred to physiotherapy for assessment and management of airway clearance techniques secondary to symptoms of weak cough and difficulty clearing secretions. They were assessed jointly by SLT/ PT. Two example studies are provided here:

Case One: Diagnosis: ALS, Time since diagnosis: 14 months, Mobility: Wheelchair.

Current airway & secretion management: Recent trial of hyoscine, found too drying. Amitriptyline 10mg od by PEG, Oral intake: Nil by mouth, PEG tube, Speech: Anarthric. Mixed flaccid/spastic bulbar signs, Spirometry: FVC 19% predicted, FEV1 21% predicted, Peak cough flow (l/min): 60-80, Chest infection history: One chest infection two weeks ago with 2-3 over course of year.

Assessment: Reports of sticky phlegm at larynx level finding difficult to clear. No audible chest or upper airway secretions. No pooled oral secretions. Nasendoscopic assessment revealed small amount of sticky secretions in pharynx. Cough and swallow ineffective in clearing. Inability to close glottis to command nor sequence with inhale/exhale. Ballooning of cheeks with supported inhalation.

Management: Review of anticholinergic medication and hydration via PEG. Consider use of carbocisteine. Use of lung volume recruitment bag for deep breaths, one at a time. Manually assisted cough.

Case Two: *Diagnosis:* Progressive bulbar palsy, *Time since diagnosis:* Three weeks, *Mobility:* Mobile short distances within the home

Current airway & secretion management: Nil, *Oral intake:* Normal diet and fluids by mouth, *Speech:* Moderate spastic dysarthria, *Spirometry:* FVC 79% predicted, FEV1: 61% predicted, *Peak cough flow (l/min):* Unable to elicit volitional cough, *Chest infection history:* None reported, *Other:* Possible bilateral vocal fold palsy under investigation by Ear, Nose and Throat (ENT).

Assessment: Audible stridor on attempts to cough and mobilise. Unable to sequence glottic closure with breaths in. Cough symptoms only present when eating and drinking. Strong-sounding reflexive cough.

Management: Deep breathing avoiding glottic involvement. ENT advice. No increase in effort or length of current physical activity. Not for cough augmentation. Dysphagia assessment.

Findings and summary: Case studies highlight benefits of MDT assessment, ensuring considerations are made relating to:

- Oral and pharyngeal secretions
- Voluntary versus reflexive cough
- Influence of unmanaged dysphagia
- Role of bulbar weakness in tolerance of positive pressure
- Psychological impact and influence of pseudobulbar affect

CW-27 Speech and Language Therapy Assistant led Voice Banking Education Groups

Rebecca Yalland[1], Hannah Davies[1], Julieanne Yates[1], Hayley Regan-Wall[1], Belinda Done[1], Stephanie Durnan[2]

[1]ABUHB Adult SLT Team, Caerleon, United Kingdom, [2]MND Care Co-ordinator, Caerleon, United Kingdom

Email address for correspondence: belinda.done@wales.nhs.uk

Keywords: voice banking, education groups

What is voice banking?

- A process where a person records a set of phrases with their own voice
- The recording is converted into a personal synthetic voice
- The more phrases recorded the more personal the synthetic voice will become
- Early referral to Speech and Language Therapy (SLT) is important to enable a better quality synthetic voice.
- The voice recording is sent away to be generated and then put into a text to speak app.

- The patient benefits from being able to retain their own voice and maintain their sense of identity.

Why change the service delivery?

- From attendance at a MND awareness day, the Speech and Language Therapy Assistants (SLTAs) proposed to the Adult Speech and Language Therapy Professional Lead, a scoping exercise about voice banking use by patients diagnosed with MND in Aneurin Bevan University Health Board (ABUHB).
- Surveys indicated 79% of respondents had a lack of knowledge about voice banking
- Results also indicated a need for education sessions and a preference for a group setting
- ABUHB SLT department approached the MND Association to pilot group voice banking education sessions delivered by SLTAs.
- The MND Association provided bespoke training on voice banking to the SLTAs. The MND Association funded three laptops and eight headsets to ensure the ABUHB SLT team can offer timely support to patients and subsequently support access to voice banking

How has the voice banking education sessions been implemented?

- We have developed a good working relationship with Stephanie Durnan, MND care coordinator. Stephanie promptly informs the SLT department of all newly diagnosed MND patients as candidates for voice banking.
- The patients are seen by a SLT for assessment and informed of the voice banking group sessions.
- The groups are bi-monthly basis across ABUHB.
- Since July four groups have been offered, comprising of twelve patients in total. All twelve patients referred to the SLT department have gone on to attend the group sessions offered. Five patients are continuing to utilise ABUHB equipment and SLTA support to complete the voice banking process. The other seven patients are completing this in their own home.

"Last night I received notification that my voice package had been built….I spent a happy couple of hours downloading it … and playing with it into the small hours of the morning. I think it's great."

"I found it very therapeutic actually recording my voice. Every day, 10am, coffee and biscuits shutting myself in my study for an hour a day for 10 days."

Acknowledgements: We would like to thank all the patients for taking part in these education groups. We would also like to that the MND association for funding the equipment required to complete these education groups. The authors declare no conflicts of interest

CW-28 Bringing Voice Banking to Dorset - lessons in time, timing & technology

Sharon C Owens

Dorset healthcare NHS university foundation trust, Bournemouth, Dorset, United Kingdom

Email address for correspondence: owenstk1@btinternet.com

Keywords: voice-banking, speech & Language therapy, AAC

Background: It is now possible to 'Bank' the sound of your own voice and later retrieve & use a synthesised version via AAC devices. Speech & Language Therapists are the specialist professionals who support people to select & get best use from these devices but often meet them too late to enable the banking process as the voice has already started to deteriorate by the time of referral. A pilot project is underway in Dorset UK allowing SALTs to work with people much earlier in their journey.

Objectives: To explore the requirements needed to establish a longterm, equitable, Community Speech

& Language Therapy-supported Voice Banking service for all local people diagnosed with MND who are able & willing to do so including at the point of diagnosis.

Methods: The local branch of the MNDAssociation gave a setup grant which allowed a Project Lead SALT to organise a training programme for 10 therapists & assistants. Each participant banked their own voice & contributed to the creation of a local 'How To Do It' Guide. Information & awareness leaflets plus VB-referral forms were distributed amongst the 3 multi-agency MND-MDTs plus to the local MNDA support forums.

An ongoing (currently 12 month limited: Nov 2017-Oct 2018) grant is backfilling all the hours used by staff to support plwMND to Voice Bank plus to explore the appropriacy & possibility of longterm provision of this service within the local NHS SALT service.

