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Biomedical Work in Progress

Clinical Work in Progress

Care Practice

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THEME BW: BIOMEDICAL WORK IN PROGRESS

BW1 MULTICENTER DATA COLLECTION FOR ASSESSING THE NATURAL HISTORY OF ALS

ARCILA-LONDONO X[1], VADER P[2], WALK D[2], SHERMAN A[3]

[1]Henry Ford Hospital, Detroit, MI, USA, [2]Massachusetts General Hospital, Boston MA, USA, [3]University of Minnesota, Minneapolis MN, USA

Email address for correspondence: walkx001@umn.edu

Keywords: natural history, epidemiology, disease progression

Background: Information on the natural history of ALS has, to date, been based largely upon data from clinical trials, which under-represent people with ALS (PALS) with advanced disease, rapidly progressive disease, or other demographic characteristics that may be associated with a lower likelihood of participation in clinical trials. Several currently recruiting registry efforts, while representing an improvement, also either rely on self-selection by PALS or have limited capacity to ensure enrollment by a broad representation of the population of people with ALS and related motor neuron disorders.

More comprehensive natural history data collection requires broad enrollment of PALS within participating clinics. Insofar as data collection via electronic health records and universal utilization of some outcome measures, such as ALSFRS-R, respiratory parameters, and major disease milestones, are in general use, it is becoming practical to collect de-identified natural history data from a large proportion of PALS utilizing widespread consenting and data capture within the clinical context.

Aims, Method and Discussion: The ALS Natural History protocol functions as a proof-of-principle study that basic demographic and longitudinal clinical data from most PALS in participating clinics can be obtained in this fashion. The study will form a platform providing longitudinal clinical data as an anchor for subsequent studies collecting biofluids and imaging data. Phenotyping of an inclusive cohort of PALS will be substantially accelerated by the presence of a mechanism to collect and store clinical and biological data on large numbers of patients with a low cost of entry for interested investigators and minimal inconvenience for people with ALS.

The ALS Natural History protocol captures basic demographic and clinical information readily available in essentially all cases, such as age and site of onset, ALS phenotype, distribution of upper and lower motor neuron findings, military veteran status, and limited laboratory findings. Initial and longitudinal ALSFRS-R, ventilatory parameters, and major disease milestones are captured as well. De-identified data can be obtained retrospectively or prospectively with consent and transferred to NeuroBank via several electronic mechanisms with appropriate data transfer agreements in place. Participating centers then have the ability to query the aggregate data with research questions or can compare aggregate data with those from their site, if indicated, for quality assurance or outcomes queries.

Because of the clinical similarity and overlap between ALS and other motor neuron disorders, patients presenting with PLS, PMA, and progressive bulbar palsy are also eligible for inclusion in this protocol.

Several emerging projects of deep phenotyping or genotyping are also collecting aggregate and longitudinal data from selected centers. The ALS Natural History project is intended to supplement such efforts by providing a broad, rather than deep, data sharing opportunity for all interested ALS clinics with research questions regarding the natural history of ALS.

BW2 PATTERNS OF DISEASE PROGRESSION IN SOD1 FAMILIAL MOTOR NEURON DISEASE: A RETROSPECTIVE STUDY OF 42 PATIENTS WITH LONG-TERM FOLLOW-UP

PAVLAKIS P[1], SHAHBAZI M[1], THOMAN A[1], BIN BIN F[1], SILANI V[2], LUDOLPH AC[3], AJROUD-DRISS S[4], MARKLUND S[5], APPEL S[6], ANDERSEN P[7], LANGE D[1]

[1]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, USA, [2]Istituto Auxologico Italiano, Milan, Italy, [3]University of Ulm, Ulm, Germany, [4]Northwestern University, Chicago, Il, USA, [5]Umea University, Umea, Sweden, [6]Houston Methodist Hospital, Houston, TX, USA, [7]Lund University, Lund, Sweden

Email address for correspondence: pavlakisp@hss.edu

Keywords: SOD1, familial motor neuron disease, disease progression

Background: SOD1 mutations are a frequent cause of familial motor neuron disease (MND) (1). Although it is assumed that patients with familial MND experience progression of disease similar to sporadic MND, there are no studies that follow long term clinical progression detailing site of onset, mode of progression and speed of progression to determine if progression is similar to sporadic MND, and if there are mutation specific patterns of progression.

Objectives: To describe the clinical features and disease course of patients with SOD1-associated MND, and compare them with sporadic disease.

Methods: Pooled data identified 47 patients with SOD1 mediated MND from two clinical trials (2, 3), studying the effect of pyrimethamine to reduce SOD1 levels in blood (study 1) and cerebrospinal fluid (study 2). Each patient had serial Appel ALS and ALSFRSr studies over a 9 month period. Data was analyzed retrospectively and all patients were receiving pyrimethamine.

Results: We reviewed the clinical data and disease course of 42 SOD1-associated familial MND patients. The most frequent mutation encountered was A4V in 12.8% of patients, followed by D90A in 8.5%, and E100G, L144F and G93S in 6.4% each. An initial review of 32 patients, the median age was 55 years, 16 men and 16 women. Among those patients, the presenting symptom was leg weakness in 62.5%, arm weakness in 25%, and bulbar weakness in 12.5%. Median age of symptom onset was 47.7 years (range 18.0-66.5). Median Appel and ALSFRSr scores at the beginning of the study were 59 and 38 (range 34-115 and 18-48) respectively. Median time of progression from first to second spinal segment was 17 months (range 5-37). Symptoms spread horizontally, from first affected limb to contralateral limb in 17 patients, vertically from upper to lower/ lower to upper ipsilateral limb in 7 patients, and remained confined in one limb in 3 patients for the duration of the study.

Discussion and conclusions: This is the first study in which the clinical characteristics, disease course and mode of progression will be analyzed and categorized, according to mutation and speed of progression relative to sporadic disease.

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Acknowledgements: Muscular Dystrophy Association

BW3 THE ICEBUCKET CHALLENGE SPORADIC ALS AUSTRALIA SYSTEMS GENOMICS CONSORTIUM: SALSA-SGC

HENDERS AK[1], HENDERSON R[2], ZIAIMATIN H[1], NGO S[3,18], GARTON F[1], BENYAMIN B[1], AL-CHALABI A[4], EDIS R[5], KIERNAN M[6], LAING N[7], LAMONT P[8], MATHERS S[9], NEEDHAM M[10], NICHOLSON G[11], PAMPHLETT R[12], ROWE D[13], SCHULTZ D[14], TALMAN P[15], VELDINK J[16], VAN DEN BERG L[16], VISSCHER PM[1], VUCIC S[17], WILLIAMS K[13], ZHAO Q[1], MCCOMBE P[18], BLAIR IP[13], WRAY NR[1]

[1]Queensland Brain Institute, The University of Queensland, St Lucia, Australia, [2]Department of Neurology, Royal Brisbane and Women's Hospital, Brisbane, Australia, [3]School of Biomedical Sciences, The University of Queensland, Brisbane, Australia, [4]Department of Basic and Clinical Neuroscience, King's College London, London, UK, [5]Sir Charles Gairdner Hospital, Nedlands, Perth, Australia, [6]Brain and Mind Research Institute, University of Sydney, Sydney, Australia, [7]Centre for Medical Research, The University of Western Australia and the Harry Perkins Institute of Medical Research, QEII Medical Centre, Nedlands, Western Australia, Australia, [8]Department of Diagnostic Genomics, Neurogenetics Laboratory, QEII Medical Centre, Nedlands, Australia, [9]Neurology Department, Calvary Health Care Bethlehem, Melbourne, Australia, [10]Western Australian Neurosciences Research Institute (WANRI), University of Western Australia and Murdoch University, Fiona Stanley Hospital, Perth, Australia, [11]ANZAC Research Institute, Concord Hospital, University of Sydney, Sydney, Australia., [12]The Stacey MND Laboratory, Department of Pathology, The University of Sydney, Sydney, Australia, [13]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia., [14]Flinders Medical Centre, Adelaide, Australia, [15]Geelong Hospital, Geelong, Australia, [16]Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands, [17]Western Clinical School, University of Sydney, Sydney, Australia, [18]UQ Centre for Clinical Research, The University of Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia

Email address for correspondence: naomi.wray@uq.edu.au

Keywords: genomics, consortium, Australia

Background: Although the biological basis of sporadic ALS remains poorly understood, progress to date has been driven, almost entirely, by a series of genetic discoveries in familial ALS that have implicated molecular pathways underlying the disease. Identification of new genomic risk factors will accelerate progress in disease mechanisms, diagnostics and treatments. Advances in the ability to measure non-genetic factors influencing ALS including epigenetic modifications of DNA, together with genetic sequencing of large, well characterised data holds significant promise for the advancement of our understanding of the etiology of onset and progression of ALS.

Objectives: Experience from other complex genetic disorder studies has demonstrated the power of large, deeply phenotyped cohorts collected under consistent protocols. Currently, only about half those diagnosed with sporadic ALS in Australia have the opportunity to participate in research. Therefore, we have established the Sporadic ALS Australia Systems Genomics Consortium: SALSA-SGC. The short-term objectives are to share and harmonise protocols for optimised collection of phenotypic data and biological samples collected in ALS research clinics across Australia. The long-term aims are to generate genetic and genomic data to contribute to identify DNA variants and modifications associated with ALS and disease progression.

Methods: We evaluated the data collection protocols of many ALS studies conducted internationally. We consulted with clinicians around Australia and have developed a secure on-line data collection tool to record demographic and clinical variables at all clinic visits. We have developed standardised protocols for ethics and consent forms, and also for collection and processing of biological samples.

Results: The on-line data collection platform has been rolled out across Australia alongside on-site and central training of research nurses. Research protocol evaluation has highlighted the importance of consistent methodologies. The training and involvement of clinic staff in data collection has provided an important sense of national identity that conveys to new participants the importance of contributing to a genomics research program.

Discussion and conclusions: The consortium hopes to ensure that the majority of people attending ALS clinics in Australia have the opportunity to participate in research to identify genetic and genomic risk factors for ALS. The implementation of consistent protocols should benefit a broad range of clinical research activities. Importantly, each site retains primary guardianship of the data collected at each site, and research conducted on the collected data requires further agreements. We are willing to share our protocols and online data collection platform, and we seek collaborations for future genomics studies.

Acknowledgements: The generous contributions of many Australians in the 2014 Ice Bucket Challenge, awarded to SALSA-SGC through the Motor Neurone Disease Research Institute of Australia (MNDRIA). The participating ALS clinics across Australia and support from the Australian National Health and Medical Research Council.

BW4 ASSESSMENT OF VARIANT CALLERS ON WHOLE-GENOME SEQUENCE AND MISEQ DATA OF ALS PATIENTS

IACOANGELI A[1,2], SPROVIERO W[1], SHATUNOV A[1], AL KHLEIFAT A[1], JONES A[1], DOBSON R[2], NEWHOUSE SJ[2], AL-CHALABI A[1]

[1]MRC Centre for Neurodegeneration Research, Department of Clinical Neuroscience, King's College London, London, UK, [2]MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Email address for correspondence: alfredo.iacoangeli@kcl.ac.uk

Keywords: variant calling, bioinformatics, whole-genome sequencing

Background: Project MinE is an ambitious international consortium aiming to sequence 25,000 whole genomes, of which 17,500 will be of people with ALS. The sequencing platform used has high accuracy, but with 3 billion base pairs of sequence per person, even a highly accurate caller will lead to hundreds or thousands of false calls. Optimization of the detection and genotype calling of genetic variants is therefore essential.

Objectives: To compare different genotype calling algorithms for comparison against a gold standard; to assess the Illumina sequencing platform, CASAVA, and other state of the art of variant calling methods on a dataset of ~100 British individuals from the Project MinE samples (coverage x 30), comparing the results to calls from the same samples sequenced using the MiSeq platform (coverage x 1000).

Methods: We analyzed the performance of 6 widely used variant callers: CASAVA, freebayes, platypus, vardict, samtools, and gatk haplotype caller. We also used an intersection based approach, in which we selected variants present in

at least n callers, performing a sophisticated comparison of the produced VCF files using the VCFEVAL utility of the RTG Tools package (1), on a subset of ~100 British samples from Project MinE. Performance was assessed focusing on a selected set of 25 ALS genes, which we have sequenced on illumina MiSeq with a deeper coverage (up to x 1000), at different depths of coverage.

Results: CASAVA has the highest variant accuracy as compared with the other variant callers alone when assessed on the WGS samples. However, a higher Tp/Fp ratio is achieved by an intersection approach in which we select variants present in at least 3 out of the 6 callers.

Discussion and conclusions: Project MinE is one of the biggest genetic initiatives in the world, and optimizing the pipelines and tools used is essential to exploit the information contained in the huge dataset. In this study we tested state of the art variant calling methods demonstrating how even an excellent tool such as CASAVA can be further improved by use of an intersection approach.

Acknowledgements: This is an EU JPND project supported through the Medical Research Council (UK) and Economic and Social Research Council (STRENGTH, ALS-CarE). AAC receives salary support from the NIHR Dementia BRU at South London and Maudsley NHS Foundation Trust and King's College Hospital. The work leading up to this publication was funded by the European Community's Health Seventh Framework Programme (FP7/2007–2013; grant agreement number 259867).

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BW5 INTEGRATING COPY-NUMBER ANALYSIS WITH STRUCTURAL-VARIATION DETECTION IN 50 ALS PATIENTS WITH TWO EXTREME SURVIVAL PHENOTYPES

AL KHLEIFAT A, IACOANGELI A, SHATUNOV A, SPROVIERO W, AL-CHALABI A

King's College London, London, UK

Email address for correspondence: ahmad.al_khleifat@kcl.ac.uk

Keywords: copy-number alteration (CNA), whole-genome sequencing (WGS), extreme phenotyping

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease predominantly of motor neurons, characterized by the progressive weakness of voluntary muscles and death from respiratory failure due to diaphragmatic paralysis, typically within 3 years of onset. Despite the very poor prognosis, there is considerable variation in the survival rate and up to 10% of people with ALS live for more than 8 years from first symptoms (1). There is a strong genetic contribution to the ALS risk factor (2). In 5% of cases or more, a family history of ALS or frontotemporal dementia is obtained, and the Mendelian genes responsible for ALS in such families have now been identified in about 70% of cases. Even in apparently sporadic cases, twin and population studies show the heritability is approximately 60% (3). Although risk genes reveal information about the mechanism of causation of ALS, it is also important to identify gene variants that modify survival. Survival genes could potentially be targeted directly, or their product augmented, to improve ALS survival rates. A number of common gene variants associated with ALS survival have been identified through genome-wide association studies or other genome-wide approaches such as studying structural variants (4).

Objectives: To investigate if the segmentation, on the basis of changes in read depth and the detection of localized structural variations, can vary between different ALS patient groups.

Methods: Analysis of somatic copy-number alteration (CNA) using whole-genome sequencing (WGS) data of 50 ALS patients with two extreme phenotypes, 25 short lived patients against 25 long-term surviving ALS patients using newly developed Copy Number Segmentation algorithm by Regression Tree in Next Generation Sequencing (CONSERTING) (5).

Acknowledgements: We are grateful to Professor Jinghui Zhang and her laboratory members for the opportunity to test our data using CONSERTING platform. We acknowledge Project Mine and the MND association (UK) for their support.

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BW6 GENOME-WIDE ANALYSIS OF POLYMORPHIC TANDEM REPEATS THROUGH THE DEVELOPMENT OF A NGS METHOD IN A COHORT OF ALS PATIENTS

CORRADO L[1], BORDONI R[2], GENOVESE LM[3], MANGANO E[2], GERACI F[3], SEVERGNINI M[2], D'AURIZIO R[3], LOCCI C[1], DE MARCHI F[4], MAZZINI L[4], BRUSCO A[5], MANZINI G[6,3], PELLEGRINI M[3], DE BELLIS G[2], D'ALFONSO S[1]

[1]Department of Health Sciences, University of Eastern Piedmont, Novara, Italy, [2]Institute of Biomedical Technology (CNR-ITB), Milan, Italy, [3]Istituto di Informatica e Telematica del CNR, Pisa, Italy, [4]Clinica Neurologica, Ospedale Maggiore della Carità, Novara, Italy, [5]Dipartimento di Scienze Mediche, Università di Torino, Torino, Italy, [6]Dipartimento di Scienze e Innovazione Tecnologica, UPO, Alessandria, Italy

Email address for correspondence: lucia.corrado@med.uniupo.it

Keywords: tandem repeat, genome-wide

Background: Polymorphic tandem repeats represent a large fraction of the human genome. These sequences can be located in exons, introns, or intergenic regions and they act as modulators of gene expression, RNAs and protein structure and function. To date, TRP analysis is a remarkable challenge using current next generation sequencing (NGS) and thus they were never systematically analyzed at the genome wide level.

Methods: We performed a comprehensive genome-wide search of TRPs in all gene regions. Different tools and strategies have been utilized in order to identify the largest number of polymorphic TRs. We developed a bioinformatics pipeline for TRP genotyping from genome-wide NGS data. The new procedure we implemented was applied to a NGS target-resequencing panel containing over 10000 TRP loci, including 37 known disease-causing TRPs. To test the capability of this new procedure to detect and genotype correctly the repeat length, 15 DNA samples from patients affected by nine different neurodegenerative diseases (HD, FRAXA, SCA1, SCA2, DM1, DM2, FRDA, SBMA) and carrying expanded alleles of different lengths/repeat motif have been included, together with one CEPH sample with about 9900 known TRPs genotyping.

Results: We correctly determined the allele size of 76% of known genotypes at 63 TR loci in the CEPH sample. When considering the typing in the 15 known disease-related loci we defined consistent genotyping in almost all cases (98% of 56 genotypes). Even considering very large expansions such as those in c9orf72 and DM, which are indeed not measurable, we identified those samples carrying a pathological expanded allele. Accordingly, our NGS approach can be applied to discover new disease loci characterized by tandem repeat expansion. With this aim, we are performing a comprehensive genome-wide search of TRPs in all gene regions in 70 ALS patients with a whole genome sequence approach.

BW7 SHARED NOVEL VARIANT ANALYSIS IDENTIFIES NOVEL GENES IN FAMILIAL ALS FROM WHOLE EXOME SEQUENCING

WONG CH[1], TOPP SD[1], LEE YB[1], SMITH BN[1], MUELLER S[1], COCKS G[1], TICOZZI N[2], LANDERS J[3], SHAW CE[1]

[1]Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK, [2]Department of Neurology, IRCCS Instituto Auxologico Itiliano, Milan, Italy, [3]Department of Neurology, University of Massachusetts Medical School, Worcester, MA, USA

Email address for correspondence: simon.topp@kcl.ac.uk

Keywords: exome sequencing, mutation, bioinformatics

Background: Whole-exome sequencing (WES) has proven to be an extremely successful technology for the discovery of novel genes and mutations in Mendelian disorders. We have sequenced all 270 available DNA samples from familial ALS patients collected by King's College Hospital, Guy's Hospital and the MNDA DNA Bank, and smaller cohorts donated by other collaborators. Combining this data with cohorts sequenced by other collaborators resulted in a total cohort size of 1008 patients, including 750 index cases for which the pathogenic mutation has yet to be identified, and 68 affected relatives of these.

Objectives: The objective of this study is to discover novel candidate genes, and novel mutations within those genes, which are causative of familial ALS.

Methods: Next generation sequence reads were aligned to the hg19 reference genome via BWA, variants called with Samtools Mpileup, annotated with Annovar plus custom perl code and quality

filtered, giving over 1 million unique exonic or splice site changes. Variants were further filtered to include only those found in 3 or more FALS probands and that were novel, defined as being absent from ExAC, EVS, UK10K, 1000 genomes and 670 local control exomes (n = >70,000). Due to the lack of large kindreds from which to perform linkage, the significance of any findings was assessed by performing simulation studies with the Non-Finnish European subset of ExAC (n = 33,374).

Results: Eight variants remained, six of which were described previously as causative for ALS in the genes SOD1, FUS and TARDBP. DxxxG in GeneA was found in 3 probands, plus the only affected relative for which DNA was available from two of these families. Sanger sequencing of the relevant exon in 180 sporadic ALS cases identified an additional DxxxG carrier. Simulations showed that under the null hypothesis, a similar variant would only be found in 16/20,000 similar cohorts (p = 0.0008). PxxxL in GeneB was also found in 3 probands and an additional sporadic (p = 0.03). Closer examination of a different low-coverage exon of GeneB elicited a novel PyyyL variant in 10 probands, 2 affected relatives and 2 sporadics, previously filtered from the results due to low read count. After Sanger sequencing of 2,150 population matched controls, PyyyL remains novel.