Results: At 6 months (May 2018) Early SALT-supported Voice Banking is possible & is well received by the SALT service, plwMND, their families, local MNDAssociation plus MDT colleagues. 9 plwMND have banked their voices with some immediately downloaded for use. More have participated in the project but not banked for a variety of reasons. The reasons, feedback & outcomes are being collated & lessons being learned.

Discussion and conclusions: Timing, time & technology appear to be the greatest challenges to successful Voice Banking. Early relationships between SALT & plwMND are being established. MDT understanding of communication change is being enhanced. There is widespread support & enthusiasm from all project particpants. The project will work with NHS providers to explore longterm options.

Acknowledgements: Thanks to: East Dorset & New Forest Branch of the MNDA for their funding of the project, Richard Cave of National MNDA for his teaching & technological expertise, Dorset HealthCare NHS University Foundation Trust for their understanding of the importance of early intervention.

References

Esther Nathanson (2017) Disability & Rehabilitation 39:1, 73-81.

CW-29 Identifying features of dysarthria as acoustic biomarkers for ALS using a tablet based speech analysis system

Julie A Stierwalt[1], Sandra L Schneider[2], Christian Poellabauer[2], Louis Daudet[2]

[1]Mayo Clinic, Rochester, MN, USA, [2]University of Notre Dame, Notre Dame, IN, USA

Email address for correspondence: stierwalt.julie@mayo.edu

Keywords: bulbar symptoms, dysarthria, differential diagnosis

Background: Speech symptoms often herald the disease in bulbar ALS, therefore, accurate diagnosis of dysarthria is critical to avoid the extended time and multiple evaluations that often precede an ALS diagnosis. Consequently, it is imperative that speech-language pathologists (SLPs) are knowledgeable and have the training and skill in the perceptual analysis of features which characterize the classic upper and/or lower motor neuron involvement [1]. To address this need, an interprofessional collaborative team consisting of engineers, software developers, and SLPs have developed a tool that integrates the perceptual method of assessment of dysarthria in a mobile device. This device captures speech samples, from which objective acoustic measurements can be derived. These samples are stored in a cloud based repository, thus, as their numbers grow more definitive patterns across dysarthria types and clinical populations emerge. These patterns will be reflected in machine learning algorithms that can be relayed through the device back to clinicians to further enhance their

diagnostic skill and offer confirmatory evidence for diagnosis.

Objectives: To analyze speech samples for the differential diagnosis of the dysarthrias, thus, identify acoustic biomarkers unique to bulbar ALS.

Methods: To examine speech features specific to dysarthria, our tablet-based software product includes 11 speech tasks based on the Mayo model MSD assessment protocol. We analyze those acoustic metrics that are most prevalent and significant to dysarthria types using statistical analysis and machine learning algorithms. In addition to mapping acoustic features to the metrics, a patient history and oral motor examination are included in the software product to address the potential for confirmatory clinical signs SLPs collect to assist with an accurate diagnosis (e.g., fasciculations, symmetry, abnormal movements, etc.).

Speech data from 75 individuals with confirmed dysarthria (25 with ALS), and 40 healthy controls have been collected with analysis currently underway. For comparison purposes, experienced SLPs (with an average of 10+ years' experience in healthcare) have been asked to identify the type of dysarthria and the speech features present.

Results: Shared at the conference.
1) Results of perceptual judgments versus objective measures with current data from the ALS population.
2) Features of dysarthria unique to ALS from samples from the cloud based repository which will allow us to refine speech analysis algorithms for specific clinical populations.

Discussion and conclusions: Our interprofessional collaborative team has developed a tool designed to identify speech characteristics which may serve as acoustic biomarkers of disease in bulbar ALS. Such a tool could assist with earlier identification, thus, offer individuals with ALS and their families access to education and resources for the management of their symptoms.

Acknowledgements: This work was partially funded by the National Science Foundation, grant IIS-1450349.

References

Green J, Yunsova Y, Juruvilla, M et al Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2013; 14:7-8, 494-500.

CW-30 Exploring Voice Measures to Track Disease Onset and Progression in Amyotrophic Lateral Sclerosis (ALS)

Jordan Green[1], Kathryn Connaghan[2], Yana Yunusova[3], Kaila Stipancic[4], Sarah Gutz[5], James Berry[6]

[1]Department of Communication MGH Institute of Health Professions Sciences & Disorders, Boston, MA, USA, [2]Department of Communication Sciences & Disorders, MGH Institute of Health Professions, Boston, MA, USA, [3]Department of Speech-Language Pathology, University of Toronto, Toronto, Canada, [4]MGH Institute of Health Professions, Boston, USA, [5]Harvard University, Cambridge, MA, USA, [6]Massachusetts General Hospital, Boston, MA, USA

Email address for correspondence: kconnaghan@mghihp.edu

Keywords: voice, speech, acoustics

Background: Voice changes are often reported as early symptoms of ALS. Perceptual vocal quality changes include increased breathiness, harshness, and tremor. Acoustic analyses reveal frequency and amplitude perturbations (jitter, shimmer), and altered fundamental frequency (F_0) and F_0 range [1]. Despite the identification of phonatory differences in ALS, their clinical utility has been limited by the variability in their presentation across individuals and the lack of correspondence between acoustic measure and perceptual changes. Novel measures conducted across the connected speech signal, such as

Cepstral Peak Prominence (CPP) [2] and CPPS [3], are potentially more sensitive in identifying vocal changes, can better reflect the underlying pathophysiology, and demonstrate stronger associations with perceptual ratings [4-5].

Objectives: The current investigation seeks to further explicate vocal dysfunction and change in ALS by exploring promising acoustic phonatory measures. Specifically, we compare traditional and novel phonatory measures produced by individuals with and without ALS across disease progression.

Methods: Thirty-six adult speakers (n=12 per group) across three groups (ALS with and without bulbar symptom onset, and neurotypical controls) participated. Data were collected at three time-points within a one-year period. Participants were recorded producing a sustained vowel and connected speech. Data analysis is currently underway. Acoustic analyses include traditional phonatory measures extracted from vowel prolongations (F_0, F_0 range, jitter, shimmer) and newer measures of phonation across connected speech (e.g., CPP, CPPS). ROC curves will be used to compare the diagnostic accuracy of the different measures of phonation for identifying bulbar motor involvement. Multiple mixed-model Analyses of Variance will be conducted to compare the measures responsiveness to disease progression.

Results: Similar to previous work, we anticipate that groups will differ on the phonatory measures of F_0, F_0 range, jitter, and shimmer [1,6]. We also hypothesize that phonatory measures extracted from the speech signal measures (e.g., CPP, CPPS) will demonstrate greater diagnostic accuracy and responsiveness to change.

Discussion and conclusions: These findings will support the development of valid and reliable measures to mark disease onset and progression, thereby facilitating intervention and mitigating the devastating impact of ALS.

Acknowledgements: This research was supported by NIH-NIDCD grants R01DC009890 and R01DC013547.