Discussion and conclusions: Few large pedigrees remain in familial ALS from which linkage can successfully be performed. Burden tests require large numbers of control exomes, which are prohibitively expensive to produce. The discovery of novel genes in FALS benefits greatly from combining multiple cohorts in order to achieve sufficient power, and one should exercise caution pursuing or rejecting variants in poorly covered regions.

Acknowledgements: Many thanks to Bradley Smith, Chun Hao Wong, Chris Shaw and the rest of his lab, and all our collaborators who are far too numerous to mention individually.

BW8 WHOLE GENOME SEQUENCING AS A TOOL TO UNRAVEL RARE VARIANTS ASSOCIATED WITH ALS SURVIVAL

MOISSE M[1], ROBBERECHT W[1,2], LAMBRECHTS D[3], PULIT S[4], VAN DEN BERG L[4], VELDINK J[4], PROJECT MINE SEQUENCING CONSORTIUM[5], VAN DAMME P[1]

[1]KU Leuven, University of Leuven, Department of Neurosciences, Experimental Neurology; VIB, Vesalius Research Center, Laboratory of Neurobiology, Leuven, Belgium, [2]University Hospitals Leuven, Department of Neurology, Leuven, Belgium, [3]KU Leuven, University of Leuven, Department of Oncology; VIB, Vesalius Research Center, Laboratory for Translational Genetics, Leuven, Belgium, [4]University Medical Center Utrecht, Department of Neurology, Brain Center Rudolf Magnus, Utrecht, The Netherlands, [5]Project Mine Sequencing Consortium, Utrecht, The Netherlands

Email address for correspondence: matthieu.moisse@vib-kuleuven.be

Keywords: WGS, survival, rare variants

Background: Amyotrophic lateral sclerosis (ALS) usually leads to death within 3 to 5 years, but a high variability in patient survival has been observed, with 5% of patients surviving more than 10 years (1). To date, several clinical factors have been associated with patient survival, eg gender, age at onset, site of onset and presence of frontotemporal dementia (2). Additionally, genetic variants, like the C9orf72 repeat expansions, have been shown to associate with survival. Recent genome-wide association studies (GWAS) using common genetic variants could only reveal the association of a small number of loci with ALS survival, leaving a large number of cases genetically unexplained.

Objectives: To identify rare genetic variants that are associated with ALS survival using whole genome sequencing (WGS) data.

Methods: We used WGS data from 1,577 Belgian and Dutch ALS patients, sequenced as part of Project MinE. Cox-regression was applied on a genome wide scale using the GenABEL-package, while correcting for age at onset, site of onset, gender, sequencing technology and the first 10 principal components for population stratification.

Results: Cox regression analysis revealed several rare variants associated with ALS survival with a P-value between 5e-9 and 6.4e-14 and a minor allele frequency up to 0.58%. The hazard ratio of the variants ranged from 3.18 to 3.46.

Discussion and conclusions: The fact that several rare variants associate with survival, underscores the importance to consider the effect of rare variants in ALS pathology, especially in survival. The discovery of these novel loci as survival modifiers in ALS is important, as they can lead to an improved understanding of the disease process, which is of crucial importance in the development of treatment options. But due to the nature of rare variants, the incidence of the variants is low and

caution should be taken with possible false positive findings, making validation in other cohorts desirable. The fact that these samples are part of Project MinE will give us an ideal opportunity to validate our findings in a larger cohort.

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Acknowledgements: Samples were sequenced as part of the MinE project. Belgian samples were collected at UZ Leuven and Dutch samples at UMC Utrecht.

BW9 FUNCTIONAL ANALYSIS OF TDP43: INTERACTION WITH THE EPIGENETIC MACHINERY

SANNA S, ESPOSITO S, MASALA A, MANCA MA, RASSU M, IACCARINO C, CROSIO C

University of Sassari, Sassari, Italy

Email address for correspondence: simosanna@uniss.it

Keywords: TDP43, epigenetics, transcription

Background: Many groups of epigenetic modifiers and consequently different epigenetic modifications have been linked to neurodegenerative processes, such as loss of normal heterochromatin (decrease in H3K9me2 and HP1α) that promotes tau-mediated neurodegeneration *in vivo* and aberrant DNA methylation in animal and cellular models of ALS. ALS is predominantly sporadic and environmental triggers may be involved in disease initiation since environmental exposure to toxins, excessive physical activity, dietary factors, and changes in immunity increase the risk of developing sporadic ALS (sALS). These factors may drive epigenetic changes (including histone modifications, DNA methylation and RNA editing), which are well suited to explain disease onset and progression in ALS, as they may be acquired throughout life (1). Among the ALS-causing genes, we focused our attention on TDP-43. TDP-43 has functions in transcription, RNA processing, microRNA biogenesis and RNA splicing. A small portion of TDP-43 is expressed in the cytosol, where it may be involved in stress granular formation and mRNA stability. Furthermore, it is associated with proteins involved in transcription, including MeCP2 (2). This interaction is of particular interest since aberrant DNA methylation has been observed in animal and cellular models of ALS and supports the idea that epigenetic modifiers and consequently different epigenetic modifications are crucial in the ALS neurodegenerative process. Finally it has been recently demonstrated that TDP-43 can be acetylated and this event reduces its RNA binding activity, once more linking TDP-43 to the epigenetic machinery (3).

Objectives: The main objectives of our work are: i) the individuation of modifications in the patterns of chromatin structure (both histone modifications and DNA methylation) and gene expression in neuronal cells expressing WT or pathological mutant TDP-43; ii) evaluation of candidate HATs and HDACs as TDP-43 interactors by co-immunoprecipitation assays.

Methods: Adenoviral delivery of TDP-43 in neuronal cells. Western blot analysis and immunohistochemistry were performed on infected SHSY5Y and NSC34. Global DNA methylation was determined by HPLC and protein interaction by co-immunoprecipitation.

Results: A detailed analysis of histone modifications and DNA methylation in cells expressing mutant TDP-43 do not reveal any significant alteration. On the contrary we were able to identify a specific TDP-43 interactor among HDACs.

Discussion and conclusions: Our results although preliminary can have a significant impact since during the past years the epigenetic treatment of various neoplastic entities and neurodegenerative disorders with HDAC inhibitors (HDACi) has demonstrated that modifications of the epigenome can be a valuable therapeutic option.

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BW10 GENOME-WIDE DNA METHYLATION PROFILING IN SPORADIC ALS

TILOCA C[1], GENTLINI D[3], VERDE F[1,2], CALINI D[1], COLOMBRITA C[1,2], PISONI S[3], BORGHI MO[4], POLETTI B[1], TICOZZI N[1,2], SILANI V[1,2], RATTI A[1,2]

[1]Department of Neurology and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano,

Milan, Italy, [2]Department of Pathophysiology and Transplantation, 'Dino Ferrari' Center, Università degli Studi di Milano, Milan, Italy, [3]Laboratory of Molecular Genetics, IRCCS Istituto Auxologico Italiano, Milan, Italy, [4]Laboratory of Immunorheumatology, Milan, Italy

Email address for correspondence: antonia.ratti@unimi.it

Keywords: epigenetics, DNA methylation, blood

Background: The role of epigenetics in ALS is still unexplored, but is supported by the increase in global DNA methylation observed in post-mortem SALS spinal cord and by the beneficial effects exerted by compounds targeting the epigenome. So far only one study has performed methylomic analysis in SALS spinal cords by genome-wide profiling, identifying differentially methylated CpG sites in genes associated with immune and inflammation response. Epigenetic changes may serve not only as potential factors influencing ALS pathogenesis, but also as novel biomarkers of disease state in peripheral tissues.

Objectives: The aim of this project is to identify epigenetic changes representing potential biomarkers associated to SALS by performing an unbiased genome-wide DNA methylation analysis in peripheral whole blood. Although DNA methylation is tissue-specific, the investigation of DNA methylation in peripheral and more accessible tissues, like whole blood, could represent a valid approach to identify signatures with diagnostic and prognostic value.

Methods: Genome-wide DNA methylation analysis was performed on DNA extracted from whole blood of 62 SALS cases and more than 100 controls by using Illumina HumanMethylation450 BeadChips, interrogating more than 485,000 CpG sites in 99% of RefSeq gene. Our sample size has over 80% power to detect methylation differences larger than 10% between cases and controls. Differential methylation analysis was conducted at site/region level according to the sample groups by using the RnBeads package. A novel analytical strategy aimed to detect subject-specific epigenetic mutations was performed by studying distribution and variability of methylation for each one of the 485,000 CpG sites using Box- and whiskers-plot analysis.

Results: Performing a genome-wide DNA methylation analysis on 62 SALS cases, our preliminary results indicate that epigenetic changes potentially related to inflammatory processes and immune response are main features of SALS patients. We are currently assessing whether variations in leukocyte subpopulations are associated to the detected epigenetic changes. Additionally, preliminary data on a subset of 26 SALS cases show epimutation enrichments localized in specific loci, including TGFB1, SHANK2, and genes encoding for G protein-coupled receptors.

Discussion and conclusions: Despite concerns regarding the use of whole blood for epigenetic studies, studies conducted in Parkinson and Alzheimer's diseases suggest that distinct methylation signatures are present in cases vs controls and may be highly informative. Our findings revealed immunological-related epigenetic changes. Epigenetic studies in blood could be useful not only to understand ALS pathogenesis, but also to define biomarkers for early diagnosis and disease progression.

BW11 MULTICENTRIC REFERRAL-BASED STUDY OF ALS-RELATED GENES IN AN ARGENTINE ALS/FTD COHORT

GARGIULO-MONACHELLI G[1,5], LEBLOND C[2], BETTINI M[3], FIGUEREDO A[4], MELE I[1], GARAU ML[1], RUGIERO MF[3], GONZALEZ DENISELLE MC[5], DION PA[2], PAGANO MA[1], ROULEAU GA[2]

[1]Department of Neurology, Fernandez University Hospital, Buenos Aires, Argentina, [2]Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, Canada, [3]Seccion Enfermedades Neuromusculares, Hospital Italiano, Buenos Aires, Argentina, [4]Hospital San Roque y Hospital Español, La Plata, Argentina, [5]Instituto de Biologia y Medicina Experimental (IBYME), UBA-CONICET, Buenos Aires, Argentina

Email address for correspondence: gisella.marianag@gmail.com

Keywords: C9ORF72, ALS-related genes in Argentina, high-throughput sequencing

Background: Genetically, C9ORF72 repeat expansions are the most common cause of ALS and FTD (1). We previously found in an Argentine ALS and FTD cohort that C9+ cases only involved patients with a positive family history of disease (ALS or FTD). C9+ ALS was associated with a young onset, rapid progression, initial bulbar symptoms and the co-existence of non-motor phenotypes (FTD and psychiatric disease) (2).

Objectives: Our objective was to expand our previous work with High-Throughput sequencing to screen for 28 ALS-related genes in a larger cohort of ALS and FTD patients in Argentina.

Methodology: To assess the mutation frequency of ALS-associated-genes in ALS cases from Argentina, we screened 28 genes (SOD1, FUS, TARDBP, C9ORF72, VAPB, VCP, UBQLN2, DAO, PFN1, hnRNPA2B1, hnRNPA1, ANG, FIG4, OPTN, DCTN1, CHMP2B, NEFH, PRPH, SQSTM1, TAF15, HFE, GRN, ARHGEF28, ERBB4, SPAST, P4HB, PDIA2 and PDIA3). Single nucleotide variations were studied using Molecular Inverted Probe (MIP) captures and Illumina sequencing (1) for the 28 genes. Hexanucleotide repeats of C9ORF72 were studied by repeat-primed-PCR (2, 3).

Results: A total of 108 patients were recruited between August 2012 and Nov 2015 of whom 52% were males. Twenty one percent were FALS cases; defined if a first or second degree relative had ALS or FTD. Mean age of onset was 53 years old. Clinical characteristics ranged: from classic ALS (n=47, 43.5%), bulbar onset ALS or progressive bulbar palsy (n=13, 12%), UMN dominant-ALS (n=9, 8.3%), ALS+FTD (n=9, 8.3%), Flail arm or flail leg (n=6, 5.5%), FALS with 1st or 2nd degree relative with ALS only (n=5, 4.6%), PLS (n=5, 4.6%), PMA (n=4, 3.7%), FTD only (n=3, 2.7%), slowly progressive ALS defined as >10 years from symptom onset (n=3, 2.7%), ALS+Parkinson's Disease (n=2, 1.8%) to respiratory onset ALS (n=2, 1.8%). High-Throughput sequencing and repeat-primed-PCR results will be presented at the 27th International Symposium on ALS/MND to be held in Dublin, Ireland 7-9 December 2016.

Discussions and conclusions: This is the first prospective, multicentric, referral-based, ALS/FTD cohort to analyze mutation frequency of ALS-related-genes in Argentina. We will present a full analysis of genotype-phenotype correlations at the ALS/MND Symposium. Patients in our country are not usually tested for ALS genes, neither sporadic nor familial cases. We encourage the implementation of a nationwide genetic screening for the most frequent ALS-and-FTD-associated genes in clinically selected cases.

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BW12 ANALYSIS OF THE PROTECTIVE EFFECT OF GENETIC ADMIXTURE IN AMYOTROPHIC LATERAL SCLEROSIS

MCLAUGHLIN R, BYRNE R, HARDIMAN O

Trinity College Dublin, Dublin, Ireland

Email address for correspondence: mclaugr@tcd.ie

Keywords: admixture, epidemiology, genetics

There is epidemiological evidence that genetic admixture protects against developing amyotrophic lateral sclerosis (ALS), with lower incidence observed in populations of mixed ancestry. This suggests that a proportion of ALS may be inherited through oligogenic, polygenic or recessive mechanisms. Using dense genome-wide single nucleotide polymorphism (SNP) and whole-genome sequence data, we mapped ancestral components and admixture in two populations of mixed ancestry. Firstly, the population of Ireland has Gaelic origin, with admixture deriving from the Anglo-Norman invasions of the 12th century and colonization by English settlers during the plantations of the 16th and 17th centuries. These ancestral components of the Irish population have high similarity but are distinguishable genetically. Secondly, the population of Cuba is a mixture of European, Amerindian and African descent, deriving mainly from several waves of immigration from Spain during the 18th and 19th centuries and the 19th century slave trade from Africa. Using ALS cases and healthy controls from both populations, we have assessed the ancestral makeup of each cohort to determine whether genetic admixture protects against ALS. Results will be discussed.

BW13 FUNCTIONAL AND GENETIC CHARACTERISATION OF TBK1 MUTATIONS IN A LARGE COHORT OF FAMILIAL ALS PATIENTS

DE MAJO M, SMITH B, GKAZI A, TOPP S, NISHIMURA A, MILLER J, VANCE C

King's College London, London, UK

Email address for correspondence: martina.de_majo@kcl.ac.uk

Keywords: TBK1, exome capture, phosphorylation

Background: ALS has a clear genetic component, in which mutations in four major genes SOD1, TDP43, FUS and C9ORF72 account for approximately 50% of familial and 15% of sporadic cases. Recently, two independent gene

hunting studies in large familial (FALS) and sporadic ALS (SALS) cohort using exome sequencing data, identified disease associated TBK1 mutations in ALS cases (1, 2).Tank Binding Kinase 1 (TBK1) is a kinase that modulates pathways involved in inflammation as well as autophagy. It phosphorylates OPTN, a gene also mutated in ALS (3), therefore, we conducted an exome sequencing project of over 800 familial ALS index cases. This supplied a large number of missense and nonsense mutations in TBK1 that are implicated to be involved in the aetiology of ALS.

Objectives: This study focuses on the genetic and functional characterisation of novel TBK1 mutations that are predicted to be damaging. We have conducted functional assays to shed light on the possible mechanisms behind the pathogenicity of TBK1 mediated ALS.

Methods: HA tagged clones of TBK1 specific ALS mutants were transfected in HEK293T and SH-SY5Y cells and immunocytochemistry (ICC) and basic protein assays performed. Furthermore, western blotting and ICC of lymphoblastoid and fibroblast cell lines from TBK1 patients are under scrutiny for disruption of TBK1 function.

Results: Within our cohort, exome sequencing elicited over 15 novel missense, nonsense or splicing mutations in TBK1. Preliminary results show that the phosphorylation of TBK1 in lines carrying mutations in TBK1 is impaired.

Discussion: We believe that this finding could give us an insight of why TBK1 mutations might be pathogenic. We endeavour to examine the phosphorylation status of TBK1 due to missense, in frame deletions and loss of function mutations.

Conclusions: We anticipate that functional assessment of these mechanisms will reveal insights into the pathogenesis of TBK1 mediated ALS. This will enable us to further unpick the mechanisms of disease in ALS and lead to the development of new drug targets for treatment of patients.

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BW14 HETEROZYGOUS DEFICIENCY OF TBK1 IN THE HIGH COPY NUMBER SOD1-G93A TRANSGENIC MOUSE MODEL

BRENNER D, BRUNO C, LUDOLPH AC, WEISHAUPT JH

Ulm University, Ulm, Baden-Württemberg, Germany

Email address for correspondence: david.brenner@uni-ulm.de

Keywords: TBK1, autophagy, SOD1-G93A transgenic mouse model

Background: Mono-allelic mutations in TBK1 (TANK binding kinase 1) cause ALS and FTD. TBK1 has a diverse spectrum of cellular functions including control of immune responses and regulation of autophagy. TBK1-dependent autophagy has previously been shown to be involved in the clearance of mutant SOD1 aggregates *in vitro*. We thus hypothesized that heterozygous knock-out of TBK1 might modify the phenotype of mutant SOD1 transgenic mice by reduced autophagic SOD1 degradation.

Objectives: The objective of this study is to assess if heterozygous deficiency of TBK1 exacerbates the mutant SOD1 proteinopathy and the motoneuron disease, in the high copy number SOD1-G93A-transgenic mouse model. To provide proof of principle that loss of one TBK1 allele is sufficient to aggravate and/or prepone onset of an exemplary “aggregopathy”.

Methods: Survival analysis, motor testing, immunohistochemistry, Western blot.

Results: TBK1+/-;SOD1-G93A mice are born and develop normally. To test for clinical symptoms of ALS and to determine the life span mice are subjected to a survival analysis. Moreover, the mice are weighted and screened for motor symptoms every 3 days, including motor testing (Rotarod) once per week. We will quantify the motor neurons and accumulation of protein aggregates in the spinal cord at the end stage. To assess impairment of autophagy we will assess the levels of autophagy proteins at various time points using Western blot and immunohistochemistry.

Discussion: Our currently preliminary analysis does not show a significant difference in body

weight and the premorbid phenotype between mutant SOD1-G93A transgenic mice and mice with an additional heterozygous knock-out of TBK1. Further behavioural and survival analysis together with immunohistochemical and biochemical evaluation will answer the question whether toxicity of loss of one TBK1 allele and mutant SOD1 expression are functionally linked.

BW14A A HUTDP-43^{Q331K} MOUSE MODEL SHOWS SIGNS OF BOTH MOTOR NEURON DISEASE (MND) AND FRONTOTEMPORAL DEMENTIA (FTD)

STEPHENSON J[1], ALIX J[1], KENNERLEY A[2], SHAW P[1], MEAD R[1]

[1]Sheffield Institute for Translational Neuroscience, University of Sheffield, UK, [2]Department of Psychology, University of Sheffield, UK

Background: As well as the devastating motor dysfunction experienced by MND patients, 10-15% will develop frontotemporal dementia (FTD). Some of these patients carry causal TDP-43 mutations, and most will have TDP-43 pathology.

Aims and methods: In a bid to find a mouse model representative of TDP-43-related MND, we characterised the progressive motor deficit in a mouse transgenic for human TDP-43^{Q331K} with an expression similar to the endogenous mouse gene (Arnold et al., 2013). During this characterisation, certain features were identified which potentially reflect a FTD phenotype as opposed to a pure motor phenotype.

Results: This model showed significantly reduced voluntary running wheel activity (0.48 ± 0.3km /night in TDP-43^{Q331K} vs 3.46 ± 4.2km /night in TDP-43^{WT}, $p<0.01$ based on 6m females) and reduced marble burying activity (6.8 ± 6.6 marbles /24 in TDP-43^{Q331K} vs 17.3 ± 4.8 marbles /24 in TDP-43^{WT}, $p<0.001$ based on 6m females). Marble burying is a surrogate marker of 'normal' exploratory behaviour, therefore, these behaviours may reflect apathy, a symptom of FTD.