References

1. Green JR, Yunusova Y, Kuruvilla MS *et al*. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(7-8):494-500.
2. Hillenbrand J, Cleveland, RA, Erickson, RL. Journal of Speech, Language & Hearing Research. 1994; 37;769-778.
3. Hillenbrand J, Houde, RA. Journal of Speech, Language & Hearing Research. 1996; 39;311-321.
4. Fraile R, & Godino-Llorente JI. Biomedical Signal Processing and Control. 2014; 14; 42-54.
5. Lowell SY, Colton RH, Kelley RT *et al*. Journal of Voice. 2011; 25(5); e223-e232.
6. Strand EA, Buder EH, Yorkston, KM *et al*. (1991). NCVS Status and Progress Report; 4; 151-167.

CW-31 Respiratory Management of Amyotrophic Lateral Sclerosis /Motor Neurone Disease patients attending the West of Scotland Long-Term Ventilation Unit (WoSLTVU)

Grace E Murphy[1], Joanne Payne[2], Alison Clarke[2], Dave Raeside[2], George Gorrie[2], Scott Davidson[2]

[1]Glasgow Royal Infirmary, GLASGOW, United Kingdom, [2]Queen Elizabeth University Hospital, GLASGOW, United Kingdom

Email address for correspondence: grace.murphy@nhs.net

Keywords: quality of life, NIV

Background: Motor Neurone Disease (MND) results in respiratory muscle weakness and progressive respiratory failure (RF). Survival and quality of life are both improved with Non-Invasive Ventilation (NIV) in patients with RF [1,2]. Respiratory management includes

assessment and monitoring of respiratory function to identify RF as well as cough assessment and management. A multidisciplinary team management approach is recommended [2].

Objectives: To evaluate current respiratory management of MND patients in the WoSLTVU.

Methods: A retrospective audit of patients referred to WosLTVU between 2013-2017 was performed. Data was collected from electronic records: age, sex, referral source, time to first review; presence or development of RF, capillary blood gas/transcutaneous carbon dioxide evaluation, NIV uptake and length of survival; cough assessment and physiotherapy referral; gastrostomy rates; anticipatory care planning, palliative care referral and recorded 'do not attempt resuscitation' rates.

Results: 188 patients were referred to LTVU; 60% were male and the median age was 64.7 years (range 35.7-86). 39% patients were bulbar subtype, with 39% on riluzole treatment. 90% of patients were referred from Neurology services.

53 patients had RF at first respiratory review and 39 further patients developed RF during follow-up (early referral). Median age was similar in patients at first review with or without RF (64.5 vs 64.7 years). Median time to first respiratory assessment from referral was 27 days for RF patients and 46 days without RF. Overall 78% of RF patients were commenced on NIV. NIV lengthened survival by 5 months. RF patients who declined NIV were older (73 vs 62 years). Early referral of non-RF patients was not seen to further improve survival. Uptake of NIV was similar between patients who presented in or subsequently developed RF. Average length of survival was 465 days in patients never developing RF and 429 days in NIV treated RF patients.

53% were referred to palliative care services and 60% had a DNAR in place. Cough assessment (clinical or peak cough flow) occurred in 63% of patients at first respiratory review. Physiotherapy referral for cough augmentation was made in 48%.

Preliminary results are presented. Further detailed results and full statistical analysis will be available.

Discussion and conclusions: Referrals to WoSLTVU continue to increase. The survival benefits of NIV appear to be confirmed in real life practice. Early referral does not clearly lead to increase survival. The impact of early involvement of physiotherapy and advance planning for these patients in context of larger MDT team, requires further assessment.

References

1. Bourke SC, Tomlinson M, Williams TL et al. Lancet Neurol 2006 Feb; 5(2):140-147.
2. National Institute for Health and Care Excellence (2016) Motor neurone disease: assessment and management.

CW-32 Optimising the management of ventilated patients with motor neurone disease through telemedicine via call centre: multidisciplinary team approach

Helen J Ashcroft[1], Hikari Ando[1], Carolyn A Young[2], Rob Halhead[3], Robert M Angus[1]

[1]Aintree University Hospital NHS Foundation Trust, Liverpool, United Kingdom, [2]The Walton Centre NHS Foundation Trust, Liverpool, United Kingdom, [3]Docobo Limited, Leatherhead, United Kingdom

Email address for correspondence: hikari.ando@nhs.net

Keywords: telemedicine, non-invasive ventilation, multidisciplinary team

Background: The National Institute for Health and Care Excellence (NICE) guideline recommends tailored approaches to people with MND. The

guideline highlights the importance of the multidisciplinary team (MDT) to address various symptoms. The management of people with MND, therefore, ought to accommodate different individual's needs whilst ensuring an effective communication amongst healthcare professionals for the optimum care.

It has been shown previously that phone call follow-up allows regular monitoring of symptom changes (1), and that review of patient-ventilator interaction (PVI) data may improve delivery of non-invasive ventilation (NIV) (2). Our objective is to examine whether optimisation of care for MND NIV users can be achieved through telemedicine, by combining symptom questions and physiological data (i.e. PVI and nocturnal oximetry).

A preparatory 6-month pilot study was conducted with 13 patients (median age=66yrs; median illness duration=14m), who were using NIV. The study showed that weekly telemedicine using a portable remote monitoring device, Careportal®, integrating the bespoke self-report symptom questions and oximetry, is effective in highlighting symptom changes allowing optimisation of ventilator support in terms of oxygen saturation levels and ventilation adequacy despite illness progression. 10 participants (77%) required interventions to optimise their care outside their existing hospital appointments, whilst three participants (23%) did not require any intervention. Subjective accounts further showed that these benefits were perceived by participants as empowering and effective in promoting their well-being.

Given the promising results from the preparatory study, we are now looking at the feasibility of taking this approach into routine practice. We propose using the Careportal® to facilitate communication of issues to the relevant clinician in the MND and ventilation teams allowing both proactive monitoring and a standard route for communicating. This could enhance and facilitate timely intervention by the relevant MDT and its members, who are based on more than one site.

In this work, we will evaluate the use of Careportal® through an intermediary call centre as a central point of contact to manage data generated through Careportal®. The call centre will monitor the data and report symptom changes to appropriate clinicians, who then decide if interventions are needed. All interventions will be logged on the database, making the information accessible to other involved clinicians. The aim of this work is to evaluate feasibility and impact of Tele-care via the call centre, for patients with MND. Mixed methods will be employed to evaluate the use of Careportal® for 6 months with 15 individuals with MND who are on NIV.

Acknowledgements: Funded by the Small Business Research Initiative.

References

1. Vitacca M, Comini L, Assoni G, et al. Disabil Rehabil Assist Technol. 2012;7:494-500.
2. Pinto A, Almeida JP, Pinto S, et al. J Neurol Neurosurg Psychiatry. 2010:81:1238-1242.