Discussion: We previously identified increased weight in this model, which in part may be due to decreased activity levels but also due to increased food intake (11.3±1.1g/72hrs in TDP-43^{Q331K} vs 9.8±1.0g/72hrs in TDP-43^{WT}, $p<0.0001$ based on 6m females). This may reflect hyperphagia, also a symptom of FTD. Brain volume measurement using MRI is currently underway to investigate cortical atrophy. Overall, these findings suggest that the huTDP-43^{Q331K} mouse may be a model of the MND/FTD continuum, and provides further parameters for evaluation of therapeutic interventions.

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BW15 HUMANISING THE TARDBP LOCUS IN THE MOUSE

DE GIORGIO F[1], DEVOY A[1], ZHU F[1], MACKENZIE K[1], ACEVEDO-AROZENA A[2], FISHER EMC[1]

[1]Department of Neurodegenerative Disease, University College London, London, UK, [2]Hospital Universitario de Canarias, Tenerife, Spain

Email address for correspondence: f.degiorgio@prion.ucl.ac.uk

Keywords: TDP-43, gene targeting, humanised mouse model

Background: Mutations in the TARDBP gene, encoding the TAR DNA-binding protein (TDP-43), are implicated in the pathogenesis of ALS with ~90% of ALS cases showing cytoplasmic inclusions rich in ubiquitinated or hyperphosphorylated TDP-43 and depletion of the wild type protein in the nucleus (1). Mutations in TARDBP are causative for ALS and so models of ALS-TDP-43 are needed to shed light on the biochemistry and the physiological mechanisms underlying ALS cases involving TDP-43.

Objectives: Our aim is to make a genomically humanised TDP-43 mouse model by replacing the coding region of mouse Tardbp gene with the human orthologue.

Methods: We propose to use BAC clones to perform gene targeting (homologous recombination) at the Tardbp mouse locus which will be maintained under the control of the endogenous mouse promoter to avoid interference with correct spatial and temporal control of expression, avoiding negative impacts of over expression.

Results and discussion: The 3'UTR of the Tardbp/TARDBP mRNA is the critical region for the auto-regulation of Tardbp/TARDBP mRNA level. However, in the mouse genome, the 3'end of Tardbp overlaps with the 3'end of the gene Masp2. Therefore targeting this region could interfere with the expression of Masp2 as already published (2). The mechanisms of auto-regulation of Tardbp/TARDBP mRNA has been shown to be conserved between humans and mice (3), validating the use of the mouse 3'UTR for this

project. Hence, we are designing a strategy to generate mice that will harbour a fully humanised TARDBP coding region, including human introns 2-5, together with the mouse untranslated regions (both 5' and 3').

Conclusions: We aim to create a reliable humanised mouse model of TDP-43 to recapitulate normal human TDP-43 expression in vivo under the physiological condition. This model will be an important contribution to the scientific community providing a useful genetic tool that, combined with other advanced genome editing techniques, could be used for future studies on ALS caused by mutations in TDP-43.

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BW16 UNDERSTANDING THE LINK BETWEEN CORTICAL INJURY AND ALS

LAGRIMAS A[1], KOZLOWSKI D[2], OZDINLER PH[1], JARA J[1]

[1]Northwestern University, Chicago, IL, USA, [2]DePaul University, Chicago, IL, USA

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

Keywords: traumatic brain injury, neuroinflammation, apical dendrite degeneration

Background: Traumatic brain injury (TBI) is linked to the development of neurodegenerative diseases in which motor neuron circuitry is impaired. In particular, professional athletes with concussion history (1) and military veterans are at greater risk of developing motor neuron diseases. Corticospinal motor neurons (CSMN) are located in the cerebral cortex and therefore are more susceptible to cortical injury (CI). CSMN are a key component of the motor neuron circuitry and play a key role in ALS pathology. CSMN can be studied using UCHL1-eGFP (U-eGFP) transgenic line, in which CSMN are genetically labelled with eGFP. By crossing U-eGFP mice with ALS mouse models, a distinct vacuolation pattern in the CSMN apical dendrite is observed. The immune response also plays a role in CSMN degeneration. Microglia activation correlates with CSMN deficits in patients and is present in the vicinity of diseased CSMN. Among the neuroinflammatory components observed, MCP1/CCR2 is a cytokine/receptor system critically involved in both in ALS and TBI (2, 3).

Objectives: Modeling TBI using mild CI to study its effect on neuroinflammation and to assess how that relates to CSMN degeneration in diseases.

Methods: U-eGFP mice are used to visualize CSMN. Apical dendrite pattern, CSMN body size, and markers of apoptosis serve as a read-out to determine CSMN degeneration. To study neuroinflammation we use the MCP1-CCR2 reporter mouse, in which cells that express MCP1 or CCR2 are labeled with red or green fluorescence, respectively. A unilateral mild CI is produced over the motor cortex using controlled cortical impact method.

Results: A mild CI that produces a small contusion cavity after 48 hrs was successfully performed in both U-eGFP and MCP1-CCR2 mice. Preliminary results show CSMN with vacuolated apical dendrites underneath the contusion cavity and decreased numbers in layer V of the motor cortex. CSMN in the contralateral side of the cortex do not present vacuoles. Microgliosis and astrogliosis is increased after 48hrs. Throughout the motor cortex and MCP1+ and CCR2+ cells are identified as microglia and infiltrating monocytes, respectively.

Discussion and conclusions: The mechanisms that lead to CSMN degeneration are not completely understood. This study allows for the development of a mild CI model in which CSMN have a common pattern of degeneration with CSMN from ALS mouse models. Moreover, the fact that immune response is increasingly present after TBI and during ALS pathology opens a venue for exploration to understand the basis of common neuroinflammation mechanisms in both contexts.

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BW17 PATTERNS OF CORTICAL ATROPHY AT DIAGNOSIS IN AMYOTROPHIC LATERAL SCLEROSIS AND IMPLICATIONS ON PROGNOSIS

ABULAILA M, RAFIQ M

University of Sheffield, Sheffield, UK

Email address for correspondence: m.k.rafiq@sheffield.ac.uk

Keywords: cortical atrophy, prognosis, radiological biomarker

Background: It has now been recognised that in ALS, the pathological process is not restricted to the motor cortex and the anterior horn cells but may also affect fronto-temporal cortex, hippocampus, thalamus, substantia nigra, spinocerebellar and sensory pathways. Up to 30% of patients with ALS have evidence of cognitive impairment. C9ORF72 gene expansion offers the genetic link between ALS and fronto-temporal lobar degeneration. The presence of clinical evidence of fronto-temporal dementia in a patient with ALS is considered as a poor prognostic factor (1). The prognostic implications of cortical atrophy in different brain regions in ALS, has however not been studied (2, 3).

Objective: 1) To understand the patterns of cortical atrophy in ALS; 2) To study the prognostic value of cortical atrophy at diagnosis in ALS.

Methods: This is a retrospective, observational study consisting of a conveniently sampled cohort of 249 patients with ALS, diagnosed at the Sheffield MND Care and Research Centre. The global cortical atrophy (GCA) scale was used to quantify cerebral atrophy on the MRI brain scans. The relationship between cortical atrophy and overall survival is assessed using Kaplan-Meier survival analysis and Cox regression analyses.

Results: 249 patients were studied; 130 males (52.2%) and 119 females (47.8%). The mean age of onset was 61.5 years and the mean diagnostic delay was 15.2 months. The commonest site of onset was lower limb (93 cases) with 79 individuals having bulbar onset. The mean survival was 36 months from disease onset. Motor strip atrophy was present in 50% of the cases, 31.3% of them showed bilateral motor strip atrophy. Moderate-to-severe fronto-temporal atrophy was present in 41% of the cases. Brain stem degeneration was seen in 34.2% of the cases. Kaplan-Meier analysis demonstrated higher degree of cortical atrophy being associated with poorer prognosis. Cox regression analysis (adjusted for gender, El-Escorial category, and diagnostic delay) also demonstrated increasing hazard with increasing atrophy. This was true for fronto-temporal and motor strip atrophy, while brainstem atrophy did not have a significant effect on prognosis.

Conclusion: Serial MRI brain scans during the disease trajectory of ALS potentially offers an objective measure for assessing disease progression. This would be especially beneficial in interventional trials such as gene therapy and stem cell transplantation trials. It would be desirable to have a structured approach to identify a radiological signature of ALS adding more value to MRI brain scans in the diagnostic and prognostic work-up of ALS.

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BW18 AN AUTOPSY CASE OF AMYOTROPHIC LATERAL SCLEROSIS PRESENTED PALLIDO-NIGRO-LUYSIAN DEGENERATION WITH TDP-43 PATHOLOGY

UCHINO A[1,2], OGINO M[3], FUJIGASAKI J[1], NISHIYAMA K[2], MURAYAMA S[1]

[1]Department of Neuropathology, Brain Bank for Aging Research, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan, [2]Department of Neurology, Kitasato University School of Medicine, Kanagawa, Japan, [3]Research and Development Center for New Medical Frontiers, Kanagawa, Japan

Email address for correspondence: akikou@med.kitasato-u.ac.jp

Keywords: neuropathology, TDP-43, pallido-nigro-luysian degeneration

Background: Phosphorylated (p) TDP-43 is a major component of neuronal cytoplasmic inclusions (NCI) in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). (1) proposed the staging (stages 1-4) of ALS related pTDP-43 pathology. In addition, (3) classified two distribution patterns, type 1 (limited) and type 2 (generalized), of TDP-43 positive NCIs and glial cytoplasmic inclusions (GCIs) in ALS. These studies have shown that pallido-nigro-luysian (PNL) system is rarely involved in pTDP related ALS pathology.

Objectives: We report an autopsy case of ALS with degeneration of PNLS, showing generalized pTDP-43 pathology.

Methods: The patient was a 71 year old man, an autopsy was performed 22 hours post mortem. At the age of 68, he had freezing gait, and his right leg showed akinesia. He was diagnosed as having Parkinson's disease and l-dopa was administered. One year later, he developed weakness of his left hand and leg, and diagnosed as ALS. He died of respiratory failure 3 years after onset. The brain and spinal cord were fixed in formalin and examined immunohistochemically using pTDP-43 antibody (PSer409/410).

Results: Macroscopically, temporal lobes were mildly atrophic. Microscopically, neuronal loss and gliosis were found in the upper and lower motor neuron system. The globus pallidus, substantia nigra and subthalamic nucleus were severely affected, where numerous pTDP-43-positive NCIs and GCIs were observed. pTDP-43-positive NCIs extended to the amygdala and hippocampus, without significant neuronal loss and gliosis. The pTDP-43 distribution was consistent with Brettschneider stage 4 and Nishihira type 2.

Discussion and conclusions: In this case, the most severe degeneration was observed in the PNL system. This finding suggests that the PNL system is also involved in the disease process of ALS and that the progress pattern of pTDP-43 in ALS with PNLD is different from that previously reported.

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BW19 ASSAYS OF CLINICAL IMPORTANCE IN RELATION TO THE CLINICAL COURSE IN ALS

MITRE ROPERO B, ROSÉN H, PERSSON L

Institute of Clinical Neuroscience, Department of Neurology, Sahlgren University Hospital, Gothenburg, Sweden

Email address for correspondence: lennartpersson@msn.com

Keywords: metabolism, hormones, exercise

Background: ALS is a multifaceted clinical disease with genetic and/or inflammatory etiology, influenced by life habits, eg long term hard physical activity, changes in BMI and in metabolic changes in life, eg in diabetes. Monitoring of disease activity is important in order to evaluate possible effects of clinical treatment. We have assayed the relationship between different assays of blood and cerebrospinal fluid (CSF) in relation to clinical metabolic and inflammatory factors. Strenuous exercise and absence of a normally rising BMI with aging is a risk factor for contracting ALS.

Methods: Patients were followed by repeated blood and CSF monitoring as well as by assessment by clinical rating scales. BMI was followed and repeated analyses of adiponectin, generated by fat cells, was performed during the course of the disease.

Results: There was a close correlation between repeated assays of CSF NFL and the rate of progression of ALS during the course of the disease. There was a further relationship between the levels of adiponectin, CSF and the rate of progression of the disease, as measured by the ALSFRS-R rating scale.

Conclusions: Increased levels of CSF NFL are closely related to disease activity in ALS and are inversely correlated to life expectancy after diagnosis of ALS. It seems fairly stable during the course of the disease in each individual. Adiponectin is a hormone with metabolic and anti-inflammatory action, released from fat cells. The fat cell volume is decreased in persons with excessive long-lasting physical activity, eg in triathlon and football athletes, which has been associated with an increased incidence of ALS. There was a relationship between the levels of plasma adiponectin, CSF NFL levels and the rate of progression of ALS, as measured by the ALSFRS-R rating scale, which may be of interest and might initiate further investigations of metabolic factors in ALS.

BW20 BIOENERGETIC PROFILING OF CELLULAR MODELS OF MOTOR NEURONE DISEASE TO IDENTIFY NEW APPROACHES FOR SUPPORTING MOTOR NEURONE HEALTH

ALLEN S, FRANCIS L, MYSZCZYNSKA M, FERRAIUOLO L, SHAW P

University of Sheffield, Sheffield, UK

Email address for correspondence: s.p.allen@sheffield.ac.uk

Keywords: metabolism, mitochondria, in vitro

Background: MND patients lose both weight and body fat as the disease progresses due in part to hypermetabolism. This coupled with hyperlipidaemia, dysregulated metabolic regulation, oxidative stress and defective mitochondria can lead to reduced ATP levels in the CNS (1). As clinical evidence supports a negative impact of dysfunctional energy metabolism on disease progression in MND, it is vital to understand how the metabolic pathways can be manipulated to increase the re-routing and catabolism of alternative fuel sources such as glycogen stores, ketone bodies and polysaccharides into the glycolytic and mitochondrial pathways.

Objectives: Using a phenotypic metabolic array, we have metabolically profiled C9orf72 and TDP43 patient derived fibroblasts and induced neuronal progenitor cell (iNPC) derived astrocytes. Our objectives were to identify metabolites that have altered metabolism in MND cases compared to controls, identifying potential metabolic pathway disease markers of both hypometabolism and hypermetabolism. The aim is then to supplement the cells with the identified dysfunctional metabolites and monitor the effect on metabolic regulation, metabolic function and energy output, as well as markers of cellular stress.

Methods: Phenotypic metabolic profiling was performed by measuring how the cells utilised 92 different metabolites to produce nicotinamide adenine dinucleotide (NADH). The assay uses redox dye chemistries that measure the NADH reductase activity over time. This methodology has been used to uncover tryptophan metabolic dysfunction in autism patients (2). Qlucore analysis of the dataset was used to identify any dysregulated metabolites and two-way ANNOVA with a Sidak multi comparison test was subsequently performed to identify the top metabolites for further functional studies.

Results: To date, eight controls, six C9orf72 and five TDP43 fibroblast cases have been metabolically profiled. As well as three C9orf72 iNPC astrocyte and three astrocyte controls lines. In the C9orf72 fibroblasts, three metabolites were identified that displayed significant hypometabolism and two that showed significant hypermetabolism compared to controls ($p \leq 0.05$). In the TDP43 fibroblasts, five metabolites were identified that displayed significant hypometabolism compared to controls ($p \leq 0.05$). When reprogrammed, five metabolites showed significant hypometabolism compared to controls in C9orf72 iNPC astrocytes ($p \leq 0.05$). Functional testing of these metabolites is currently underway.

Discussion: We have potentially identified novel dysfunctional metabolites using our phenotypic metabolic profiling approach in C9orf72 and TDP43 MND patient models. Functional analysis is underway to ascertain how these metabolites affect metabolic regulation, function and energy output.

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BW21 ANALYSIS OF AXONAL TRANSPORT IN CULTURED NEURONS DERIVED FROM AN ALS MOUSE MODEL BY USING THE MICROFLUIDIC CELL CULTURE SYSTEM

OTOMO A[1,2], ARAKI R[3], ISHIDA T[3], SHIRAKAWA R[1], MITSUI S[1], SATO K[1], ONO S[1], YOKOYAMA S[2], KIMURA H[2,3], HADANO S[1]

[1]Department of Molecular Life Sciences, Tokai University School of Medicine, Isehara, Kanagawa, Japan, [2]Micro/Nano Technology Center, Tokai University, Hiratsuka, Kanagawa, Japan, [3]Department of Mechanical Engineering, Tokai University School of Engineering, Hiratsuka, Kanagawa, Japan

Email address for correspondence: asako@tokai-u.jp

Keywords: SOD1H46R, axonal transport, microfluidic device

Background: Several recent studies on the pathogenesis of ALS caused by mutations in SOD1, ALS2, SQSTM1, TDP-43, and OPTN have revealed deficits in the autophagy-endolysosomal pathway in diseased neurons. Consistently, we have previously reported that autophagosome-like structures with membrane whorls are accumulated in the spinal axons of a SOD1H46R transgenic mouse ALS model (SOD1H46R) as disease progresses (1). Our findings together with recent reports indicate that defects in autophagy-lysosomal degradation itself and/or autophagosome transport might be implicated in the pathogenesis of ALS. However, the exact causal relationship between neuronal deficit and inefficient autophagosome formation and/or transport in diseased neurons is still unknown. Furthermore, it remains unclear whether axonal transport of

autophagosome is affected in diseased neurons in the first place.

Objectives: To determine whether the axonal transport of acidic vesicles including autophagosome was affected by mutant SOD1 expression, we compared the axonal transport of the vesicles in primary cultured neurons derived from SOD1H46R mice and wild type (WT) littermates.

Methods: We fabricated a microfluidic device which allowed us to analyze the movement and direction of axonal transport in cultured neurons. We independently cultured cortical neurons obtained from, at least, 4 individual mice with each genotype; SOD1H46R and WT. Then, acidic vesicles were labeled with LysoTracker. For the collection of data, we captured the sequential images of LysoTracker-labeled acidic vesicle (LT-vs) in the distal axons through micro slit for 120 seconds. To visualize trajectories of LT-vs, kymographs were generated from the sequential images using ImageJ. According to kymograph data, we counted the number of LT-vs and categorized the LT-vs into “moving” or “stationary”. After that, “moving” LT-vs were sub-classified into 2 groups; “anterograde” or “retrograde”, depending on their directions of the movement.

Results and discussion: Our results showed that a total number of LT-vs in the distal axon was unchanged by SOD1H46R expression. Interestingly, LT-vs that were continuously moved along the distal axon over 120 seconds observation period of time were significantly increased in SOD1H46R compared to those in WT, indicating an enhanced transport of the acidic vesicles including autophagosome in diseased axons. These results suggest that a transport of acidic vesicles is, at least, dysregulated in SOD1H46R-derived neurons. To clarify the mechanism underlying the accumulation of autophagosome in SOD1H46R mice, analysis of autophagosome transport is currently underway.

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BW22 C9ORF72 G4C2 HRE-MEDIATED NUCLEOCYTOPLASMIC TRAFFICKING DEFECTS ALTERS AUTOPHAGIC TARGETING

MANN J, GLEIXNER A, MARKS M, PANDEY U, DONNELLY C

University of Pittsburgh, Pittsburgh, PA, USA

Email address for correspondence: jrm218@pitt.edu

Keywords: autophagy, C9orf72, proteostasis

Background: Working in conjunction with the ubiquitin-proteasome system (UPS), the autophagy-lysosomal pathway (ALP) plays a crucial role in the targeted degradation of damaged or aggregated proteins and dysfunctional organelles. Dysregulation of the ALP has been implicated in the pathogenesis of Amyotrophic Lateral Sclerosis (ALS), a progressive and fatal neurodegenerative disease affecting motor neurons of the brain and spinal cord. The G4C2 hexanucleotide repeat expansion (HRE) in C9orf72 is the most common genetic cause of familial and sporadic forms of ALS, accounting for up to 30% of familial and 8% of sporadic cases. Toxicity associated with expression of this C9orf72 HRE has recently been linked to impairments in nucleocytoplasmic trafficking that result in the nuclear retention of RNA species and sluggish import of proteins destined for the nucleus. Interestingly, these nuclear import defects correlate with enhanced levels of cytoplasmic TDP-43, a pathological hallmark of roughly 97% of all ALS patients. While the exact mechanisms underlying these nuclear transport defects remains unclear, both G4C2 RNA and dipeptide repeat protein products of the repeat expansion have been linked to this dysfunction. Given the role of autophagy in the degradation of aggregated cytoplasmic proteins, it is possible that C9orf72-mediated mislocalization of aggregate-prone proteins such as TDP-43 may alter the degradation profiles of autophagosomes responsible for delivering cytoplasmic components to the lysosome for degradation.