CW-33 Home-monitoring in ALS/MND care: Evaluation of a Tailored eHealth care process for personalized ALS/MND care

Remko M Van Eenennaam[1,2,3], Jochem Helleman[2,3,1], Anita Beelen[2,1,3], Esther T Kruitwagen-van Reenen[3,1], Willeke Kruithof[1,3], Marja Slappendel[3,1], Leonard H van den Berg[3,4], Anne Visser-Meily[1,3,2]

[1]Center of Excellence in Rehabilitation Medicine, Brain Center Rudolf Magnus, University Medical Center, Utrecht, Netherlands, [2]De Hoogstraat Rehabilitation, Utrecht, Netherlands, [3]ALS Centre, Utrecht, Netherlands, [4]Department of Neurology, Brain Center Rudolf Magnus, University Medical Center, Utrecht, Netherlands

Email address for correspondence: r.m.vaneenennaam@umcutrecht.nl

Keywords: personalized care, ehealth, self-monitoring

Background: eHealth has the potential to enrich standardized care and stimulates personalized care by optimizing the timing of care, patient participation and continuous exchange of information between patient and healthcare professional. For this reason a tailored eHealth care process was developed for ALS care. This new care process consists of an interactive eHealth application for self-monitoring, automated alerts, personalized feedback, and tailored ALS care.

Objectives: The aim of this study was to assess the feasibility of the tailored eHealth care process and to evaluate patients' experiences with the eHealth care process.

Methods: Patients diagnosed with ALS/PSMA, and referred to the multidisciplinary ALS care team of the academic hospital in Utrecht, were invited to use the tailored eHealth care process. Key features include 1) self-monitoring of well-being (single question "How are you today?"), body weight and functional impairment (ALSFRS-R), 2) alerting, and 3) nurse practitioner follow-up. Feasibility was assessed from adoption rate of eHealth care in newly diagnosed patients, and compliance of all users with 75% of agreed upon frequency of self-monitoring. Patients' experiences and satisfaction with the eHealth care process were assessed with an online questionnaire administered after 4 months participation and further explored through semi-structured interviews. Descriptive statistics were used for questionnaire data and content analysis was conducted on the transcribed interviews.

Results: Of 27 newly diagnosed patients with ALS/PSMA, 23 patients (85%) have adopted the eHealth care process as part of their usual care, three have not been approached (one due to nursing home residency, one having life expectancy < 6 months, one due to comorbid psychiatric disorder), and one declined participation. Compliance rates with self-monitoring were 68% for well-being, 84% for body weight, and 95% for functional status. Preliminary results from 19 users on satisfaction showed that 16 patients (84%) indicated that the eHealth care process increased their control over their care, 16 considered the eHealth of added value, all would recommend it to other patients and none consider the monitoring a burden. Themes that emerged from 12 interviews were: easy to use eHealth application; insight in and reflection on health and wellbeing; sense of reassurance resulting from continuous monitoring by the care team; flexible consultations based on needs and symptoms.

Discussion and conclusions: This eHealth care process is feasible with a high adoption rate and monitoring compliance at a minimal burden to the patient. Furthermore, the majority of patients perceived an increased control over their care. It also allows for a more flexible care based on patients' needs. Therefore, eHealth should be considered a useful addition to the usual care for patients with ALS/PSMA.

Acknowledgements: This study was funded by The Netherlands ALS Foundation (project ALS thuismeten & coachen).

CW-34 Case Report Elective withdrawal of Non-Invasive Ventilation in an MND patient at home – a partnership approach but only possible with experienced staff with the right skills

Beata J Le Bon

Phyllis Tuckwell Hospice Care, Farnham, United Kingdom

Email address for correspondence: beatalebon@gmail.com

Keywords: NIV, withdrawal, community

Background: Elective withdrawals of Non-Invasive Ventilation (NIV) in MND are undertaken as part of the management of advanced illness and stopping burdensome interventions. They can be also requested by more stable patients who withdraw their consent to be ventilated and to continue with life-prolonging measures.

Phyllis Tuckwell Hospice Care (PTHC) provides community specialist palliative care in SW Surrey and NE Hampshire. It includes a Hospice Care at Home team which provides nursing care. PTHC looks after approx. 70 MND patients at any time.

A 70 old MND patient requested to stop NIV due to perceived poor quality of life and to die at home. He was in Stable OACC Phase of Illness with Australia-modified Karnofsky Performance Status of 50% at the time of the request. He had full mental capacity and no bulbar symptoms. He timed the withdrawal with reaching a significant birthday and his favourite season.

Management: Extensive multi-disciplinary input was mobilised to:

- Develop a comprehensive management plan
- Obtain appropriate drugs and administration equipment
- Ensure co-ordinated arrival of the palliative medicine consultant, consultant physiotherapist, GP and the team of nurses remaining continuously at home including a Registered Nurse overnight
- Ensure availability of a counsellor to support the family and to debrief.

The local community nursing team struggled ethically with the case and felt unable to participate.

On the day of the withdrawal the request was confirmed by the patient. NIV settings were: IPAP 15cm H20/EPAP 4 cm H20.

The Withdrawal of Assisted Ventilation guidance by UK Association for Palliative Medicine was followed. A total of 25mg morphine and 30mg midazolam were administered s/c to achieve satisfactory sedation. NIV back up rate and later IPAP were incrementally reduced. NIV was subsequently stopped and the mask was removed.

As there were no sign of rapid deterioration within the next few hours a s/c pump was set up with morphine, midazolam and levomepromazine.

The night nurse took over care at 10pm. Further symptom control drugs were required overnight including glycopyrronium for secretions. The patient died peacefully the following morning.

Discussion: This successful elective withdrawal at home was possible due to meticulously co-ordinated multi-provider input on site for the first 24 hours.

Should the patient survive beyond that it would have very challenging to provide continuous nursing care at home beyond the first day.

The whole team found the experience extremely rewarding although withdrawal had unexpected emotional impact on some hospice nurses due to close prior relationship and rapid death in a relatively stable patient.

In hindsight – more than one nurse should have stayed with the patient overnight to provide mutual support. A second pump should have also been provided at home for use of the 4th drug (glycopyrronium).

CW-35 A Pocket Tool for those with ALS/MND seeking Urgent Medical Care

Patricia P Wilkinson

University of Virginia, Charlottesville, VA, USA, Med Inc, Charlottesville, VA, USA

Email address for correspondence: patriciaw@medinc.net

Keywords: practical, informative,

educational

Background: The tool was inspired by the frustration of patients seeking urgent medical care only to discover the medical staff knew little to nothing about motor neuron disease. Inappropriate treatment given often made things worse

Objectives: Patients, families and care providers have the tool readily available to share with Emergency Department staff in the care and treatment of those with neurodegenerative disease. Providing the laminated information card in different languages is also an objective.

Methods: Relevant information from slurred or absent speech, unstable gait and shortness of breath is provided on a wallet sized, laminated card. If/when medical staff is unfamiliar with the symptoms, what they may mean and what to do and what not to do; a card is presented with explanations and recommendations.

Results: The information has provided peace of mind for the ones carrying the card and has given them the ability to steer treatment in the right direction. Medical staff has expressed appreciation for the information.

Discussion and conclusions: The demand for the card has gone beyond those from the ALS clinic at the University of Virginia to states on the west coast. If it will provide help for those in other countries as well, I would like to facilitate making it available.

Acknowledgements: Outpatient Neurology at UVA and Med Inc, a respiratory equipment company provide funding for the cards to be made and will contribute to the posters.

References

Created by Patricia Wilkinson, Respiratory Therapist at the ALS Clinic, University of Virginia, Charlottesville VA, USA

CW-36 Development of a Motor Neurone Disease Patient Concerns Inventory (MND PCI) for identifying MND patients' main concerns in the outpatient clinic setting

Mary R O Brien[1], Jennifer Kirton[1], Emma Pearson[1], Suresh Chhetri[2], Simon Rogers[1]

[1]Edge Hill University, Ormskirk, United Kingdom, [2]Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom

Email address for correspondence: obrienm@edgehill.ac.uk

Keywords: patient concerns, outpatient, consultation

Background: The systematic nature of disabilities in MND leads to wide-ranging issues, including physical/functional well-being, treatment-related concerns, social care/social well-being, and psychological, emotional, and spiritual well-being which can impact on people living with MND (plwMND), which may not be immediately detected by specialists responsible for their care. Furthermore, healthcare professionals may not always appreciate which issues are of greatest concern to individual patients given MND's variable presentation and progression.

Numerous assessment tools have been utilised to assess disease progression or Quality of Life (QoL) [1] including ALSFRS-R [2], ALSSCN [3] and MND Social Withdrawal Scale [4] amongst others. QoL has been measured with disease specific [5] and generic tools, including SEIQoL-DW, SIP and SF-36 [6]. Perhaps the greatest limitation with these tools is patients' needs and concerns are not prospectively obtained, rather, they are perceived from poor results in key domains.

A possible solution is the Patient Concerns Inventory (PCI), a disease-specific item prompt list of potential concerns, a concept originally created for patients with head and neck cancer

[7], from which the patient selects the most relevant items to discuss during their consultation. This should ensure that the consultation addresses issues within multi-professional support of importance to the patient.

Development of the MND PCI will occur over four phases. We will report on the first two phases**:** 1. A literature review (e.g. patient reported outcome questionnaires and qualities studies used in MND) to identify issues of relevance to, and concerns of, people with MND. 2. Consultation with MND multi-disciplinary team members, via a Delphi survey, to identify, from the list generated from the literature review, items they feel should be included on the prompt list.

Information gleaned from 1&2 will be combined to generate a list of ~50 items. Further feedback will be sought on these items from specialists present at the ALS/MND Symposium before, in phase 3, the items are discussed with plwMND and carers in focus groups. The MND PCI, developed in phases 1-3, will be evaluated in phase 4 in a before and after pilot study in an MND Care & Research centre.

Acknowledgements: Funding: Lancashire Teaching Hospitals RCF

References

1.Mitchell, JD, O'Brien MR. J Neurol Neurosurg Psychiatry 2003; 74:287.
2. Cedarbaum JM, Stambler N, Malta E, et al. J Neurol Sci 1999;169:13–21
3. Oh J, Oh S-I, Kim JA. Palliative and Supportive Care, 2018;1 –6.
4. Rigby SA, Thornton E, Tedman F, et al. J Neurol Sci; 1999 169: 26–34
5. Jenkinson C, Norquist JM, Fitzpatrick R. J Neurol Neurosurg Psychiatry; 2003 2:242–245.
6. Neudert C, Wasner M, Borasio GD. JNeurolSci; 2001;191: 103–109.
7. Rogers, S.N., El-Sheikha, J. and Lowe, D., Oral Oncology 2009; 45, 555-561.

CW-37 Purpose of a Functional Hydration Scale on Motor Neuron Disease / Amyotrophic Lateral Sclerosis

Adriana L Oda[1,2,3], Luciana M Frabasile[1,2], Cristina C Salvioni[1,2,3], Percília C Alves[1,2], Rosana M Borges[1,2], Juliana W Neves[1,2], Helena N Sierra[1,2], Eduardo V Carvalho[1,2], Acary S Oliveira[1,2]

[1]Federal University of São Paulo, São Paulo, São Paulo, Brazil, [2]Brazilian Association of Amyotrophic Lateral Sclerosis, São Paulo, São Paulo, Brazil, [3]Neuroqualis, Clinical, Teaching and Research in Health and Educational Area Ltd., São Paulo, São Paulo, Brazil

Email address for correspondence: adrileico.oda@uol.com.br

Keywords: hydration, evaluation scale, dysphagia

Background: The hydration of the patient may be compromised by several factors, such as: dysphagia for liquids, inappetence, cognitive alterations, metabolic alterations, mechanical alterations and neuromotor changes, as is the case of Amyotrophic Lateral Sclerosis. Faced with so many variables, it becomes a challenge for the interdisciplinary team to verify if the amount of water ingested is adequate to the needs of the patient. There's a shortage of instruments in literature that assist in assessing the patient's hydration profile.

Objectives: To report on the development and psychometric evaluation of a clinical scale to document changes in functional hydration level.

Methods: Based on the clinical and speech-language evaluations performed in the Neuromuscular Disease Research Sector, the most common clinical situations were categorized in dysphagic patients, in order of frequency: reduction of fluid volume intake, changes in consistency, use of swallowing maneuvers, change of the utensil used. In cases in which there is a report of cognitive relegation or behavioral change, inappetence and

non-acceptance were the predominant items.

Results: The proposed scale presents ten levels, which vary according to the need of utensils adaptation, change of pace, control of the gulp and modification of consistency, as facilitating resources. It was also considered the presence of the alternative route of feeding, favoring a mixed or exclusive diet, since the oral route may or may not be sufficient to maintain the patient's hydration. The consistency changes foreseen in this scale were based on the IDDSI scale (International Dysphagia Diet Standardization Initiative). The literature recommends that an adult person needs 30 to 35 milliliters of water per pound of weight.

Discussion and conclusions: Dehydration can bring a number of intercurrences to the clinical picture of the patient. Dysphagia to liquids appears before the nutritional depletion; which reinforces the need for an instrument as an indicator for the risk of dehydration. The Functional Scale of Hydration Levels consists of a scale that is easy to apply to patients and can help the therapist to understand the dynamics related to the hydration theme and to define appropriate behaviors for each level presented, helping to prevent dehydration and contributing to an adequate nutritional status.