Methods/Objectives: We developed a simple immunoprecipitation-based method to isolate pure and intact autophagosomes and found that these LC3-positive autophagosomal vesicles contain diverse protein and RNA species. Using this technique in conjunction with screening methodologies, we assessed how G4C2 RNA, C4G2 RNA, and their repeat-associated non-ATG translation (RANT) protein products altered the autophagosome degradation profiles in cell culture and iPSC neurons. In addition, we tested whether expression of WT and ALS-linked mutant TDP-43 and FUS proteins revealed common

autophagosomal targets. Alterations in degradation profiles are currently being confirmed in ALS-patient CNS tissue regions that show G4C2/C4G2 RNA foci or RANT protein accumulation. The data generated from this work will be used to catalogue unique and common targets of the ALP among genetic subtypes of ALS.

BW23 SYSTEMATIC EVALUATION OF THE POTENTIAL FOR REPURPOSING AUTOPHAGY TARGETING DRUGS IN THE TREATMENT OF ALS-FTLD

SERVANTE J, SCOTT D, GOODE A, COX A, LAYFIELD R

University of Nottingham, Nottingham, UK

Email address for correspondence: mbxds1@nottingham.ac.uk

Keywords: autophagy, repurposing, treatment

Background: Considerable evidence points to disturbance of autophagy as a pathophysiological mechanism in sporadic and familial ALS-FTLD. Several autophagy modulating compounds have previously been trialled in ALS patients, albeit with limited success. Autophagy is a multi-step catabolic process and therapeutic outcomes may in part depend on the particular stage in the process which is pharmacologically targeted. A number of drugs with autophagy-enhancing properties that target different stages of the autophagic pathway are already in clinical use for a variety of disorders.

Objectives: To evaluate whether autophagy-enhancing drugs including those that are already in clinical use for other disorders could be considered for repurposing in cases of ALS-FTLD with autophagy disturbance.

Methods: We are performing a comprehensive and systematic literature analysis of over 70 autophagy-enhancing compounds, considering criteria including: currently or previously evaluated in the treatment of CNS disorders/cancers without significant side-effects; not yet evaluated in ALS-FTLD models or clinical trials.

Results: A number of autophagy-enhancing compounds which have already undergone pre-clinical testing and that meet the above criteria were highlighted. As exemplars, temozolomide (glioblastoma multiforme) and trifluoperazine (schizophrenia and other psychoses) have reported autophagy-enhancing properties but have, to the best of our knowledge, not yet been evaluated in ALS-FTLD models or patient studies.

Discussion and conclusions: This work has the potential to inform the repurposing and clinical positioning of autophagy-enhancing drugs in the translational pipeline, some of which after testing in appropriate model systems could be fast-tracked towards evaluation in patients.

Acknowledgements: RL is supported by the UK MND Association.

BW24 GENE THERAPY FOR AMYOTROPHIC LATERAL SCLEROSIS WITH MIGRATION OF BONE MARROW-DERIVED CELLS

TERASHIMA T[1], OGAWA N[2], KOBASHI S[2], KATAGI M[1], OKANO J[3], KAWAI H[2], MAEGAWA H[2], URUSHITANI M[2], KOJIMA H[1]

[1]Department of Stem Cell Biology and Regenerative Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan, [2]Department of Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan, [3]Department of Anatomy and Cell Biology, Shiga University of Medical Science, Otsu, Shiga, Japan

Email address for correspondence: tom@belle.shiga-med.ac.jp

Keywords: gene therapy, bone marrow-derived cells, migration

Background: A number of treatments have been tested in ALS animal models and patients, but no satisfactory treatment has been established yet. Bone marrow-derived cells (BMDCs) have migrated into pathological lesion, which were related to the pathogenesis in ALS. This phenomenon could be useful for new gene therapy to target neurological tissues with gene transfer into BMDCs.

Objectives: Investigating the usability of the new strategy to deliver therapeutic genes to the spinal cord by the migration of BMDCs.

Methods: 1) Bone marrow (BM) cells from normal mice were infected with lentiviral vectors expressing YFP driven by EF-1 promoter (LV-BOS-YFP) or CD68 promoter (LV-CD68-YFP). Infected BM cells were transplanted into normal mice. After 3 or 6 weeks, leukocytes were collected from recipient mice and the percentage of YFP positive cells were analyzed with flow cytometry. 2) Infected BM cells with LV-BOS-YFP or LV-CD68-YFP were transplanted into human SOD1 G93A transgenic (SOD1-tg) mice at the pre-symptomatic condition (8 weeks old). The percentage of YFP positive leukocytes were analyzed with flow cytometry at 3 or 6 weeks after

transplantation. YFP expression was histologically analyzed in spinal cord of the mice at 6 or 10 weeks after transplantation. 3) As the treatment of SOD1-tg mice, LV-CD68-glutamate transporter 1 (LV-CD68-GLT1) vectors were infected into BMDCs, which were transplanted into SOD1-tg mice. The treated mice were evaluated for motor function and survival curve.

Results: 1) YFP positive leukocytes were observed at approximately 10-20% in peripheral blood of wild type recipient mice at 3 and 6 weeks after transplantation of lentiviral vectors. 2) The same as in wild type mice, YFP positive leukocytes were observed in peripheral blood from SOD1-tg mice. In addition, YFP positive BMDCs were observed in spinal cord from SOD1-tg mice after transplantation of infected BM cells with LV-CD68-YFP and LV-BOS-YFP. 3) The transplantation of BM cells infected with LV-CD68-GLT1 delayed the progression of motor function loss and extended survival compared to control non-treated mice.

Discussion and conclusion: Endogenous physiological function as migration of BMDCs observed at the neurological tissues in ALS/MND is very useful for new gene therapy with BM cells transferred treatable gene. This strategy is expected to have high therapeutic potential; that treatable gene expression gradually increases as much as disease becomes worse because many numbers of BMDCs migrate into neurological tissues by the development of inflammation. It was suggested that this strategy had high potential to provide a new gene therapy.

BW25 A PILOT STUDY ON THE EFFECTS OF PLASMA EXCHANGE WITH ALBUTEIN® 5% ON MOTOR AND COGNITIVE FUNCTION OF ALS PATIENTS

PAIPA A[1], DOMINGUEZ R[1], MASSUET L[2], ORTEGA S[2], BARCELÓ M[3], WOODWARD M[3], PÁEZ A[3], POVEDANO M[1]

[1]ALS Unit, Neurology service, Bellvitge University Hospital, Hospitalet de Llobregat, Spain, [2]Banc de Sang i Teixits, Barcelona, Spain, [3]Clinical Development, Instituto Grifols S.A., Barcelona, Spain

Email address for correspondence: andres.paipa@bellvitgehospital.cat

Keywords: clinical trial, albumin, plasma exchange

Background: Albumin, the most abundant protein in plasma, has metabolic properties beyond osmotic equilibrium such as antioxidant and anti-inflammatory properties. As such, it has been tested as a neuroprotector in preclinical models of stroke (1) while in Alzheimer's disease a Phase III trial is currently underway (2). Plasma exchange (PE) was tested on ALS patients over 30 years ago; however, the lack of established diagnosis criteria and validated evaluation tools for disease progression were methodological constraints that limited prior investigations.

Objectives: We report preliminary results from a pilot, open-label study to assess safety, tolerability, and efficacy of PE with albumin (Albutein® 5%, Grifols) on motor and cognitive function of ALS patients (EudraCT: 2013-004842-40).

Methods: A total of 10 subjects were treated over 6 months (intensive phase of bi-weekly PE during 3 weeks followed by maintenance phase with weekly PE). All patients were followed for an additional 6 months. ALS patients meeting probable or definite diagnosis through El Escorial criteria were enrolled, with no more than 18 months from symptom onset and a forced vital capacity (FVC) >70%. ALS Functional Rating Scale-Revised (ALSFRS-R), FVC, muscle strength, and compound CMAP of 4 muscles were assessed. Cognitive and quality of life evaluations were performed at baseline, end of treatment, and end of follow-up period.

Results: A total of 13 subjects were enrolled, 8 of which completed the treatment phase as per protocol. Age ranged from 33-66 and there were 10 males and 3 females, 7 presenting bulbar onset and 6 spinal onset. Overall mean ALSFRS-R at baseline was 40.2 declined to 32.9 at week 25 (decline rate: -1.22/month). However, analysis of per-protocol population revealed a decline rate of -0.67/month. Baseline FVC was 85.8% declining to 66.8% at week 25 (decline rate: -3.2%). Significant changes from baseline were not detected with the ALS-CBS scale (16.5 ± 3.1 at baseline and 17.1 ± 3.0 at week 25) and ALSAQ40 index (30.2 ± 15.0 at baseline and 43.7 ± 19.4 at week 25). No serious adverse events related to the investigational product or procedure were registered.

Discussion and conclusions: PE is safe and well tolerated in ALS patients. Average ALSFRS-R and FVC declined as expected but there was a subgroup of subjects that showed a slower progression. Larger clinical trials should be considered to further test efficacy.

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Acknowledgements: Jordi Bozzo PhD (Grifols) is acknowledged for editorial support

BW26 CANNABINOIDS FOR SYMPTOM MANAGEMENT IN AMYOTROPHIC LATERAL SCLEROSIS: A PILOT STUDY

MAGNUSSEN C[1], SEGUIN R[1], O'CONNELL C[2,3], GENGE A[1,4], WARE M[5]

[1]Clinical Research Unit, Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada, [2]Stan Cassidy Centre for Rehabilitation, Fredericton, New Brunswick, Canada, [3]Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada, [4]Department of Neurology, McGill University, Montreal, Quebec, Canada, [5]Alan Edwards Center for Research on Pain, Montreal, Quebec, Canada

Email address for correspondence: claire.magnussen@mcgill.ca

Keywords: cannabinoid, clinical trial, symptom-management

Background: There is a relative paucity of evidence for effective treatments to manage the many symptoms experienced by those living with motor neuron disease. Spasticity, pain, mood alterations, reduced appetite, sialorrhea and sleep disturbances can interfere with function and negatively affect quality of life in patients with amyotrophic lateral sclerosis (ALS). Cannabis-based medicines have been shown to be effective at easing many of these symptoms in other neurological diseases, however the therapeutic potential of cannabinoids in ALS has never been formally studied.

Objective: This phase II, randomized, placebo-controlled clinical trial will assess the short term safety and efficacy of oral cannabinoid extracts in patients with ALS. Oral cannabinoid extracts, containing defined ratios of Δ9tetrahydrocannabinol (THC) and cannabidiol (CBD), are hypothesized to reduce the subjective and objective symptoms in ALS patients compared to placebo.

Methods: 34 patients with ALS will be recruited from two Canadian tertiary care centres: the Montreal Neurological Institute and Hospital in Montreal, Quebec and the Stan Cassidy Centre for Rehabilitation in Fredericton, New Brunswick. Using a 4-way crossover design, each patient will be randomly assigned to receive a predetermined sequence of the four study medications. Standardized cannabis extracts are provided by Green Sky Labs, and include 3 unique THC:CBD ratios formulated in a food-grade oil, and a placebo. In this 12 week trial, each 5-day treatment period is separated by a 9-day washout period. The primary endpoint is change in ALSAQ-40 score, with secondary endpoints investigating spasticity (Modified Ashworth Scale, Penn Spasm Frequency Scale), pain intensity and pain relief (0-10 Numeric Rating Scale), mood (Short-Form Profile of Mood States and Subscales), sleep (Insomnia Severity Index), appetite (Visual Analogue Scale), patient global impression of change, and patient oral cannabis preference. Detailed inclusion/exclusion criteria, and study design will be presented.

Conclusion: The data from this trial will be used to inform the development of further long term studies investigating the efficacy of cannabinoids in the treatment of ALS.

Acknowledgements: This clinical trial is supported by a clinical management grant from ALS Canada, with matching funds and IP from Green Sky Labs.

BW27 A REGISTRY-BASED RANDOMIZED CONTROLLED, DOUBLE-BLINDED CLINICAL TRIAL OF PIMOZIDE IN PATIENTS WITH ALS

MARTINEZ J[1], ROBITAILLE R[2], PARKER A[2], KABASHI E[2], JULIEN J-P[3], DRAPEAU P[2], ZINMAN L[4], KORNGUT L[1]

[1]University of Calgary, Calgary, Alberta, Canada, [2]Universite de Montreal, Montreal, Quebec, Canada, [3]Universite Laval, Quebec City, Quebec, Canada, [4]University of Toronto, Toronto, Ontario, Canada

Email address for correspondence: korngut@gmail.com

Keywords: clinical trial, pimozide, therapy

Background: Clinical and electrophysiological correlates of muscle fatigueability suggesting an element of neuromuscular junction (NMJ) transmission dysfunction have been described in patients with ALS over the past 50 years. Abnormal decremental responses on repetitive nerve stimulation correlate with NMJ transmission dysfunction. Pimozide has been recently demonstrated to cause partial reversal of the ALS phenotype in TDP-43 or SOD1 *C. elegans*, zebrafish and mouse models of ALS. One of pimozide's mechanisms of action is facilitating presynaptic NMJ activity by altering ionic channels. Through facilitation of NMJ transmission pimozide may act to enhance motor unit function early in the disease course of ALS.

Methods: We conducted a placebo-controlled, double-blinded, randomized controlled trial of pimozide versus placebo, in subjects with ALS at one centre. The primary outcome measures were: change in ALSFRS-R, slow vital capacity, and change in abnormal decremental responses. The secondary outcome measure was adverse effect reporting.

Results: The study is nearing complete recruitment of the 25 subjects. Data analysis will be performed after data collection is completed and the database is locked. This clinical trial will be completed by the time of the symposium and the full results will be presented.

BW28 INTERIM RESULTS FROM AN OPEN-LABEL, SINGLE-CENTER, HYBRID-VIRTUAL 12-MONTH TRIAL OF A LUNASIN REGIMEN FOR PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

BEDLACK R[1], SADRI-VAKILI G[2], DIOS A[2], SPECTOR A[3], MORGAN E[3], WICKS P[3]

[1]Duke University, Durham, NC, USA, [2]MassGeneral Institute for Neurodegenerative Disease, Charlestown, MA, USA, [3]PatientsLikeMe, Cambridge, MA, USA

Email address for correspondence: bedla001@mc.duke.edu

Keywords: Lunasin, virtual, trial

Background: Lunasin, a soy peptide that may alter histone acetylation, has been associated with an ALS reversal (1). We recently launched a patient-centric pilot trial of Lunasin to test the following hypotheses: 1. Lunasin decreases the rate of ALSFRS-R progression by 50% relative to historical controls; 2. Lunasin increases the frequency of ALS reversals (defined by an improvement of 4 or more points in the ALSFRS-R over the course of 12 months) to at least 2%; 3. Lunasin alters histone acetylation in PALS; 4. Participants can accurately measure their ALSFRS-R score and record it on PatientsLikeMe with high concordance to clinical ratings; 5. Participants can accurately measure their own weight and record it on PatientsLikeMe with high concordance to clinical assessment; 6. The novel features of this pilot trial will be associated with improved participant enrollment compared to prior more traditional ALS trials where this is 2 participants per site per month; 7. The novel features of this pilot trial will be associated with improved participant retention compared to prior more traditional ALS trials where the drop out rate is 22%.

Methods: This is a single center pilot trial of 3 products, collectively referred to as "Lunasin." The trial employs a number of novel design features that we hope will make it more attractive to patients – for both recruitment and retention in the trial. These include broad inclusion criteria, use of historical (rather than placebo) controls, biomarkers, 3 total in-person visits with the majority of data collection happening virtually via PatientsLikeMe and results available in real time. Participants are being taught to measure their own ALSFRS-R score, weight and perceived efficacy of Lunasin, and to record these monthly on PatientsLikeMe. Blood is being collected at screening and month 1 visits to look for changes in histone acetylation and gene expression.

Results: To date, the trial has been open for 1 month, and has enrolled 16 out of 50 planned participants. We anticipate completion of enrollment in June 2016, and will be able to present participant demographics, final enrollment rate, biomarker data, interim drop out rate, and interim safety and efficacy at the next International Symposium in Dublin.

Conclusions: The Lunasin Virtual Trial employs a number of patient-centric features designed to circumvent problems encountered in more traditional studies. Our initial enrollment rate of 16 participants per site per month is higher than any other published ALS trial (2). Final enrollment rate, and other analyses will be presented.

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BW29 THE GENERVON CASE: ANALYSIS AND IMPLICATIONS ON THE RIGHT-TO-TRY DEBATE IN ALS

RINGKAMP G, ZOUGHLAMI A

Montreal Neurological Institute, Montreal, Canada

Email address for correspondence: gregory.ringkamp@mcgill.ca

Keywords: ethics, right-to-try, advocacy

Background: The slow progress of drug development and approval has provoked debate

over patients' right to try new drugs without proven efficacy (1). In this descriptive study, we examine one case that engendered debate over right-to-try (RTT) within the ALS patient community. This case attracted wide attention and may have significantly influenced the debate over RTT for ALS patients.

Objectives: To describe the manner in which the biotech company Genervon Biopharmaceuticals presented the experimental drug GM604 to the ALS community, and to explore the implications of their approach.

Methods: To gauge the impact Genervon's release had on the community, searches were performed on two major public ALS forums (ALSForums.com and ALS Therapy Development Institute), and a major petition about access to GM604 was reviewed (change.org) (2). To qualify Genervon's presentation of GM604 to the public, a thematic analysis was performed on both Genervon's press releases and the mediums through which patients were advocating.

Results: The debate over access to GM604 received wide coverage within the ALS community. A topic about GM604 was ranked 4th/616 topics in views on the ALSforums.com "ALS Research News" subforum. A separate topic about GM604 on the ALS Therapy Development Institute forum ranked 4th/122,168 topics in views. The change.org petition for accelerated approval for GM604 received 799,649 signatures. Genervon's press releases (1) highlighted a lack of alternatives to GM604 for patients. They (2) claimed sufficient data was present to justify FDA approval for GM604, and furthermore, that (3) GM604 has robust safety and efficacy data. They (3) asserted that the current clinical trial framework is detrimental to current ALS patients because new ALS drug development takes longer than patients' lifespans. They (5) describe GM604 as a "paradigm shift" encountered with strong resistance from the "medical-industrial complex". Genervon's press releases were referenced or quoted by advocates in all of our surveyed mediums.

Discussion and conclusions: While some of Genervon's themes are common to existing RTT legislation (3) and Model Act (4), we conclude that that at least some of the themes put forward by Genervon have influenced the debate over RTT in ALS. The Genervon debate produced sentiments that the scientific community and government health organizations are either unwilling or unable to offer novel treatment options. The size of the movement behind GM604 has in turn led to calls from within the community to circumvent the regular process for developing new treatments. Implications may be profound for the ALS community.

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THEME CP: CARE PRACTICE

CP1 INVESTIGATING THE USE OF DIGITAL LEGACIES WITH PEOPLE AFFECTED BY MND

CLABBURN O, O'BRIEN M, JACK B, KNIGHTING K

Edge Hill University, Ormskirk, Lancashire, UK

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

Keywords: palliative care, whole family, technology

Background: Dignity therapy is a proven palliative care intervention which encourages people, at the end of their life, to reflect and record their past experiences and memories by creating a legacy document. An alternative format, the 'digital legacy', is a purposefully recorded selection of video messages regarding a person's life, memories and achievements using a webcam or iPad/iPhone. The topic of creating a digital legacy, specifically for a child, using 'RecordMeNow' was presented at the APF (Allied Professionals Forum) meeting in 2014. To date, there is little published research about how children/young people are affected when a family member has the disease and subsequently dies. As such, there is a dearth of literature on how to best support these young people.

Objective: This research is investigating the use of a 'digital legacy' with people who are affected by MND. This means people living with MND (plwMND) create a series of video messages of their memories and accomplishments, specifically for a child in their family, which are later copied to a DVD or digital source. The process allows a period of reflection for the person with MND to document their life, whilst also creating a tangible resource for a young carer and/or bereaved young person.

Methods: The study is underpinned by Interpretative Phenomenological Analysis (IPA) meaning a small homogeneous sample is required. Recruitment is currently underway and being achieved through MND care centres, traditional newsletter publications and utilisation of numerous online social media platforms (blogs, forums, Twitter and Facebook). Individuals who are interested in participating then establish contact with the research team. Data collection involves a single, unstructured interview with each participant. This offers a time for participants to discuss their experiences of creating/using a digital legacy. Written transcripts are then analysed in accordance with the IPA methodology.