CW-38 Improving Outcomes in Feeding Tube Placement for ALS/MND patients using an Interdisciplinary, Collaborative Approach

Paula Brockenbrough, Rebecca Rhodes, Michelle Gebhardt, Amanda Butler, Kathleen Pearson, Scott Vota

Department of Neurology, Virginia Commonwealth University Health System, Richmond, VA, USA

Email address for correspondence: rebecca.rhodes@vcuhealth.org

Keywords: feeding tube placement, respiratory considerations, multidisciplinary

Background: ALS/MND patients have a combination of impairments that predispose them to malnutrition. Respiratory insufficiency, dysphagia, depression, hypermetabolism, fatigue, difficulty preparing meals, and self-feeding can contribute to decreased caloric intake. ALS/MND patients with malnutrition are at an increased risk for more rapid decline in their disease and adverse effects on quality of life [2].

The population reviewed consisted of patients in an academic hospital, interdisciplinary outpatient ALS/MND clinic in the United States. Nutritional status was assessed upon enrollment in our clinic and at subsequent visits. Education regarding nutrition in ALS/MND, the role of malnutrition in disease prognosis, and feeding tube placement timing were addressed at each visit. Several challenges were observed related to feeding tube placement and follow-up care. Barriers included delays in obtaining surgical times, respiratory complications exacerbated by inexperience with ALS/MND, insurance denials for enteral formula, unfamiliarity at outlying hospitals in non-invasive ventilation (NIV), and heightened patient/caregiver anxiety.

Objectives: To optimize the ALS/MND patient's nutritional status with a collaborative approach to feeding tube placement.

Methods: The interdisciplinary ALS/MND staff identified a dedicated surgeon from our institution and collaboratively devised a coordinated plan for pre-operative and post-operative care. An Anesthesiologist, with experience in motor neuron disease and the specific respiratory needs, was also identified as a crucial team member [1]. The surgeon and anesthesiologist met with patients and caregivers in a support group setting to provide a review of the feeding tube procedure, answered questions, and helped to decrease

patient/caregiver anxiety. Upright and supine respiratory mechanics and NIV usage and settings were documented electronically for in-hospital transition of care. Staff worked closely with a respiratory home health company for assistance with further education regarding the importance of NIV, secretion clearance techniques, and breath stacking. Additionally, a specialty infusion service completed pre/post feeding tube teaching and worked with insurance companies to mitigate enteral formula denials.

Results: This collaborative approach to feeding tube placement has achieved zero insurance denials for enteral formula and significantly reduced readmissions following placement. Time to feeding tube insertion has decreased.

Discussion and conclusions:
ALS/MND clinic teams should utilize a collaborative approach to feeding tube placement involving a dedicated surgeon, anesthesiologist, specialty infusion service, and home health company to improve overall care and outcomes related to feeding tube placement.

Acknowledgements: Funding for this study was provided in part by the Harper's Hope Fund. The authors declare no conflict of interest. Special thanks to our patients and families as well as the expertise of Dr. Stephanie Goldberg, MD, FACS and Dr. L. Robert Stallings, MD.

References

1. Prabhakar A, Owen CP, Kaye AD J Anesth 2013; 6: 909-918
2. Greenwood D Nutrition in Clinical Practice 2013; 3:392-399

CW-39 Development of the South Wales MND Care Network Gastrostomy Placement Guidance

Stephanie J Durnan[1], Idris Baker[2,3], Andrea Lowman[1], Joanne Bradburn[3], Elizabeth Green[4], Victoria Prendiville[4], Linda Morgan[4]

[1]Cardiff and Vale University Healthboard, Cardiff, United Kingdom, [2]Swansea University, Swansea, United Kingdom, [3]ABM UHB, Swansea, United Kingdom, [4]Hywel Dda University Health Board, Camarthen, United Kingdom

Email address for correspondence: stephanie.durnan@wales.nhs.uk

Keywords: gastrostomy, nutrition, medical decision making

Background: The Network's ethos is to support the development and delivery of equitable care for all people with MND (pwMND) in a 2.3m population, across five health boards, including urban centres with proximity to teaching hospitals and sparsely populated rural areas.

Gastrostomy is commonly considered in pwMND. The decision-making is sometimes urgent, but its placement and use is complicated by other features of the illness and practical considerations.

We knew of guidance that covered some aspects of decision-making on gastrostomy, but none specific to MND, that dealt with all the considerations and variations we encountered in practice.

Objectives: We identified a need for a guidance document applicable across our network.

Methods: To identify existing guidance we searched the MNDA website[1-5] and discussed with the British Dietetic Association neuro-specialist group. We didn't find perfect guidance elsewhere, so we have written new guidance.

We considered evidence from relevant studies including ProGas[6] and NICE guideline NG42[7] and Network experience. We identified clinical and practical considerations that should be covered.

We used an iterative process with several discussion cycles, in a multi-professional group from the wider network team and developed an initial

draft. Each cycle included detailed scrutiny and discussion of the developing content. Following several cycles, a final working draft was circulated to the Network Steering Group, allowing further discussion, until we reached consensus regarding content.

Results: We found no existing comprehensive MND-specific guidance. We now have a Network guidance document, adopted by each team. It includes a feedback mechanism to the core team and a review date at one year

Discussion and conclusions: We identified themes including implications for palliative care, capacity, consent, practical considerations and barriers. We also considered the question of balance: how to give enough detail for the guidance to be useful in supporting equity without introducing unnecessary constraints in local application? What kinds of variation are acceptable? We will discuss these themes in the presentation.

Acknowledgements: South Wales MND Care Network, MND Association

References

1. Leeds Centre for Neurosciences (2015) Leeds MND PEG Pathway https://www.mndassociation.org/forprofessionals/mndmanagement/best-practice-guidelines-and-pathways/care-pathway-and-clinical-guideline-examples/#Nutrition accessed June 2017
2. Middlesbrough MND Care Centre (2014) Assessment for gastrostomy tube placement in MND patients https://www.mndassociation.org/forprofessionals/mndmanagement/best-practice-guidelines-and-pathways/care-pathway-and-clinical-guideline-examples/#Nutritionaccessed June 2017
3. Oxford care and research centre (2012) Gastrostomy placement risk assessment for patients with potential respiratory muscle weakness https://www.mndassociation.org/forprofessionals/mndmanagement/best-practice-guidelines-and-pathways/care-pathway-and-clinical-guideline-examples/#Nutritionaccessed June 2017
4. MND Care Centre Southampton (2011) Nutrition Care Pathway for People Living with MND in Dorset https://www.mndassociation.org/?s=gastrostomyhttps://www.mndassociation.org/forprofessionals/mndmanagement/best-practice-guidelines-and-pathways/care-pathway-and-clinical-guideline-examples/#Nutritionaccessed June 2017
5. Leicestershire and Rutland MND Supportive and Palliative Care Group (2011) Enteral Feeding Referral Pathway for Patients with MND https://www.mndassociation.org/forprofessionals/mndmanagement/best-practice-guidelines-and-pathways/care-pathway-and-clinical-guideline-examples/#Nutrition accessed June 2017
6. National Institute for Health & Care Excellence. Motor neurone disease: assessment and management (NG42). London: NICE (2016)
7. ProGas Study Group†. Lancet Neurology 2015; 14:702-709