Discussion: Although recruitment is a challenge, the initial findings suggest that a digital legacy creates benefits for the plwMND. The process of creating a digital legacy requires little input from health care professionals. It is paramount for plwMND to be made aware of creating a digital legacy at the appropriate point in their disease trajectory. Acceptance of the disease, vocal ability and physical dexterity are crucial factors to consider when discussing the intervention with plwMND.

CP2 THE CARERS' ALERT THERMOMETER (CAT): IDENTIFYING THE SUPPORT NEEDS OF FAMILY CARERS OF PEOPLE LIVING WITH MND

O'BRIEN M[1], KNIGHTING K[1], JACK B[1], FAIRFIELD H[2], DRINKWATER N[2]

[1]Edge Hill University, Ormskirk, UK, [2]MND Association, Northampton, UK

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

Keywords: Carers' needs; support; Carers' Alert Thermometer

Background: Burden and distress experienced by family carers of plwMND is well known and reported widely within the published literature. Evidence-based screening tools to help identify carers at risk of breakdown and plan appropriate support to meet carers' needs are urgently needed (1). The Carers' Alert Thermometer (CAT) was developed in a study funded by the NIHR (2011-2014). It is a quick and easy-to-use alert tool designed to be completed collaboratively by carers and non-specialist health staff to identify the needs of carers of family members with cancer and advanced progressive illness in their last year of life (2). The CAT has 10 questions to identify the support needed by the carer to provide care and for the carer's own health and well-being. A traffic light system indicates the level of need for each alert and a visual thermometer signifies the extent of the carer's needs. There is a guidance section for alerts which can be tailored to local services and an action plan to complete with review dates. (www.edgehill.ac.uk for more details).

Objectives: To modify the CAT and pilot it with family carers of plwMND to determine its usefulness in identifying their need for support.

Methods: A workshop was held with MND Association Visitors (AVs), Regional Care Development Advisers (RCDAs) and a Regional Delivery Manager (RDM) to review the CAT, provide training on its implementation and demonstrate resources including a DVD. The CAT was modified to ensure its wording and format were appropriate for non-healthcare staff to use eg removing some patient information and replacing the term 'risk' with 'need'. Participants then trialled the CAT with family carers during routine appointments. Feedback on the utility of the CAT is obtained through a self-completed online survey and telephone interview.

Results: Piloting is currently underway. To-date preliminary data reveals that AVs and RCDAs who trialled it found the CAT very useful in their discussions with family carers and intended to continue using it. It was felt particularly beneficial for monitoring changes in the caring role as the disease progresses. Further roll out and piloting of the CAT is underway and additional findings will be presented.

Discussion and conclusions: Participants found the CAT relevant and feasible. It is an easy-to-use tool to facilitate discussions with family carers regarding their own specific needs and how these may be addressed. Use of the CAT with carers, supports the MND Association's mission to ensure that support is there not just for the person diagnosed with MND, but for the relatives and friends who care for them too.

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CP3 WELL-BEING AND CARE BURDEN OF CLOSE RELATIVES TO PERSONS WITH ALS-FTD

GREDAL O, HOVMAND B

National Rehabilitation Centre for Neuromuscular Diseases, Copenhagen, Denmark

Email address for correspondence: olgr@rcfm.dk

Keywords: managing ALS/FTD, care burden for relatives

Background: Changes in personality in patients with ALS are well-documented. In some cases, signs of FTD are prominent already in the early disease stages, and close relatives know without a doubt that the personality/cognition of the affected person has changed. RCFM offers rehabilitation to the entire family. Spouses (to persons affected with ALS with personality changes or diagnosed with FTD) report a heavier care burden and decreased well-being.

Objective: To investigate whether RCFM can reduce the care burden of close relatives by: identifying ALS/FTD problem areas in the family; verbalizing daily problems such as changing roles, care burden and well-being; informing about the causes and background for personality changes; offering psychologist sessions and teaching strategies for coping with abnormal behavior.

Methods: The intervention begins with a home visit where we investigate the patient's cognitive and behavioral problems and the role, burden and well-being of the relative using questionnaires, tests and interviews. The interview may reveal problems associated with shame, sorrow, anger or frustration which have previously not been addressed. The relatives are asked to prioritize the five most critical problem areas which will subsequently be the focus of our intervention.

Results: The study showed that ALS-FTD appeared in many different ways and that the relatives felt relieved by being able to address the problems. Their well-being was affected by FTD and the care burden increased dramatically when reduced functional ability was added to mental changes. The intervention could not take away the burden from the relatives but they learned new strategies for living and coping with the affected person. We present the results from the first 15 ALS patient/relative interventions at the Symposium.

Conclusion: ALS-FTD is a progressive disease causing physical and mental changes. Focusing on the mental changes helps relatives understand the situation better and gives them a better understanding of their own capabilities in terms of help and care. The intervention calls for an individual design, and information should also address helpers, adult children and professional caregivers. RCFM is planning to set up a network for relatives to FTD. It is important that local professionals with expertise in dementia/FTD are involved in the intervention.

CP4 PSYCHOSOCIAL SUPPORT FOR ALS INFORMAL CAREGIVERS: STUDY PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL

DE WIT J[1], SCHRÖDER C[1], BEELEN A[2], VAN DEN BERG LH[3], VISSER-MEILY A[1]

[1]Brain Center Rudolf Magnus and Center of Excellence for Rehabilitation Medicine, University Medical Center Utrecht and De Hoogstraat Rehabilitation, Utrecht, The Netherlands, [2]Department of Rehabilitation, Academic Medical Centre Amsterdam, Amsterdam, The Netherlands, [3]Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands

Email address for correspondence:

j.m.m.dewit-8@umcutrecht.nl

Keywords: caregivers, psychological support, emotional functioning

Background: Informal caregivers are key figures in ALS care. ALS caregiving is an intensive task and studies show a worsening of burden and overall psychological well-being of ALS caregivers during the disease course. Offering psychosocial support to the caregiver may increase the wellbeing of both caregiver and patient.

Objectives: In this presentation, we describe a psychosocial intervention for the informal caregivers of people with ALS and the design of the trial to evaluate its effectiveness. The main objective of the trial is to compare the effects of the psychosocial intervention and care as usual on the emotional functioning of informal caregivers. Secondly, our study will investigate the direct influence of the emotional functioning of the caregiver on the emotional functioning of the patient.

Methods: The effects of the psychosocial support program will be investigated in a randomized waitlist controlled trial in which 140 ALS caregiver-patient dyads will be included. The intervention will take 3 months and the waiting list control group will start with the intervention 6 months after recruitment. The intervention is focused on the specific needs of the caregiver and will be offered partly online and partly face-to-face. Eligible caregivers are partners of ALS patients, 18 years or older and have access to the Internet. Exclusion criteria are: inability to complete questionnaires due to insufficient mastery of the Dutch language, caregivers with severe disorders and patients who are diagnosed less than three months ago or have a life expectancy of less than six months. Caregiver-patient dyads will be asked to fill in questionnaires on 4 occasions during the study: baseline, 3 months, 6 months and 9 months. The primary outcome measure is caregivers' emotional functioning. Secondary outcome measures are caregiver burden, patients' emotional functioning and patients' and caregivers' quality of life. Included covariates are caregiver self-efficacy, patients' physical functioning and patients' behavior changes. A linear mixed model for repeated measures will be used for each outcome measure.

Discussion and conclusions: At present, there are limited interventions aimed at supporting informal caregivers of people with ALS. This study aims to provide evidence for the effectiveness of a supportive intervention for caregivers. Results will be available in 2018 and may enhance the quality of care for ALS caregivers and patients.

Acknowledgements: This study is supported by the ALS Foundation Netherlands.

CP5 A PROSPECTIVE STUDY OF QUALITY OF LIFE IN NEWLY DIAGNOSED ALS PATIENTS

JAKOBSSON LARSSON B, NYGREN I, ENGLUND T

Department of Neurosciences, Neurology, Uppala, Sweden

Email address for correspondence: birgitta.jakobsson.larsson@akademiska.se

Keywords: quality of life, psychological well-being, newly diagnosed

Background: ALS is a fatal disease with impact on physical function, social life and psychological well-being from the time of diagnosis and during disease progression. Despite this knowledge, there is a lack of knowledge about quality of life among newly diagnosed ALS patients.

Objects: The aim was to prospectively study how the patients evaluate their quality of life and if there were any changes in perceived quality of life during the first six months after diagnosis. Another aim was to determine if individual quality of life correlated with physical function or emotional well-being.

Methods: A total of 36 patients were included in the study. Individual quality of life was measured using the Schedule of Evaluation of Quality of Life- Direct Weighting (SEIQoL-DW) (1), psychological well-being was measured with the Hospital Anxiety and Depression Scale (HADS) (2) and physical function was estimated with the revised ALS Functional Rating Scale (ALSFRS-R)

(3). The evaluation was made one to three months after diagnosis and six months after diagnosis.

Results: The mean ALSFRS-R score was 38/48 at baseline and 33/48 at the second assessment. Four patients had symptoms of clinical anxiety, the number decline to three at the second assessment. There were two patients with symptoms of clinical depression at baseline and at the second assessment. The quality of life index was 68.1/100 at baseline and 67.1/100 at the second assessment. Individual quality of life did not correlate with physical function; however, individual quality of life correlated with depression at six months after diagnosis.

Conclusion: Most patients rated their quality of life as relatively good, and there were no changes during the first six months after the diagnosis, despite the changes in their physical function. There was a correlation between quality of life and depression at six months after diagnosis, indicating that patients with a lower score on the quality of life index suffered more for symptoms of depression compared to those with higher scores.

Acknowledgment: This study was founded by Uppsala University, Uppsala University Hospital, Ulla-Carin Lindqvist ALS research Foundation and Norrbacka-Eugenia Foundation.

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CP6 INFLUENCES ON QUALITY OF LIFE FOR PEOPLE WITH MND/ALS: PROGRESS OF THE TRAJECTORIES OF OUTCOME IN NEUROLOGICAL CONDITIONS STUDY

YOUNG C[1,2], DYAS-WOLLF L[1], TENNANT A[3], ON BEHALF OF THE TONIC GROUP[1]

[1]Walton NHS Foundation Trust, Liverpool, UK, [2]University of Liverpool, Liverpool, UK, [3]Swiss Paraplegic Research, Nottwil, Switzerland

Email address for correspondence: profcyoung@gmail.com

Keywords: quality of life, patient reported outcome measures, TONiC

Background: Quality of life (QoL) is subjective, multidimensional and reflects the individual's positive and negative experiences of interacting biological, psychological and social factors.

Objective: The Trajectories of Outcomes in Neurological Conditions (TONiC) study aims to analyse factors selected by people with motor neurone disease (PwMND) as influential on their QoL, along with demographic, clinical and health economics data, in order to improve future care and services for patients.

Method: This is a prospective, longitudinal, multicentre study open to all PwMND in the UK. Data are collected by questionnaires for patient, carer and clinician. The patient questionnaire has many Patient Reported Outcome Measures (PROMS) which reflect factors deemed important for quality of life in baseline qualitative work with PwMND. For factors which could not be matched to an existing measure with face validity among PwMND, measures were developed specifically for the study. Participants can contribute just once for cross-sectional analysis (M0), or re-join the project to provide longitudinal data at months 4, 9, 13, 18, 24, 36, or 60. Clinicians provide data on date of diagnosis, onset subtype (limb/bulbar/respiratory) and revised amyotrophic lateral sclerosis rating (ALS) scale. Carers provide ALS-frontotemporal dementia questionnaire.

Results: By March 2016, there were 19 sites, with four more in set-up and others expressing interest; and questionnaires along with clinician data had been returned for 477 PwMND (66.5% response rate) along with 339 carers (66.3% response rate). Clinical data are held for PwMND who declined questionnaire participation, allowing analysis of biases in the responding participants. New PROMS for spasticity, hope, coping, social isolation (1), and fatigue (2), developed to Rasch measurement standards, are being made freely available for any academic or not-for-profit user. The first model is published from pilot work, demonstrating the importance of coping on QoL (3).

Conclusions and future directions: The piloted PROMS allow the development of biopsychosocial models of QoL to be developed incorporating a range of disabilities, durations and person factors. In addition, TONiC is part of an international collaboration with the ICF Research Branch, partner of the World Health Organisation Collaborating Centre, for the development of a standardised reporting architecture for health information based on the International Classification of Functioning, Disability and Health. This will facilitate comparison of functioning information between MND and other health conditions and meta-analysis of international MND-specific data.

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Acknowledgements: We thank the participants, without whom this study would not be possible, and also the MND Association and NIHR CRN for support.

CP7 PEOPLE LIVING WITH MOTOR NEURONE DISEASE FACING THEIR OWN MORTALITY

HARRIS D

University of Salford, Manchester, UK

Email address for correspondence: denise.harris13@outlook.com

Keywords: lifeworld, loss of temporality and spatiality, melancholia

This paper presents the findings from a hermeneutic phenomenological study that asked four participants to talk about the meaning of their existence (1) with motor neurone disease (MND), a life limiting illness. Naturally they all talked about first noticing the impact of MND on their lifeworld. In addition, they talked about the meaning of facing their own mortality, which included thoughts on assisted suicide, living with certainties and uncertainties, the fear of becoming a burden, and making future plans. The findings suggest that the participants are experiencing mixed degrees of loss of temporality (2) and spatiality, (3) and although they may not be depressed, they may be experiencing melancholia. (4) Early recognition of the loss of temporality and spatiality is essential for people newly diagnosed with MND.

(1) Existence - Heidegger outlines the key structures of existence (also called Lifeworld). He argues that we all have an embodied sense of self, which is always in relation to others, while our consciousness is shared with others through language, discourse, culture and our history.

(2) Temporality - We are 'temporal', as we are our history, moving from birth to death. But this movement is not experienced as a linear one-after-the-other, as the hand of a clock moves from one moment to the next, but the past is carried along by a present that is already anticipating the future.

(3) Spatiality - If existence is 'being-in-the-world', it is 'spatial' – that is, part of a wider context to which it is related. But the space between different parts of this context is not measurable in feet and yards but is experienced differently at different times; what is close today, can be distant tomorrow.

(4) Melancholia - In a modern context, "melancholy" applies only to the mental or emotional symptoms of depression or despondency; historically, "melancholia" could be physical as well as mental, and melancholic conditions were classified as such by their common cause rather than by their properties.

CP8 PREPARING FOR END-OF-LIFE AFTER CARTER: A REVIEW OF END-OF-LIFE EXPERIENCES AND PERSPECTIVES OF PEOPLE WITH ALS, THEIR FAMILIES AND HEALTH CARE PROVIDERS

LUTH W[1], MOIR M[1], LEE A[2], VALE C[1], BUBELA T[1], JOHNSTON W[1]

[1]University of Alberta, Edmonton, Alberta, Canada, [2]University of Calgary, Calgary, Alberta, Canada

Email address for correspondence: wluth@ualberta.ca

Keywords: communication, quality-of-life, end-of-life

Background: In 2015 the Canadian Supreme Court struck down the prohibition against medical aid in dying (MAiD) (1). Gloria Taylor, a person with amyotrophic lateral sclerosis (ALS) was central to that case, and ALS patients have been among the first patients to seek MAiD in Canada (2-3). Interest in MAiD is linked to hopelessness, insomnia, pain and other manifestations of declining quality of life (QoL) (4). Therefore, this decision inspired broader introspection about the QoL for people with ALS, and end-of-life (EoL) care in Canada. In this rapidly evolving context, a review of research on ALS research on QoL and EoL will provide an evidence base for future research and communication guidelines.

Objectives: To identify strengths and deficits in EoL care and communications, we review the current state of the literature on the EoL experiences and perspectives of people with ALS and their families and health care providers.

Methods: We conducted a scoping review of empirical articles published before October 14, 2015 in databases including: Medline, CINAHL, Scopus, and LexisNexis. The search produced 1815 unique papers. After applying our inclusion and

exclusion criteria, we identified 152 relevant articles. We used an a priori coding frame to summarize how researchers are addressing QoL and EoL in the literature. We conducted a more detailed qualitative analysis on articles about communication between health care providers and ALS patients and their families.

Results: Our preliminary results suggest the physical and psychological/emotional QoL, of people with ALS are dominant themes in the literature. The experiences of family caregivers, particularly the psychological burdens associated with caregiving, also feature prominently. Physicians' experiences and perspectives are well represented, but other health care professionals are under-examined. The mode and substance of communication between health care providers and ALS patients and their caregivers are also recurring topics. Articles on ALS patient experiences with and perspectives on EoL care options are common, but very few address MAiD.

Discussion and conclusion: While certain aspects of ALS patient QoL and EoL have been addressed in the literature, others are conspicuously absent. Very little research has addressed patient, family caregiver, or health care provider experiences or perspectives with MAiD in the context of ALS. This research gap must be addressed in light of the Canadian Supreme Court decision on MAiD.

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CP9 PORTRAYALS OF ALS PATIENTS AND END OF LIFE ISSUES: MEDIA ANALYSIS POST CARTER V. CANADA (2015)

MOIR M, BUBELA T, JOHNSTON W

University of Alberta, Edmonton, Canada

Email address for correspondence: moir@ualberta.ca

Keywords: media, discourse, end-of-life

Background: After an ALS diagnosis, patients and family members commonly seek additional information from traditional media and the internet (1, 2). Unfortunately, they encounter stories with inherent biases that are not readily apparent to readers. In the context of biomedical breakthroughs, and experimental treatments like stem cell therapies, stories are framed as hopeful (3) which may lead patients to seek out unproven therapies (4). In contrast, recent Canadian media coverage on medical aid in dying (MAiD) frames the experience of ALS patients more negatively. Our preliminary scan of Canadian media articles covering MAiD shows that neurological conditions and ALS are discussed the most. In Carter v. Canada (2015) (5) the Supreme Court of Canada struck down the criminal prohibition against MAiD. This ruling has triggered changes in clinical communication about end-of-life (EOL) decisions for Canadians with terminal illness, including ALS. The attitudes of ALS patients towards MAiD are complex (6). Health care providers will require communication strategies that account for these perspectives. These strategies will require tools that address the spectrum of information available to patients and caregivers outside the clinic.

Objectives: We are conducting a quantitative and qualitative media analysis of Canadian print and broadcast news media to identify dominant portrayals of people with ALS with a particular focus on the end-of-life debate.

Methods: A standardized search strategy will be developed for Canadian media (newspapers, magazines, TV and radio transcripts) and Internet content (social media, blogs and advocacy sites) available to Canadians; using media databases including Factiva and Canadian Newsstand. Key themes, framing and general content of articles will be analysed using a combination of an *a priori* coding frame and qualitative discourse analysis (7).

Discussion and conclusions: We hypothesize that the recent legal changes and media coverage of Carter (2015) (4) has created an environment of conflicting information, rather than clinical evidence, across Canada. Our analysis will inform guidelines that help stakeholders affected by ALS navigate this challenging environment and effectively communicate clinically complex and emotionally sensitive issues related to EOL care and MAiD.

Acknowledgements: This project is supported by the SPOR Graduate Studentship in Patent-Oriented Research and the James and Jeanie Brown ALS Research Fund dedicated to improving the lives of people living with ALS.

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CP10 PALLIATIVE CARE IN A US VETERANS HOSPITAL ALS PROGRAM: STRUCTURE, PROCESS AND OUTCOMES

RATNER E[1,2], BRADSHAW K[1], GREENWOOD D[1]

[1]Minneapolis VA Medical Center, Minneapolis, Minnesota, USA, [2]University of Minnesota Medical School, Minneapolis, Minnesota, USA

Email address for correspondence: edward.ratner@va.gov

Keywords: palliative care, hospice, end of life care

Background: Palliative care for patients with Amyotrophic Lateral Sclerosis (ALS) is challenging due to impairments in strength, cognition and communication, combined with uncertain course of illness and complex decisions regarding use of life prolonging therapies (eg enteral nutrition and ventilatory support). Palliative care in ALS includes symptom management near the end of life but also facilitating discussions of goals and preferences. United States Veterans Affairs hospitals began recognizing the association of ALS and military service in 2008, providing financial benefits and offering ALS clinical programs. An urban Veterans Affairs hospital ALS clinic added a palliative care focus to its program in late 2012.

Objectives: This study examined the structure, processes and outcomes of an ALS palliative care program.

Methods: Palliative care disciplines include medicine, nursing, social work, psychology, rehabilitation therapies, nutrition and chaplaincy. Palliative care visits occur in clinic, on the adjacent rehabilitation ward, on other hospital wards and in patients' homes and community nursing homes. A key intervention in this palliative care program is disease-specific advance care planning (ACP). Activities best performed in the home include such ACP, environment assessment, evaluation of caregiver stress, observation of mobility and function, medication reconciliation and discussion of spirituality. Home-based palliative care has also included organizing emergency out-of-home respite when a caregiver has become incapacitated, installation of electronic environmental controls and withdrawal of life-sustaining treatments (e.g. discontinuation of ventilatory support or enteral feedings). Referral to government-funded hospice programs is promoted as soon as patients meet government payer criteria, which includes forced vital capacity < 30% predicted (if not using invasive ventilation) or inability to maintain weight (without or despite enteral feedings). Outcomes among deceased patients were compared between 2009-2012 and 2013-2016.

Results: There have been approximately 150 veterans who have died in this program from ALS since 2009. In the first three years of the program, less than ¼ of patients were referred to hospice. Since 2013, about 2/3 have been enrolled in hospice. The average length of enrollment in a hospice program increased from about 90 days to 114 days. At the same time, use of life prolonging therapies has increased. Among 65 currently living patients, feeding tubes and invasive ventilation are being used more often than is typical in US programs, with over 50% of patients fed enterally and four patients (6%) at home with tracheostomies.

Discussion and conclusions: Palliative care in ALS requires even more health professionals than the typical diagnostic and therapeutic ALS team. Home-based care can assess many problems better than in clinic and allows more time for discussion of complex issues. A comprehensive ALS palliative care effort can greatly increase use of hospice services, but may also lead to greater use of life-prolonging therapies.

CP11 STREAMLINING PRIMARY CARE FOR VETERANS WITH AMYOTROPHIC LATERAL SCLEROSIS

SLUDER K[1], JOHNSON J[2]

[1]Eastern Colorado Healthcare System, Denver Veterans Affairs Medical Center, Denver, Colorado, USA, [2]University of Colorado School of Medicine, Anschutz Campus, Aurora, Colorado, USA

Email address for correspondence: marie.sluder@gmail.com

Keywords: patient centricity, care coordination, multidisciplinary care

Background: Amyotrophic lateral sclerosis (ALS) patients receiving care in one Western United States Veterans Medical facility have experienced a complex network of providers and suppliers. Fragmented communication has imparted the overutilization of resources, re-work and lack of therapeutic empanelment, in addition to caregiver burnout. Delivery of care was of concern following the discharge of two patients failing to obtain the proper equipment for home mechanical ventilation and another that suffered an untimely death because of a delay in supportive services.

Objective: Identify a best practice model of care for veterans with ALS.

Methods: The Six Sigma quality improvement model provided the foundation from which healthcare providers better identified problems and possible solutions. A multidisciplinary group of key stakeholders met weekly for a year to identify opportunities for improvement in ALS care. Participants were divided into three focus groups including communication, patient education/caregiver support and supply. Each group was asked to record chart audit findings onto a data collection tool. Data analysis was completed using descriptive statistics.

Results: There is a high volume of individuals with ALS with no streamlined standard for communication or patient education delivery. We found there was haphazard scheduling, a revolving door of providers, and lack of feedback to the primary care team. ALS patients were seen by over 50 different healthcare providers across time and multiple services. Continuity of care during follow up appointments occurred in only 30% of neurology and 50% of physical therapy visits. Primary care providers were co-signed on progress notes by neurology less than 5% of the time and 25% for pulmonology. Other notable findings included unnecessary, frustrating, and expensive Emergency Department visits, and potentially avoidable nursing home placements.

Discussion and conclusions: An ALS patient's clinical progression and symptom management necessitates an efficient and effective approach to care. Key stakeholders identified best practice as having a dedicated ALS Advanced Practice Nurse (Nurse Practitioner) who would serve as primary care provider (General Practitioner) for all ALS patients and would be fluid across: spinal cord injury clinic, specialty clinics, inpatient, and community domains. Other aspects of the best practice model of care includes: consolidating ordering of supplies; revitalizing patient education materials; and working on obtaining initial funding for the Advanced Practice Nurse position through a research grant.

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CP12 PROVING OUR WORTH – DEVELOPING OUTCOME MEASURES FOR THE MOTOR NEURONE DISEASE MULTI-DISCIPLINARY CLINIC

PRENDIVILLE V[1], GLEW R[2], HIRST C[1,2], THOMAS A[1], ANNANDALE J[1], WILLIAMS C[1], SAMUEL ANNE[1], HOOKWAY A[2], THOMAS C[1], O'CONNELL D[1], CROFT R[1], FURLONG K[1]

[1]Hywel Dda Health Board, Carmarthen, UK, [2]South Wales MND Care Network Morriston Hospital, Swansea, UK

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

Keywords: outcome measure, multi-disciplinary clinic, evaluation

Background: The South Wales Motor Neurone Disease Care Network have supported Hywel Dda University Health Board to optimise the care of patients diagnosed with Motor Neurone Disease (MND) through supporting the planning, delivery and implementation of multi-professional MND operational teams and Consultant led multi-disciplinary team (MDT) clinics.

Objectives: The Hywel Dda MND multi-disciplinary team were keen to explore whether the clinics were meeting standards of care published nationally such as the MND Association Standards of Care, Welsh Government Neurological delivery plan (2014) and Hywel Dda University Health Board key drivers by developing outcome measures that would demonstrate the impact of the clinic on patient outcome.

Methods: A quality improvement team led by the MND team Dietetic service lead including: MND Regional Lead Network co-ordinator, Speech and Language Therapist, Respiratory nurse, Palliative care Clinical Nurse Specialist, Consultant

Neurologist, Physiotherapist, Occupational Therapist and Database Project Manager was set up, whose aim was to agree the following: 1. Key outcomes for the Hywel Dda MND clinic; 2. Robust outcome measures (quantitative and qualitative); 3. System(s) for recording and evaluating outcomes. A series of workshops were undertaken utilising quality improvement methodology such as mapping against key drivers and results based accountability.

Results: Quality improvement methodology enabled the team to capture key outcomes for the MND clinic along with quantitative and qualitative outcome measures which will be presented. Overarching aims encompassing the standards of care relating to MND and specific professional standards included: timely and supported diagnosis; fast effective and patient centred care; optimising patient experience. Outcome measures agreed included: quantitative measures - for example number of clinics in a year with full MDT representation; qualitative patient experience measures such as patient satisfaction questionnaires, wellbeing assessments and patient stories; therapy specific measures - for example % of patients receiving texture modified dietary advice and support. To enable the recording of quantitative outcomes the team utilise the MND patient care database developed by Mark Wardle, Consultant Neurologist and Network Co-director.

Discussion and conclusions: The team have run an initial pilot audit using the database to identify problems with collection of quantitative data and analysis. Some initial issues have been identified and resolved. Two patient stories and a patient clinic satisfaction survey have been carried out. The team plan to use the data recorded to formulate reports that demonstrate the value of the team in terms of impact and patient centred outcomes. Further work is being undertaken to link these outcome measures fully with the NICE guidelines and further evaluation will be undertaken on an annual basis.

Acknowledgements: We would like to acknowledge the contribution of the Carmarthenshire MND MDT clinic team members to this work.

CP13 IMPROVING THE CLINIC EXPERIENCE FOR PATIENTS: DECREASING WAIT TIME IN MULTIDISCIPLINARY CLINICS

SHAHBAZI M

Hospital for Special Surgery, NY, NY, USA

Email address for correspondence: shahbazim@hss.edu

Keywords: clinic visit experience, clinic wait time, process improvement for clinic

Background: ALS clinic visits have shown to increase both quality of life as well as survival rate. Patients and families are able to meet with their neurologist and multiple members of the multidisciplinary team. These visits usually last 3 or more hours, which are gruelling for patients, especially when in wheelchairs and when travelling long distances.

Objectives: The aim of the study was to evaluate the average time patients spend in clinic waiting, including time to be seen and time spent in between staff member visits. The second objective of the study was to identify the primary causes of wait times and thirdly to plan a process improvement strategy to decrease this "non value" time by 50% for patient visits.

Methods: This was a 3 month study from April 1, 2016 to June 30, 2016 in 2 clinics in a busy NYC ALS program. Patients were timed from arrival and start of the clinic, including waiting time and time between staff until discharged. The time not spent face to face with a practitioner was measured per patient per visit and averaged. A total of 120 patient visits were analyzed. This data was then used to identify what parts of clinic experience had the longest wait and to initiate a plan to improve the wait time.

Results: Results are currently being analyzed. To date of submission, the average wait time of patient for an average 3 hour visit was 43 minutes.

Discussion: While multidisciplinary clinics have been shown to improve quality and survival of life for PALS, the 3-4 hour visits every 3 months can be difficult and uncomfortable for patients. The aim of this study was to find the average wait time for patients in clinic and to plan a process improvement strategy to improve the experience and reduce this time for patients, which can improve their visit.

CP14 CARE, AUDIT, RESEARCH AND EVALUATION (CARE-MND) IN THE SCOTTISH MOTOR NEURONE DISEASE POPULATION

LEIGHTON D[1,2], STEPHENSON L[1,2], COLVILLE S[1,2], NEWTON J[1,2], DAVENPORT R[1], GORRIE G[1], SWINGLER R[1], CHANDRAN S[1,2], PAL S[1,2]

[1]Euan MacDonald Centre for Motor Neurone Disease Research, University of Edinburgh,

Edinburgh, UK, [2]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

Email address for correspondence: dleighto@exseed.ed.ac.uk

Keywords: care, patient-centred, technology

Background: The Scottish Motor Neurone Disease Audit, Research and Trials (SMART-MND) network, launched in 1989, has provided a unique resource for collaborative, population-based prospective clinical data storage for a rare and devastating disease. Historically, these data have been collated from various sources by members of the SMART-MND team and inputted into a web-based user interface. However, 2015 marks a pivotal change in the approach to care and research in Scotland, and, fuelled by support from MND Scotland and the Scottish Government, we have initiated a process for real-time and standardised data capture.

Objectives: To develop a harmonised national data platform which fully integrates care, audit and research to allow: 1) A patient-centred approach to care based on recognised standards, 2) Standardised data sharing between healthcare professionals in 'real-time', 3) Regular audit of care to facilitate timely improvements in service delivery, 4) Patient participation in research studies including clinical epidemiology, caregiver burden, psychology, genetics, palliative care, pathology and clinical trials.

Methods: We developed a national clinical care paper proforma in collaboration with MND specialist teams throughout the fourteen health boards in Scotland. Other international data repositories were examined to ensure alignment and compatibility of the proforma. The proforma was piloted in paper format over a six month period, and then transferred onto an electronic platform to permit 'real-time' data storage and sharing. The proforma development coincided with an NHS Scotland and Scottish Government initiative to double the number of MND care specialists. Feedback from the full complement of care specialists was used to refine this system.

Results: From February 2016, there has been a standardised approach to MND care and research with the adoption of the national paper proforma. Based on emerging literature and patient feedback, new data fields have been incorporated with a focus on 1) the extended phenotype of MND through the documentation of extensive family history and 2) exogenous factors such as: toxin exposure, occupational history and exercise participation. This integration of care and research is unique to Scotland. A beta version of the electronic platform is currently being tested and results from this e-platform pilot will be presented.

Discussion: In a condition for which systematic data collection is challenging and for which treatments are tragically limited, we hope to provide a system by which patients throughout Scotland can be included in a routine audit of care and research. In this way we anticipate an improvement in equity of care and service provision and a stratification of the population for research, including clinical trials. In a technologically advancing climate, we hope to optimise on available resources and pave the way for other neurodegenerative diseases.

Acknowledgements: SMART-MND contributors

CP15 SCOTLAND THE BRAVE – CHANGES IN FUNDING OF MND CLINICAL SPECIALISTS IN SCOTLAND

NEWTON J[2,3], BETHELL A[1]

[1]NHS Highland, Scotland, UK, [2]University of Edinburgh, Scotland, UK, [3]MND Scotland, Scotland, UK

Email address for correspondence: andrew.bethell@nhs.net

Keywords: funding, Sturgeon, future

Introduction: Historically in Scotland MND Clinical Nurse Specialists (MNDCNS) were funded solely by MND Scotland. The first MND nurse was funded in Glasgow following inspirational financial gifting from the John McLeod family in the 1970's. Over decades, more nurses were introduced throughout Scotland and at the point of 2014 there were 7 MND CNS's based at the four Scottish Neurological Centres: Aberdeen, Dundee, Glasgow and Edinburgh. MND care in Scotland over the last five years has been positively influenced and encouraged to change by people diagnosed and living with the disease. During the run up to the Scottish Referendum, Mr Gordon Aikman, head of the "Better Together Campaign" was diagnosed with ALS, MND. With the eyes and ears of the Scottish and National cross parties on him, MND was harshly highlighted and put on the political agenda. Gordon set about with his "5 point Fightback campaign". Point one: the funding of the Scottish MND Nurses to be from the public purse and not charitable organisations. Gordon challenged the then newly appointed First Minister of Scotland, Nicola Sturgeon with this task and in January 2015 an announcement was made that £700k per annum would be distributed to the 14

Scottish Health Boards to in effect "double the MND nurses in Scotland".

We would like to present the following: the pre 2015 announcement on how MND Care was delivered in Scotland; the transitional phase of how MND care is being planned during the re-configuration of the newly funded team; to present in future symposia the real time impact this doubling of nurses has had on the main care milestones in MND, Respiration, Cognition, Nutrition, Function and Palliative Care by sharing our pre and post 2015 data.

CP16 SUPPORTING LIFELONG CARE IN THE COMMUNITY USING THE LONG TERM CONDITIONS REGISTER: PATIENT FEEDBACK

PREMA R, CANOVA C

The Royal Free London NHS Foundation Trust, London, UK

Email address for correspondence: rakhee.prema@nhs.net

Keywords: community care, multi-disciplinary working, patient feedback

Background: The Community Neurological Conditions Management team (CNCMT) is a specialist neurological team based in the London borough of Barnet, aiming to support clients with long term neurological conditions such as motor neurone disease (MND). Offering timely, responsive intervention to support individuals through the progression of their condition can be a challenge, especially in light of the unpredictable nature of the condition. The team uses a secure database called the long term conditions register (LTC-Register) to enable regular reviews and to support timely access to the service as recommended by the NICE guideline for MND 2016 (1). The register has been in use since 2003 and supports over 550 individuals with a long term neurological condition, 22 of these individuals have a diagnosis of MND. Although the LTC-register has become a well-established system within the team, the views and experiences of service users on the LTC-register has not been sought. The team is also unaware if the LTC-register provides broader benefits to health and wellbeing.

Objectives: To establish if the LTC-register is considered of benefit and value by service users with MND.

Methods: A structured postal questionnaire was sent to all service users on the LTC-register. Service users were requested to either complete a paper copy of the questionnaire or to complete an online format. Results were analysed using Microsoft Excel.

Provisional results: A total of 9 returned questionnaires were identified as being from individuals with MND (41% response rate from MND population). Although most respondents were aware of being on the LTC-register (67%) a significant proportion of respondents did not know when they were next due a review. When asked about how helpful individuals felt the review was 78% of respondents felt that the reviews were either very helpful or helpful with the remaining respondents not finding the review helpful. The questionnaire also sought to find out if individuals felt the register to have overall benefits to health and wellbeing. All respondents indicated that they felt there was benefit to being on the register; with the majority of respondents relating being on the LTC-register to reducing anxiety, reassuring family and carers, enabling self-referral, and reducing the need to visit the GP.

Discussion: The provisional results from this survey indicate that a significant proportion of service users with MND felt having regular reviews to be of benefit and value. Service users were also able to specify that being on the LTC-register provided additional benefits to health and wellbeing. Respondents however were unclear on when they were having their next review, indicating further work on ensuring this information is communicated effectively needs to be done.

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CP17 THE ”UPPSALA MODEL”-THE CARE AND TREATMENT OF MND PATIENTS AT UPPSALA UNIVERSITY HOSPITAL ENTAILS A MULTIDISCIPLINARY MND PROGRAM

DEN DULK C, FRANKE C, CIDH Å, BANIEGHBAL B

Department of Neuroscience, Uppsala University Hospital, Uppsala, Sweden

Email address for correspondence: asa.cidh@akademiska.se

Keywords: Uppsala model, team, multidisciplinary

Background: MND is a life-limiting, neurodegenerative disease that is characterized by fasciculations, paralysis and wasting of voluntary muscles (1). In most cases death occurs from respiratory failure within 5 years of diagnosis (2); most patients are still living at home within weeks of their death, requiring support from nursing and allied health workers to supplement in home care and provide respite (3).

Objectives: The purpose with this poster is to present our model, the "Uppsala model", for the care and treatment of MND patients and their family members.

Methods: At the time the patient is informed about the diagnosis, she/he is offered an opportunity to participate in the MND program. Regional and national patients are also referred to the program. The patients stay at the ward for one or two days about every ninth week and then meet all or parts of the MND team which consists of a neurologist, a nurse, occupational therapist, physiotherapist, speech and language therapist, dietician, social worker and members from the hospital church. The disease is also monitored with quantitative measurements of strength performed by biomedical analysts. Team members contact the patient and/or the family members, as needed, even between sessions at the ward. One of the goals is to achieve close co-operation with other programs and occupational categories, such as district occupational therapists, district nurses, district physiotherapists, speech and language therapists, dieticians at local hospitals, home services, home care, personal attendants and the National Social Insurance Office etc, who may have contact with the patient in her/his local community. The MND program in Uppsala also collaborates with a hospice unit to which patients can be sent in the terminal stage of their illness.

Results: There is considerable evidence that multidisciplinary care improves both survival and quality of life in MND. In a prospective Dutch study, patients treated by multidisciplinary MND care teams had a significantly better psychological quality of life than those looked after by a general care group (4, 5).

Acknowledgements: University Hospital, Uppsala, Sweden

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CP18 PHYSIOTHERAPY, OCCUPATIONAL THERAPY, SPEECH AND LANGUAGE THERAPY IN AMYOTROPHIC LATERAL SCLEROSIS – EXPERIENCE OF 5 YEARS MANAGED CARE IN GERMANY

MAIER A, STEINFURTH L, FUNKE A, KETTEMANN D, KECK M, WALTHER B, MÜNCH C, MEYER T

Charité, Universitätsmedizin Berlin, Ambulanz für ALS und andere Motoneuronenerkrankungen (AAM), Berlin, Germany

Email address for correspondence: andre.maier@charite.de

Keywords: multidisciplinary therapy, physiotherapy, speech and language therapy

Background: Multidisciplinary treatment (MT) including physiotherapy (PT), occupational therapy (OT) and speech and language therapy (SLP) is a crucial element of symptomatic and palliative treatment of people with amyotrophic lateral sclerosis (ALS). Despite a wide use of all aspects of MT in Germany and other countries, the reality of provision and prescription is rather unknown.

Objective: The study aimed to evaluate the current state of provision of physical therapy, occupational therapy and SLP in ALS. By analysing the actual provision and prescription reality of MT we intend to support the development of future standards of MT.

Method: We analysed the data of 431 patients of the ALS outpatient department of Charité, University medicine Berlin, Germany. All patients were included in the Internet-supported managed care network www.AmbulanzPartner.de, where 338 providers of MT treated the patients between 2011 and 2016. We collected clinical data like age, gender, disease duration and ALSFRSr to show group differences.

Results: Throughout the evaluation period 149,126 therapy units on 7,502 prescriptions were analysed. With 72.1% physical therapy showed the largest percentage of MT. Within PT specific forms of treatment have been applied: Bobath concept (23.5%), chest physiotherapy (16.4%), massage (14.2%), lymphatic drainage (13.1%). 21.3% of

prescriptions of PT encompass colon massage, heat therapy and other CNS techniques. OT comprises 16.9% of the prescriptions. 87.8% requested sensomotoric perceptive techniques, motoric functional treatment was applied in 5.7% and mental and psychological training was performed in 4.3%. The speech-language therapists aimed on communication disorders in 84.5% of treatments whereas 15.5% dealt with swallowing disorders.

Discussion and conclusion: ALS demands a complex and comprehensive multidisciplinary treatment. The preferences of prescription are dominated by physical therapy. Special therapy techniques are at the forefront. Due to a significant number of therapy units per patient over the course of the disease the providers gain a key role in the treatment of ALS. This fact is well underrepresented in terms of therapist qualification and interprofessional communication. Multicentre studies are required to reproduce our monocentric approach and to enable guideline development for multidisciplinary treatment in ALS.