CW-40 Exploring the effectiveness of communicating wellbeing and quality of life information in Motor Neurone Disease to multidisciplinary teams

Gillian Medley[1], Clarissa Giebel[2,3], Maria Thornton[1], Michelle Ennis[1], Sandra Smith[4], Paula Sutton[4], Moira Furlong[4], Carolyn A Young[1]

[1]The Walton Centre for Neurology and Neurosurgery NHS Foundation Trust, Liverpool, United Kingdom, [2]Liverpool University, Liverpool, United Kingdom, [3]NIHR CLAHRC NWC, Liverpool, United Kingdom, [4]Motor Neurone Disease Association, Liverpool, United Kingdom

Email address for correspondence: gillianmedley@gmail.com

Keywords: quality of life, multidisciplinary teams, TONiC

Background: Increasing evidence shows that services for people with Motor Neurone Disease (MND) need to address strategies to enhance psychological and social care in addition to physical needs (1).

Objectives: This project aims to educate staff about the importance of psychological and social wellbeing in Quality of Life (QoL) to people with MND, joining these with recent findings of the Trajectories of Outcome in Neurological Conditions (TONiC) research (2) via a one-off workshop.

Methods: A mix of clinical healthcare professionals working with people with MND were recruited via a snowball technique. The workshop included talks about MND and QoL, and the link to health inequalities. After the talks, staff were divided into four groups moving between different topics for discussion (awareness and knowledge of MND; skills and practicalities in MND; acceptance of beliefs and motivation for change in MND; health inequalities). The group work was arranged in a world café approach, whereby each group added information to the previous group. Participants were asked to complete a pre-workshop questionnaire to assess baseline knowledge on QoL, followed up with a post-workshop questionnaire two weeks later and a 10-minute telephone interview after a further two weeks.

Results: Nineteen people attended the workshop, including dieticians, physiotherapists, psychologists, occupational therapists, and speech and language therapists. Clinicians had a high degree of experience with MND (mean 12.5 years), and expressed a diverse range of interests in MND issues, primarily involving physical care and supporting people with MND and their families. When focusing on QoL, holistic and cohesive work was emphasised. The TONiC study was well known to the majority of attendees (53%). Two people were aware of outcomes to date and outlined how TONiC findings apply to their practice.

Discussion and conclusions: The next step is to compare these views with data from the post-workshop questionnaire and interviews, to understand how TONiC findings can be implemented. The lack of acknowledgement of social issues in the MND team interests, and importance to QoL, may need to be addressed in practice.

Acknowledgements: This work is part-funded by NIHR CLAHRC NWC. The views expressed here are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

References

1. Van Groenestijn AC et al. Health and Quality of Life Outcomes 2016; 14:107.
2. Young CA et al. Amyotrophic Sclerosis & Frontotemporal Degeneration 2016;17(S1):26.

CW-41 Motor Neurone Disease: supporting people to die at home in Lancashire and South Cumbria

Maddy A Bass[1], Philomena Swarbrick[1], Pauline Callagher[2]

[1]St Johns Hospice, Lancaster, United Kingdom, [2]Lancashire and South Cumbria Care Centre, Preston, United Kingdom

Email address for correspondence: maddy.bass@sjhospice.org.uk

Keywords: preventing hospital admission

Background: In 2016, twenty people with Motor Neurone Disease (MND) in the Lancashire and South Cumbria region were admitted and died in hospital.

Following a meeting in early 2016 with the MND Association, the local Hospices were approached to consider how the MND ice bucket challenge money could

be utilised for future MND patient support.

Objectives: From this, local MND Association and Care Centre staff met with St Johns Hospice staff to look at how the Hospice could support MND patients through our already existing services.

Methods: The group looked at the gaps in services and staff knowledge, what causes a crisis leading to hospital admission, and what skills are required to keep people with MND at home, if that is their preferred place of care and death. The main issues often leading to admission were documenting and managing advance care planning; supporting cognitive impairment difficulties; and supporting family carers using practical skills such as taking blood gases, managing non-invasive ventilation (NIV) and using cough assist devices.

Results: For family support and education, the Hospice day services team set up a "STAR" group (Support, Time-out, Advice, Recovery: named by the attendees) for people with MND and their main carer. This addressed advance care planning; hospice services and what they can provide; support to carers; nutrition, and speech and language advice. This would run weekly, following on from the quarterly MND clinics, for 4 weeks.

The team also set up a successful MND study day for professionals, which was well evaluated and covered diagnosis, prognosis, and symptom management. The Hospice at Home and ward teams are presently being developed in the practical skills listed above, in order to support people to stay in their own homes when near end of life.

Discussion and conclusions: It is clear that the support of people with MND at home is important in order to prevent inappropriate hospital admission. Community services can be upskilled to support this.

CW-42 Developing the optimum clinical skill mix for the care of people with motor neurone disease

Jo Joyce

LOROS Hospice, Leicester, United Kingdom

Email address for correspondence: jojoyce@loros.co.uk

Keywords: skill mix, effectiveness

Background: In 2014 LOROS Hospice motor neurone disease (MND) nurse specialist team comprised of one 0.5 whole time equivelant (wte) band 7 and one 0.9 wte band 6. Gradually over years prior to that the caseload which covers Leicester, Leicestershire and Rutland had risen from 45 to 76 people.

Managing this number of patients with complex needs was felt to be unsustainable and posed the risk the high-quality level of service provided would be compromised. Succession planning was also a consideration.

The MNDA funded this two year project to develop the optimum skill mix for the care and support of pwMND.

Objectives: to continue to develop the LOROS MND MDT service offered and provide support to the MND nurse specialists and wider team by recruiting and developing one full time(wte) assistant practitioner (AP) band 4 post and one staff nurse band 5 post for one day per week to assess the effectiveness of interventions of a different skill mix (1).

Methods: AP worked along side and under direct supervision of the MND nurse specialists and multidisciplinery team, patients were triaged using integrated palliative outcome scale(IPOS). AP supported less complex or more stable patients, AP undertook less specialist tasks eg demonstrating suction unts/nebulisers, staff nurse shadowed MND nurses and took on similar tasks as the AP. Interviews were

held with staff, patients and carers to evaluate project at intervals (1).