CP19 CASE STUDY IN RESEARCH: A VIABLE METHOD FOR ENHANCING UNDERSTANDING OF MND WITHIN OCCUPATIONAL THERAPY

CAREY H

Glyndwr University, Wrexham, UK

Email address for correspondence: h.carey@glyndwr.ac.uk

Keywords: case study, occupational therapy, interventions

Background: The nature of disease presentation within MND is individualistic (1) which creates difficulty in researching MND within a positivist paradigm. In addition, the practice of occupational therapy is subjective and this provides a challenge in reflecting the essence of practice for MND within research methodology. The individualistic practice of client centredness and the importance of context are core elements of occupational therapy and require a research approach that reflects these. The case study approach is explored as a viable research methodology for therapists investigating MND.

Objectives: To define the elements of the case study approach; to ascertain its effectiveness within occupational therapy research; to provide recommendations for its effectiveness in understanding MND in relation to occupational therapy.

Method: An integrative literature review was carried out to explore contemporary occupational therapist's application of case study as an approach. A comprehensive electronic search of the following databases was conducted: Cinahl, Medline and Psychinfo followed by a search of the College of Occupational Therapists online dissertation database. Keywords of "case study method", "case study approach" and "case study methodology" were combined with "occupational therapy". A ten year period enabled contemporary occupational therapy practice to be reflected on, whilst producing a robust number for comparison.

Results: Thirty papers were synthesised demonstrating a global uptake of the case study approach, yet occupational therapy application of the case study approach was limited. Whilst there was a breadth of case study approaches, there had been no case study approach focussed on MND and occupational therapy.

Discussion and conclusions: The elements of a case study approach is a strongly viable and acceptable research tool to reflect the elements of occupational therapy practice within the individual presentation of MND. Occupational therapy research in MND would benefit from a higher number of case study designs to reflect the complexity, subjectivity and person centredness of the profession and the individualistic aspect of MND presentation. The criticisms in terms of lack of generalisation and replication (2) do not outweigh the depth of understanding gained through a multi-angled depth of study within case studies. Occupational therapists should embrace the case study approach as a familiar, viable tool to reflect the individual context of MND to enhance understanding of the impact of occupational therapy interventions within MND.

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CP20 WHAT DRIVES DRIVING HABITS IN PATIENTS WITH ALS?

CIANI G[1,2], SHABAZI M[1], HOLZBERG S[1], LANGE D[1]

[1]Hospital for Special Surgery, New York, New York, USA, [2]Hofstra University, Hempstead, New York, USA

Email address for correspondence: gioia.j.ciani@hofstra.edu

Keywords: driving habits, driving cessation, quality of life

Background: Driving is a multifaceted instrumental activity of daily living that provides freedom and autonomy and quality of life. Because of this many people resist driving cessation, even those with declining health. Progressive loss of motor functioning impacts one's ability to drive safely (1,2). Drivers with neurological disorders have twice the rate of at-fault crashes than controls (3). PALs may push the limits of driving safely. It is often difficult to determine just when driving becomes unsafe. At some point, the decision to stop driving must be made. Socio-economic status, social support, insight and self-regulation may play a role in the decision to continue or to stop driving (2). To date, there have been no studies done that investigate the factors involved in the decision to continue or to stop driving in PALS.

Objectives: This study examines factors that are involved in the decision to stop driving or to continue driving in PALS.

Methods: This study employs a convenience sampling of patients who attend multidisciplinary clinics. Only those patients with a diagnosis of ALS that are currently driving or who stopped driving after diagnosis were included. Patients with cognitive limitations/dementia were excluded. Two measures were used in relation to driver demographics: The Driving Behavior Scale and The Driving Habits Questionnaire. Additionally, open-ended questions designed to further explore patient experiences, perceptions and quality of life were incorporated. A web-based commercial survey management service was utilized.

Results: Currently, 12 patients have participated in this study. Preliminary results are varied. Surveys are open and analysis of results is ongoing.

Discussion and conclusions: As motor functions decline in PALs, the decision to stop driving has to be made at some point. Findings suggest that the decision to stop driving is not just linked to the ability to drive. Environmental and socio-demographic factors greatly influence the decision to stop driving. There is a need for health care providers to discuss driving cessation or limitations with patients and their families. It is important for patients and the multidisciplinary health care providers to understand all factors involved in this process so that the decisions and possible consequences of driving cessation can be properly addressed.

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CP21 TELEBCI – AN ONLINE PLATFORM FOR BRAIN-COMPUTER INTERFACE TRAINING

GERONIMO A, SIMMONS Z

The Pennsylvania State University, Hershey, PA, USA

Email address for correspondence: ageronimo@hmc.psu.edu

Keywords: brain-computer interface, telemedicine, P300

Background: The promise of telemedicine in ALS is to expand the reach of multidisciplinary clinics by making virtual medical care more accessible and at lower cost. A clear gap in the practice of telehealth by ALS clinics is the lack of integration with augmentative and alternative communication (AAC) technologies. Many patients, including those who might receive virtual care, rely on such technologies for basic communication. This proposal is an expansion of our ALS telemedicine program as a platform for training, monitoring, and communication with a brain-computer interface (BCI).

Objective: The primary aim is to incorporate a brain-computer interface (BCI) training module into a teleconferencing communication platform in order to evaluate the utility of in-home telemedicine visits by the clinical team for patients who possess limited verbal communication. The primary endpoint of the study involves communication of the patient and the clinical team using the BCI device in their home.

Methods: Study participants are delivered study equipment on the first session, consisting of computer, EEG system, eye tracker, and mount. The remaining eight sessions are conducted over the teleconferencing interface, through which the team will learn to use the BCI system for communicating using a P300 speller. Data from each session will be shared securely with the research team over a cloud storage platform. The training period will culminate in a virtual visit with an ALS nurse. Questionnaires will be administered to the patient, caregiver, and clinical nurse

immediately after the study endpoint. These will ask about the value of the telemedicine interface, the ease of BCI operation, the satisfaction with accuracy and speed, and other wants or concerns for the system.

Results: The first three months of this project have been spent sourcing equipment, obtaining institutional review board approvals, creating a study database, and generating recruitment materials, protocol, and data collection instruments. Additionally, software has been created and installed on the research computers to guide participants through the setup and operation of the system. In August 2016, a pilot participant will be recruited to test the functionality of the system so that another three systems can be prepared for the full assessment in nine additional patients over the next six months.

Discussion and conclusions: We hope to show that this type of remote BCI training can be easily accomplished by patients and caregivers, and that it proves beneficial to quality of life. Following the assessment, the patient may be granted an extension for an additional period of use in order to facilitate ongoing telemedicine communication at home and with the clinical care team.

Acknowledgments: This work is supported by the ALS Association Clinical Management grant 17-CM-325.

CP22 A PRELIMINARY EVALUATION OF EXOSKELETAL TRAINING FOR ALS PATIENTS IN AN AMBULATORY SETTING

FUNKE A[1], KETTEMANN D[1], KECK M[1], SPITTEL S[1], MEYER T[1,2]

[1]Charité, Universitätsmedizin Berlin, Ambulanz für ALS und andere Motoneuronenerkrankungen (AAM), 13353 Berlin, Germany, [2]Charité, Universitätsmedizin Berlin, Neurologische Hochschulambulanz, Projektgruppe AmbulanzPartner (PGAP), 13353 Berlin, Germany

Email address for correspondence: andreas.funke@charite.de

Keywords: assistive device, exoskeleton, mobility

Background: Exoskeletons are a new device that enables patients with paraplegia to get in an upright position and train walking. Currently Exoskeletal training (EST) is used in neurological rehabilitation after spine injury with positive impact on mobility and patient's quality of life (QoL). EST may be suitable for other neurological conditions with a spastic paraparesis. Although Exoskeletons receive a relatively high public attention, studies evaluating the effect of EST in degenerative neurological diseases including ALS do not exist until now.

Objectives: The aim is to evaluate if EST could be applied safely in ALS and if there are potential benefits for patients in a preliminary observation of this new technology.

Methods: In an ambulatory setting, patients diagnosed with ALS volunteered in 60 minutes EST with the Ekso GTTM exoskeleton (Ekso Bionics Inc, Richmond, CA, USA) under guidance of a specially trained physiotherapist. Video recordings of the training session were made and compared to video recordings of standing and walking without the exoskeletal device. After EST patients were asked on tolerability, effects and experience of the training. A total number of four patients received EST. All patients had predominant upper motor neuron involvement of the legs; three were permanently wheelchair bound with involvement of axial musculature.

Results: EST was well tolerated by all patients. All patients reported a positive effect of EST. Most notably standing in an upright position and walking was stated as a positive experience. Two patients reported a physical exhaustion after training because they were not able to walk for longer distances as before. Nevertheless, three out of four wanted to continue EST on a regular basis.

Discussion: The patients receiving EST reported a positive effect of the training without negative side effects. The number of patients who underwent EST was very small, there is no prospective design of the investigation and so far no systematic evaluation of EST has been done over a longer period. Long term effects on the disease and QoL remain unknown. Nevertheless we were able to show that EST may be a promising target for further investigations in ALS as a new therapy device.

Conclusions: EST can be applied to patients with ALS without negative side effects under guidance of a trained therapist. Even a single training unit has positive impact on the reported QoL. Weakness of axial musculature is no contraindication for EST. We showed that EST may be part of ALS treatment in the future but further studies are needed to evaluate the effects on spasticity, disease progression and QoL. Furthermore, limitations of EST regarding disease progression and clinical phenotype have to be defined.

Acknowledgements: The authors wish to thank Dennis Veith and Arne Toerber for assistance with the provision of the device and training.

NEALS 1 THE EFFECTS OF NUEDEXTA ON SPEECH PAUSE TIME

GREEN JR, ALLISON K, PIORO E, PATTEE G, SMITH R

NEALS 2 MOUTHMETRICS: A TOOL FOR ASSESSING BULBAR MOTOR INVOLVEMENT USING A LOW-COST, 3D DEPTH SENSING SYSTEM

GREEN JR, RICHBURG BD, MARKAN S, BERRY J

THEME CW: CLINICAL WORK IN PROGRESS

CW1 PRELIMINARY RESULTS FROM BREATHE MND-1 TRIAL: NATURAL HISTORY OF SLEEP DISORDERED BREATHING IN MOTOR NEURON DISEASE; AND RANDOMISED CONTROLLED TRIAL OF A NEW MODE OF NON-INVASIVE VENTILATION

AIYAPPAN V[1,2], MCEVOY D[1,2], CATCHESIDE P[2], SCHULTZ D[1,2], ALLCROFT P[1], KEIGHLEY-JAMES G[1], GLAETZER K[1], ANTIC N[1,2]

[1]Southern Adelaide Local Health Network (SALHN), Adelaide, Australia, [2]Flinders University, Adelaide, Australia,

Email address for correspondence: vinod.aiyappan@sa.gov.au

Keywords: sleep disordered breathing, ventilatory failure, non-invasive ventilation

Background: Non-invasive ventilation (NIV) has been shown to improve morbidity and mortality in a select group of MND patients who develop sleep disordered breathing (SDB) and ventilatory failure, which is traditionally thought to be due to hypoventilation due to muscle weakness. We have reported the heterogeneity of SDB including a high prevalence of clinically silent obstructive sleep apnea (67%), which may explain why patients with bulbar symptoms were found not to benefit from NIV in the RCT conducted by (1).

Objectives: 1. A prospective study of 40 patients to delineate the nature and time course of SDB and respiratory failure, in MND patients. 2. A 2-night cross-over RCT of a new mode of non-invasive mask ventilator vs. conventional non-invasive mask ventilator, followed by a one year post-randomisation observation of patient tolerance, response to treatment and efficacy, in patients with motor neurone disease and respiratory dysfunction.

Materials and methods: Consecutive patients who attended the MND clinic have been enrolled into the study. Muscle strength scores, supine and prone dyspnea scores, quality of life questionnaire measurements, pulmonary function tests and sleep studies were performed at 0, 3, 6 and 12 months to assess progression of disease. Patients who met the NICE criteria for NIV were randomised to a 2 night (consecutive nights) cross-over trial using either a hybrid ventilator (BiPAP A40 on AVAPS AE mode with auto pressure support, auto EPAP and auto back-up rate) or standard bi-level ventilator (using BiPAP A40 with standard S/T mode). The primary end-point is adequacy of nocturnal ventilation on NIV both acutely and 2 monthly as measured by time spent with oxygen saturation <90% (T90) via oximetry/sleep study.

Results: Among 25 patients thus far enrolled (Males=15, Females=10), ALS was the commonest type of MND (ALS 16: Bulbar 8: Other 1), the mean ±SD age was 61 ± 10.5 yrs. At time of enrolment FVC 81.2 ± 23.2 % predicted, Maximal Inspiratory pressure 50 ± 15.1% predicted, maximal expiratory pressure 39.6 ± 15.9% predicted, PCO2 39.51 ± 6.14 mm Hg. Of the 11 patients who have completed the 6 month follow up, SDB severity increased with time, (mean ± SD (Baseline AHI 6.8 ± 8.7, six month AHI 12.6 ± 19.3, p = 0.014)). Of the 5 patients who were randomised to NIV, there is a trend towards better control of SDB with the new mode versus standard NIV (mean AHI 8.4 ± 9.3vs 17.7 ± 22; Cohens d 0.52 (indicating moderate effect)).

Conclusions: Preliminary results from the Breathe MND-1 trial suggest development of SDB in association with disease progression, in MND patients. The new mode of NIV may control SDB better than standard NIV.

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CW2 REVIEW OF PERSONALISED VENTILATION PROGRAMMES AND CHANGES IN PRESSURE SUPPORT OVER TIME IN PATIENTS WITH MND/ALS

ROGERS C[1], BANERJEE S[1], OLIVER D[2]

[1]Medway Maritime Hospital, Gillingham, UK, [2]University of Kent, Chatham, UK, [3]Wisdom Hospice, Rochester, UK

Email address for correspondence: charlotte.rogers@doctors.org.uk

Keywords: non-invasive ventilation, quality of life, pressure support

Background: Breathlessness and respiratory muscle weakness are key symptoms to manage in motor neurone disease (MND). These impact on general well-being, physical and mental health of this population group. At Medway Maritime Hospital, patients are reviewed in a multi-disciplinary clinic including a respiratory consultant, specialist ventilation nurse and palliative care consultant. Therapy is targeted on ventilation methods to maximise activities of daily living, quality of life and easing symptoms. This includes the ventilation mode AVAPS-AE (average volume assured pressure support–auto end positive airway pressure) and using hand-held and mouthpiece ventilators for more mobile ventilation.

Objectives: A review of patients' quality of life and the impact of non-invasive ventilation (NIV) on this. Also, a review of pressure support (PS) requirements of patients on our newer ventilation mode AVAPS-AE and whether there is a change in this over time.

Methods: All 5 current patients with MND requiring NIV were sent a patient satisfaction survey and a shortened quality of life questionnaire based on the Short Form-36, looking at general health and bodily pain. Data of all patients with MND requiring NIV usage on AVAPS-AE mode over the past 3 years were reviewed. Data of the 5 patients on AVAPS-AE for over 6 months was collected, looking at average PS and usage per day over 3 month periods.

Results: Patients felt satisfied with their NIV, feeling their machine matched their everyday needs. Patients used different devices including hand-held, mouthpiece and facemask breathing devices. Despite NIV they felt their health had worsened and bodily pain was an issue. Of the 4 patients on prolonged use of AVAPS-AE, 3 out of 4 saw an increase in PS requirements over time (range 0.7-7.4cm H2O). All patients saw a gradual increase in average NIV usage hours per day, with the increase being predominantly short bursts then prolonged usage over the daytime.

Discussion: Breathlessness is a difficult symptom to manage and individualised therapy plans are important to effectively manage each case. Anxiety must be tackled as well as the physical respiratory muscle weakness. Mouthpiece and hand-held devices can help to provide a patient with more autonomy and freedom from NIV as the disease progresses. We have shown that the number of usage hours steadily increases. It appears that the amount of pressure support increases over time, although more patient numbers are required to illustrate this to any statistical significance. AVAPS-AE is a useful mode to safely provide increasing pressure support in the community as higher pressure levels can be delivered according to patient demand without the need for regular checks on patients' ventilators.

CW3 UNDERSTANDING THE USE OF NONINVASIVE VENTILATION IN THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS: RESULTS OF AN INTERNATIONAL PHYSICIAN SURVEY

HEIMAN-PATTERSON T[1], ANDREWS J[2], CUDKOWICZ M[3], DE CARVALHO M[4], GENGE A[5], HARDIMANN O[6], JACKSON C[7], KULKE S[2], LECHTZIN N[8], MITSUMOTO H[9], RUDNICKI S[2], SILANI V[10], VAN DEN BERG LH[11]

[1]Drexel Neurological Institute, Philadelphia, PA, USA, [2]Cytokinetics, Inc, South San Francisco, CA, USA, [3]Massachussetts General Hospital, Charlestown, MA, USA, [4]University of Lisbon, Lisbon, Portugal, [5]Neurologic Institute, Montreal, Canada, [6]Biomedical Sciences Institute of Neurosciences, University of Dublin, Dublin, Ireland, [7]University of Texas Science Center, San Antonio, TX, USA, [8]Johns Hopkins School of Medicine, Baltimore, MD, USA, [9]Eleanor and Lou Gehrig ALS Center, Columbia University, New York, NY, USA, [10]IRCCS Instituto Auxologico Italiano, University of Milan Medical School, Milan, Italy, [11]University Medical Center, Utrecht, The Netherlands

Email address for correspondence: terryheimanpatterson@gmail.com

Keywords: NIV utilization, NIV timing, respiratory support

Background: Patients with amyotrophic lateral sclerosis (ALS) require respiratory support as their symptoms progress and non-invasive ventilation (NIV) can improve quality of life and extend survival. While there is evidence to support the use of NIV in ALS, it is less clear when to initiate NIV and what is the best indication for NIV initiation. As a result there is lack of uniformity regarding when and why a physician may prescribe NIV. In addition, it is not uncommon for the decision to initiate NIV to be driven at least in part by requirements from insurance carriers or health care services to fulfil specific criteria for the device to be covered.

Objectives: To identify the state-of-the art practices of NIV utilization amongst ALS specialists and to better understand the similarities and differences regarding NIV initiation, obstacles to use, preferred equipment, and other areas of unmet need in the use of NIV for ALS.

Methods: A brief questionnaire on the use and timing of initiation of NIV was developed by the authors. The survey is being sent out to physicians practicing at ALS centers in several countries in North America, Europe and Australia via SurveyMonkey. ALS specialists were identified through membership in NEALS, ENCALS, and ALS Canada (removing any duplicates). Results from SurveyMonkey will be analyzed by two independent individuals. Descriptive statistics and simple comparisons between North America and EU responders will be summarized.

Results: The NIV survey is being sent to the physicians at all sites identified via NEALS, ENCALS, and ALS Canada. Full results of the survey will be shared at the meeting.

Discussion and conclusions: It is important to understand the variability of prescription/acceptance of NIV across ALS treatment centers. Differences in NIV prescription may influence survival and are potential confounders in studies seeking to identify new therapeutic treatments. The information may also prove useful in moving forward with future studies to provide additional evidence-based guidelines regarding use of NIV in ALS.

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CW4 DOES NIV AND AGE INFLUENCE SURVIVAL RATE IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: EXPERIENCE IN A MULTIDISCIPLINARY CLINIC. A RETROSPECTIVE REVIEW

MAGNAN N[1,3], VITALE T[1,2], GENGE A[2], SALMON K[2]

[1]McGill university health center, Montreal, Canada, [2]Montreal Neurological hospital, Montreal, Canada, [3]National Program for home ventilatory assistance, Montreal, Canada

Email address for correspondence: nathalie.magnan@muhc.mcgill.ca

Keywords: non invasive ventilation, survival, age

Background: The literature on ALS often mentions factors that can predict a slower prognosis. One of the factors referenced is age. Both (1) and (2) in a review of prognostic factors found that older age and bulbar onset predicted the worst outcome. How does the role of NIV influence all this? It has been widely shown in various studies that initiation of non-invasive ventilation (NIV) has a positive effect on the pulmonary function capacity such as FVC and hypoventilation in patients with amyotrophic lateral sclerosis (ALS). The hypoventilation due to respiratory muscle atrophy is the most common cause of death. There is a lack of consensus on whether or not age and NIV are related, where the survival rate of ALS patients is concerned. In their retrospective review of 84 patients, (3) found that NIV was associated with better outcomes in patients older than 65 years of age. Whereas (4) found in a cohort of 33 patients that median survival from NIV initiation is 8, 4 months and was poorer in patients with advanced age. At the Montreal Neurological Hospital ALS clinic, patients benefit from a provincial home care based program for their ventilator needs: the National Program for Home Ventilatory Assistance (NPHVA). This program provides both the equipment and the services of a combined nurse/respiratory therapist follow-up at home. They also document hours of NIV use and follow ventilated patients closely, regardless of NIV or PAV, with routine progress notes.