Results: AP role did not add sufficient value to the service in comparison to other possible models and potentially added some risks for patients and an additional burden for the Nurse Specialists. The Band 5 role proved more valuable, especially in fostering a potential succession plan for the experienced Bands 6 & 7 Nurse Specialists. Significant challenges faced in delivering the project both from an operational and managerial perspective (1).

Discussion and conclusions: Service now comprises two band 6 MND nurse Specialists equivalent to 1.9 WTE. Elements of the AP role could be designated to admin staff. AP role could develop in the area of OT assistant. The limitations of the AP role are significant and given limited resources the inclusion only of team members with a broader capability is seen by most as more optimal. It is hoped that this project has provided valuable information that can be utilised by other services in relation to developing a skill mix approach in the care provision of patients with MND (1).

Acknowledgements: Thanks go to the Motor Neurone Disease Association for funding the project.

References

1. Developing the optimum skill mix for the care of people with Motor Neurone Disease. A two-year project funded by MND Association, Mandy Mitchell; Head of day care and community services , Professor Christina Faull; Consultant in Palliative Care, Jo Kavanagh Director of Care.

CW-43 The Challenges of Addressing the Needs of Family Carers across South Wales.

Caroline Bidder[1], Ruth Glew[1], Carol Smith[2]

[1]South Wales MND Care Network, Swansea, United Kingdom, [2]MND Association, Northampton, United Kingdom

Email address for correspondence: ruth.glew@wales.nhs.uk

Keywords: carers, support, audit

Background: Supporting carers in MND is a key objective for the South Wales MND Care Network (SWMNDCN). The challenge for the Network team is to achieve this across 5 local Health boards with different demography, local service structures and geography. This demands a creative approach and consideration of several options.

Objectives: 1) To scope carers' needs, including psychological support across the Network area. 2) To identify potential sources of support across the network area. 3) To identify gaps in provision and explore ways to fill these. 4) To pilot identified solutions.

Methods: To identify family carer need, an audit was carried out via questionnaire at the 12 MND MDT clinics across South Wales (September – December 2017) and by post for those not able to attend clinic. We also carried out face to face discussion with carers at clinic to identify their ongoing needs and how they wish to be supported. This included how the clinic appointment itself can be tailored to include time and space for the carer to liaise with the team away from the patient if they wished. Care co-ordinators scoped third sector support for carers available across their areas and thus identified gaps where there was limited provision. With this information we were then able consider what interventions may be helpful and went on to pilot two solutions.

Results: The audit showed that carers preferred informal support and each area of support listed on the questionnaire was scored as highly relevant. Local databases of services provided by third sector agencies in each Health Board area have been set up. We

have established good links with agencies such as the Alzheimer's Society and Carers' Centres across the network area. Whilst these provide a very useful service they do not directly or specifically address the complex nature of MND or offer mutual support. Where gaps have been identified we have piloted 2 solutions at the current time: 1) An education programme in association with Education Programme for Patients (EPP) – which enables patients and carers to have separate sessions. 2) A carers support group – held in Swansea and attended by a small number of carers. Feedback has been very positive in terms of providing a safe arena to air feelings and obtain information.

Discussion and conclusions:
The two pilot interventions have yielded positive feedback, however, it is difficult to provide such services with limited resources within the SWMNDCN. By continuing our work with the MND Association and other third sector organisations we hope to jointly develop further interventions that meet the needs of MND carers in South Wales and correspond to the SWMNDCN aims of equity of access and equality of care across South Wales.

Acknowledgements: Carers who completed the questionnaire and attended groups

CW-44 'Many hands make light work' - the success of the South Wales MND Care Network Multidisciplinary Team days

Ruth Glew[1], Katie Gibbon[2], Caroline Bidder[1], Sara Mallams[1], Alice Richards[3], Richard Pawsey[4], Stephanie Durnan[5], Idris Baker[4]

[1]South Wales MND Care Network, Swansea, United Kingdom, [2]South Wales MND Care Network, Cardiff, United Kingdom, [3]Cardiff and Vales University Health Board, Cardiff, United Kingdom, [4]Abertawe Bro Morgannwg University Health Board, Swansea, United Kingdom, [5]Cardiff and Vale University Health Board, Cardiff, United Kingdom

Email address for correspondence: ruth.glew@wales.nhs.uk

Keywords: MDT working, service development, engagement of professionals

Background: The South Wales MND Care Network (SWMNDCN) has established 12 Multi-disciplinary team (MDT) clinics across South Wales with input from local clinicians and therapists. The aim of the SWMNDCN is equity of access to and equality of care for people with MND (pwMND). The challenge for the Network team has been to achieve this across 12 clinics involving over 90 professionals taking into account differences in demography, local service structure and geography.

Objectives: To achieve standardisation of practice and team development across all MDT clinics in South Wales by engaging MDT members in delivering, developing and maintaining the service offered to pwMND.

Methods: All MDT members are invited to attend a free annual MDT day. The aims of this day are to promote networking and good practice, and to thank professionals for their commitment to the work of the SWMNDCN.

Aims 2016:
- promotion of networking between professionals across South Wales.
- development of professional groups to take forward service development and standardised practice.
- clinic group time to consider good practice, areas where improvement is required and development of action plans and to focus improvements to be achieved over the following year

Aims 2017
- Promotion of networking, taking forward developments in professional groups.
- Transforming care audit results.

- Celebration of work done by MDT members in short presentation format.
- Self care (presentation from psychologist).

Both days encompass educational components in terms of discussion of network care pathways, research and MND Association updates.

Results: Physiotherapy, Occupational therapy, Dietetic, Speech and language therapy, Respiratory and Neurology/Palliative Medicine Consultant working groups have been established. Therapy groups maintain contact throughout the year via e-mail, working on standardising assessment within clinic and providing useful information and support. Care pathways have been developed for respiratory assessment and enteral feeding. Enabling professionals to have time out to discuss care has resulted in improved interest, enthusiasm and motivation, which has had a positive impact on care. By involving all MDT members, progress in terms of meeting the SWMNDCN objectives and developing the service has excelled as many professionals are prepared to invest time in improving services. Professionals feel more supported by the SWMNDCN and also by each other. Feedback from participants attending these 2 days has been exceptional.

Discussion and conclusions: Whilst this method of working is essential as part of a Network approach to care, the introduction of days such as this in other service models could be extremely valuable in promoting helpful links, engagement and improvements in service provision. We plan to hold annual MDT days to continue to improve care provision, to support professionals providing care to pwMND and to celebrate progress across the SWMNDCN.

Acknowledgements: Team members of all 12 clinic MDT's in South Wales, MND Association for part funding.