Hypothesis: Based on the NPHVA experience with ALS patients, we hypothesize that NIV increases survival in patients with older age of onset.

Method: A retrospective review of patient cohort during the period of January 2012 to April 2016 was done. Patient lists from the multidisciplinary clinic and from the NPHVA, were compiled. The following data was collected: age, date of diagnosis, site of symptom onset, pulmonary function measure (most common will be forced vital capacity), ALSFRS-R score (analysis of the subset of R score), BiPAP use, presence of PEG and survival rate.

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

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CW5 BODY COMPOSITION AND DISEASE PROGRESSION IN PATIENTS WITH MOTOR NEURONE DISEASE

SALVIONI C, STANICH P, LELLIS R, OLIVEIRA AB

Federal University of São Paulo, São Paulo, Brazil

Email address for correspondence: cris.salvioni@gmail.com

Keywords: nutritional assessment, ALSFRS R, bioelectrical impedance analysis

Background: Malnutrition is a well-known independent survival factor in ALS. During the progression of disease, changes in body composition may be contributing to a worse prognosis.

Objective: To evaluate body composition of patients according to severity of disease evaluated by functionality scale (ALSFRS-R).

Methods: Patients were classified according to disease manifestation (limb/bulbar onset) and divided according to score ALSFRS-R (≤24 and >24 points). The assessment of body composition by Bioelectrical impedance analysis (BIA) was performed. The assessments were conducted by the dietician team at the Neuromuscular Disease Research Department Federal University of São Paulo.

Results: There were 21 patients evaluated: 15 (71.5%) limb onset (5 (33.3%) women and 10 men (66.7%)), 6 (28.5%) had bulbar onset (4 (66.6%) women and 2 (33.4%) men). 53.3% of patients with limb onset presented ≤ 24 score and 46.7% >24 points at ALSFRS-R. Of those which had low scores, the body mass index (BMI) was 22.7 Kg/m^2, the percentage of weight loss (% WL) 9.1% (0-25.4%), the percentage of fat-free mass (% FFM) was 68.4%, and the phase angle (PA) 3.40. Patients with limb start values > 24, the average BMI was 25.2 Kg/m^2,% WL of 10.2% (0-21.7%), % FFM 73.3% and largest average value found for PA was 5.10. Patients with bulbar onset, 50% showed values ≤ 24 and 50% > 24 points in ALSFRS-R. The BMI with ALSFRS-R ≤ 24 was 16.6 Kg/m^2 are classified low weight, % WL 38.3% (22.6-55.3), % FFM 60.5% and PA 3.00. Those with scores of > 24, didn't present low weight according to BMI (22.1 Kg/m^2) and all other parameters analyzed showed a higher average, demonstrating better nutritional condition: % WL 19.3% (12.9-23.3), % FFM69.7% and PA 4.6.

Discussion: Analyzing body composition of patients with bulbar onset, limb onset and severity of disease, found greater impairment in bulbar patients. Oropharyngeal dysphagia, more present in this population, and reduction of body weight can be managed with consistent modification of diet, fitness and nutritional needs from dietary nutritional supplementation. Regardless of disease manifestation, patients with minor functional scale score showed more change in body composition.

Conclusion: Greater change in body composition were observed in bulbar patients and with low functional scale scores, with increased risk of malnutrition and dehydration.

CW6 GAIN OF BODY FAT IN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS: THE GREAT NUTRITIONAL CHALLENGE

STANICH P, SALVIONI C, LELLIS R, OLIVEIRA A

Federal University of São Paulo, São Paulo, Brazil

Email address for correspondence: pstanich@uol.com.br

Keywords: fat mass, amyotrophic lateral sclerosis, nutritional therapy

Background: It was recently postulated that a nutritional intervention aiming at achieving weight gain might increase survival in ALS patients. With the increased energy expenditure and reduction of food, promoting weight gain is a challenge.

Objective: Present nutritional conduct adopted to promote the gain of body fat and weight.

Methods: Nutritional monitoring happens every three months with verification of body weight, BMI and analysis of food intake. In reduction of weight do orientation of high-calorie nutritional supplement and high protein value, preferably those with a higher fat content. Milk, eggs, vegetable cream, mayonnaise, sour cream, vegetable oil and olive oil should be recommended. Encourage the exclusion of low-fat food products.

Results and discussion: The restriction of foods high in fat for preventing cardiovascular diseases is a global concern. In recent decades campaigns have aimed to guide and encourage risk reduction via reduction in calorie and fat intake. The discovery that weight gain seems to have a protective role in the development of ALS revolutionized nutritional treatment. However, this contradicts the culture of exclusion of fats which may be why some professionals and patients are resisting the current advice. We believe in the need for nutrition education, carried out by specialized nutritionists, to break this paradigm.

Conclusion: The professional updating of the teams, in particular dieticians, can ensure greater adherence to treatment for the increase in intake of fats in a balanced, safe and effective way to weight gain, in the early stages of disease.

CW7 UNDERSTANDING THE IMPACT OF GASTROSTOMY AND QUALITY OF LIFE IN PATIENTS WITH ALS

CIANI G[1,2], HOLZBERG S[1], SHAHBAZI M[1], LANGE D[1]

[1]Hospital for Special Surgery, New York, New York, USA, [2]Hofstra University, Hempstead, New York, USA

Email address for correspondence: gioia.j.ciani@hofstra.edu

Keywords: gastrostomy, patient perceptions, PEG tube

Background: Gastrostomy feeding is frequently used in the provision of care for patients with amyotrophic lateral sclerosis who develop dysphagia, accelerated weight loss and malnutrition, and has been shown to improve the prognosis of the disease (1-4). Gastrostomy may be one of the major interventions leading to longer survival of PALs. However, longer survival does not necessarily equate with quality of life. Increased quality of life is often provided as a reason for patients to undergo gastrostomy. To date there is limited research that looks at the impact and experiences of living with gastrostomy from the patient's perspective. The impact of this intervention on quality of life in PALS has not been clearly demonstrated and is not well understood (1,4).

Objectives: The objective of this study is to examine the perspectives of patients regarding their experiences and the impact that gastrostomy has on their quality of life.

Methods: A convenience sample was used to recruit patients who attend an interdisciplinary ALS clinic. Only those patients with a diagnosis of amyotrophic lateral sclerosis and who were at least 3 months post percutaneous endoscopic gastrostomy tube insertion were included. Patients with dementias/cognitive impairment were excluded. Demographic information was collected. Semi-structured, in-depth interviews were conducted with patients using open ended questions designed to explore patient views. McGill Quality of Life Scale was administered during the interview. Results were compared with scores obtained prior to PEG placement.

Results: Currently, 11 patients were interviewed. Identified themes include; experiences living with PEG, strategies for coping, autonomy, choices around PEG decision, and acknowledgment of the value of PEG. Interviews and analysis of results is ongoing.

Discussion and conclusions: It has been proven that gastrostomy feeding can prolong a person's life. What is not known is how this affects a person's lived experience and quality of life. Issues regarding quality of life should be considered. This research will add to the body of literature regarding patient experiences and quality of life with gastrostomy.

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CW8 CLINICAL MANAGEMENT OF ORAL HYGIENE FOR PATIENTS WITH ALS

MCDONAGH M[1], RIGGS M[1], BANKER-HORNER L[3], BARKHAUS P[2], STICH D[4], DOMAGALA A[5], FEE D[2]

[1]Froedtert Hospital, Milwaukee WI, USA, [2]Medical College of Wisconsin, Milwaukee WI, USA, [3]The ALS Association-Wisconsin Chapter, Milwaukee WI, USA, [4]Brookfield Dentistry S.C., Milwaukee WI, USA, [5]Marquette University School of Dentistry, Milwaukee WI, USA

Email address for correspondence: michelle.mcdonagh@froedtert.com

Keywords: oral hygiene, dental care, quality improvement

Background: To date there are no practice parameters for oral hygiene as a component of ALS management. As ALS progresses and care burden increases oral hygiene can often be overlooked. Barriers to routine oral care include general fatigue, upper extremity weakness, inability to maintain open-mouth posture, sialorrhea, and ultimately dependency on others for oral care. Oral hygiene remains important even when the oral cavity is no longer used for nutrition. Oral hygiene is imperative to minimize risk for dental caries, halitosis, to control bacterial build up which could

enter upper airways and lead to respiratory infection, as well as to maintain the patient's quality of life. The ALS Association-Wisconsin Chapter (ALSA-WI) has partnered with the Froedtert and Medical College of Wisconsin (F-MCW) ALS Multidisciplinary Clinic (MDC) and Marquette Dental School Advanced Care Clinic (MDSACC) in Milwaukee, Wisconsin, to assess the need for support for oral hygiene in patients with ALS (PALS).

Objectives: Assess how PALS are maintaining their oral health at home; identify barriers to receiving routine dental care; provide education and resources to PALS and their caregivers to maintain routine oral care.

Methods: A thirteen question survey was created to assess if PALS are able to maintain their oral health at home, if they are receiving routine dental care and what barriers exist to maintaining oral hygiene. Our MDC's Speech Language Pathologist and Dietitian administered the survey to thirty PALS attending the F-MCW MDC. Participants ranged in age from 41-81 years, ALSFRS-R ranging from 4-45, seven PALS had bulbar onset and twenty three had limb onset ALS, fourteen were male and sixteen were female.

Results: Seven of the PALS surveyed did not have a regular dentist and their last appointment coincided with onset of ALS symptoms. Twelve PALS had not seen a dentist in over a year. Sixteen PALS did not schedule a follow up appointment. Reasons cited were cost n=4, lack of insurance coverage n=2, transportation n=2, ALS diagnosis n=2, and concerns regarding excess saliva n=2. Three out of the sixteen PALS without a follow up appointment confirmed that they had oral discomfort. Twelve patients were interested in a referral to the MDSACC.

Discussion and conclusions: There are multiple barriers to maintaining oral hygiene in PALS. The ALS clinic must educate patients and their caregivers on the importance of oral hygiene and provide resources to maintain oral care at home to reduce secondary oral health complications. The preliminary survey results are generating an evolving list of resources for patients seen in the Froedtert and MCW ALS MDC including basic educational materials, a list of special needs dentists, grant information for transportation costs, and routine referrals to the MDSACC for affordable basic dental care.

CW9 STANDARD OF CARE FOR DYSPHAGIA MANAGEMENT IN ALS PATIENTS

EPPS D, KITILA M, DIAZ-ABAD M, KWAN J

University of Maryland School of Medicine, Baltimore, Maryland, USA

Email address for correspondence: depps@umm.edu

Keywords: dysphagia, standard of care, bulbar symptoms

Background: Dysphagia contributes to declining respiratory status and causes considerable distress which may lead to altered ingestion patterns causing malnutrition and dehydration in ALS patients. Early diagnosis and management of dysphagia is important to avoid complications such as under-nourishment, dehydration, or aspiration pneumonia. To date, no clear or specific guidelines for dysphagia management or treatment in ALS have been offered or established (1, 2).

Objectives: The purpose of this study is to determine the evaluation and recommendations of speech-language pathologists in the care of ALS patients.

Methods: A 15 question survey was sent to speech-language pathologists (SLPs) who are active in clinical practice. The survey queried each practitioner's perception of the current standard of care provided by SLPs to ALS patients with symptoms of dysphagia.

Results: Forty-five SLPs completed the survey. A variety of dysphagia protocols in the initial assessment of ALS patients were being used. Most respondents (82%) performed a FEES or MBS in ALS patients. Forty-three percent recommended a baseline FEES or MBS in ALS patients who did not have bulbar symptoms. Respondents varied greatly in how soon they would recommend a FEES or MBS after the initial assessment, with some SLPs recommending an instrumental assessment immediately and others recommending an instrumental assessment within a specified time frame or as symptoms arise. All responding SLPs reported that they would provide consultative information on aspiration precautions to ALS patients even if the swallowing function was normal.

Discussion and conclusions: There is currently no uniform recommendation for the timing and method to evaluate dysphagia in ALS patients. Most SLPs perform FEES or MBS to evaluate dysphagia in ALS patients. There is no agreement

on the need for FEES or MBS in ALS patients who do not have bulbar symptoms.

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CW10 VIDEOFLUOROSCOPIC ASSESSMENT OF SWALLOWING DYSFUNCTION IN ALS

EPPS D, ALAPATI J, KITILA M, DIAZ-ABAD M, KWAN J

University of Maryland School of Medicine, Baltimore, Maryland, USA

Email address for correspondence: depps@umm.edu

Keywords: videofluoroscopy, swallowing dysfunction, penetration-aspiration scale

Background: Dysphagia is one of the most critical problems in ALS patients. Early diagnosis and treatment of dysphagia is important to avoid complications such as undernourishment, dehydration, and/or aspiration pneumonia. Careful follow-up of the clinical progression of dysphagia is necessary to determine the appropriate timing for interventions. Therefore evaluation of the swallowing function at the initial diagnosis is necessary (1). Clinical diagnosis of dysphagia by history and bedside examination has low specificity and often requires confirmation by videofluoroscopy (VFS). Videofluoroscopy is currently the recommended examination for evaluating swallowing disorders. The exact timing for a radiographic evaluation of swallowing in ALS patients has not been well-studied and videofluoroscopy does not have a defined role in the assessment of swallowing disorders in amyotrophic lateral sclerosis (2).

Objectives: The aims of this study are: 1. To determine whether videofluoroscopic assessment of swallowing function in patients who do not have bulbar symptoms can detect subclinical aspiration; 2. To determine the severity of swallowing dysfunction on a videofluoroscopic assessment in ALS patients who do not have bulbar symptoms; 3. To determine which functional guidelines for the diagnosis and management of swallowing disorders in ALS patients is appropriate.

Methods: A retrospective chart review was conducted for all ALS patients diagnosed at University of Maryland ALS Clinic between 2008 and 2015. Information extracted includes: ethnicity, gender, revised El Escorial diagnostic criteria classification at the time of diagnosis, date of symptom onset, date of diagnosis, site of symptom onset, clinical measures of motor function, ALSFRS-R and forced vital capacity. Videofluoroscopic studies between 2008 and 2015 were reviewed. In ALS patients who have a score of 5 or above using the Penetration Aspiration Scale (PAS), non-oral methods to provide nutrition is strongly recommended. ALS patients who have ALSFRS-R bulbar score of 6 or above are considered to have mildly abnormal bulbar function not requiring a gastrostomy tube.

Results: Of the 74 patients who had a VFS study, 15 studies reviewed thus far included a full PAS. In 11 patients, the VFS study showed dysphagia as defined by score 3 or above on the 8-point PAS. Five of the patients have bulbar onset ALS, 5 have limb onset ALS, and 1 has onset in other regions. In 13 of the VFS studies, the patients have an ALSFRS-R bulbar score greater than 6. Among these patients, 6 studies show a PAS score of 5 or greater.

Discussion and conclusion: In this preliminary analysis, the ALSFRS-R bulbar score may be an insensitive method for determining the need for non-oral feeding.

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CW11 ALS FUNCTIONAL COMMUNICATION SCALE: A TOOL FOR STANDARDIZING AND EXPANDING SPEECH THERAPY INTERVENTIONS AND DOCUMENTING IMPROVEMENT IN COMMUNICATION

ROMAN A

Forbes Norris ALS Research and Treatment Center, San Francisco, CA, USA

Email address for correspondence: amy.roman@sbcglobal.net

Keywords: communication, AAC, scale

This poster introduces the ALS Functional Communication Scale (ALS FCS) which includes 7 competencies that encompass the wide breadth of communication abilities patients with ALS/MND

should expect to maintain from diagnosis onwards. The ALS FCS includes the ability to: 1. Alert others, not in one's immediate environment, to a need or emergency; 2. Demonstrate strategies that improve communication success, efficiency, speed and reduce fatigue; 3. Communicate novel messages via low-tech methods or written modalities; 4. Communicate novel messages with a voice (SGD or speech); 5. Communicate with those at a distance (phone, email, TM, IM); 6. Independently set-up, customize and use the elements of an AAC system; 7. Describe pro-active strategies to prepare for typical changes in speech and/or access associated with ALS.

The reasons for establishing a list of core capabilities in the form of a scale are numerous. Clinicians must document a patient's improvement resulting from interventions. While it is impossible to improve dysarthric speech in individuals with ALS, our interventions do result in improvement in functional communication.

Currently, the measurement tools for gauging improvement in the US and many countries are based on a remediation model rather than a compensation model. A scale that matches the appropriate model of intervention provides documentation that justifies reimbursement and improves research capabilities by providing a standardized way of reporting. The Scale also serves as a teaching tool. While using it, clinicians are guided to address each of the competencies rather than "just getting someone a speech generating device" or giving them a low-tech communication board. Many of the ALS FCS competencies are overlooked by new or non-specialized clinicians when working with patients with ALS.

Individuals with ALS are also empowered when provided with a simple list to which they can refer when consulting with their speech therapists. Members of the multidisciplinary team also benefit from understanding communication capabilities that can and should be addressed. Every team member communicates with patients, be it through face to face contact or via email or phone. Opportunities are provided in these everyday interactions to recognize and report when a capability is jeopardized or already absent.

The Scale is being used successfully in electronic medical chart notes and by AAC Specialists in the US to meet Medicare guidelines for reporting improvement resulting from therapy intervention. It is also used in support groups as a Communication Checklist to educate patients and caregivers and encourage discussion. Additionally, it is used as a training tool to teach ALS Association Care Managers and general practice speech therapists how to address each of the communication competencies through the implementation of an inexpensive, non-Rx equipment AAC Toolkit which include items such as adapted call chimes, communication boards, and voice amplifiers.

CW12 MOBILE TECHNOLOGY TOWARDS AUTOMATIC DETECTION OF EARLY-STAGE ALS FROM SHORT SPEECH SAMPLES

WANG J[1], KOTHALKAR P[1], HERNDON B[1], CAO B[1], HEITZMAN D[2]

[1]University of Texas at Dallas, Richardson, TX, USA, [2]Texas Neurology, Dallas, TX, USA

Email address for correspondence: wangjun@utdallas.edu

Keywords: mobile technology, machine learning, automatic detection

Background: Speech performance decline in terms of acoustic and articulatory data is amongst the earliest indicators of bulbar ALS (1). Thus, in theory, it is possible to detect early-stage (pre-symptom) bulbar ALS from short speech samples. This work investigates the feasibility to detect early-stage ALS from short speech samples with acoustic and articulatory (lip movement) information using mobile technology and machine learning techniques.

Method: The brief design of this technology contains two components: 1. front-end for data capture and user interaction; and 2. back-end for data analysis. An iOS app, as the front-end, is under development for capturing speech acoustic and lip movement data (through video capture). Data will then be transferred to the back-end (server), where machine learning techniques are used to predict if the speaker has ALS or not. The prediction results are then sent back to and displayed at the front-end.

A pilot data set was used to test our ALS detection approach. The data set was collected from 22 subjects: 11 early diagnosed ALS patients with normal speech (95% speech intelligibility) and 11 healthy subjects, who produced short phrases (eg how are you?) or isolated vowel samples. The (audio and lip) data were recorded using two electromagnetic articulographs (NDI Wave and Carstens EMA AG500) by attaching small sensors on lips (3). The data set contains a total of 2,567 speech samples (2). For each sample: 11,173 acoustic and articulatory features were initially extracted but only the best 100 features were selected using randomized logistic regression

(RLR) plus 20 voice features for each speaker. Deep neural network (DNN) was used for classifying the data samples in a 2-fold cross-validation manner, where training data and test data are unique.

Results: Using acoustic data only obtained a sensitivity of 81.5% and a specificity of 95.85%. Adding lip data improved sensitivity to 89.12% and the specificity to 98.58%. The preliminary results indicated the feasibility of automatic detection of early ALS from speech samples and the benefit of adding articulatory features.

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CW13 LANGUAGE CHANGES IN ALS: PRELIMINARY RESULTS ON A POPULATION-BASED STUDY

PINTO-GRAU M[1,2], BURKE T[1,2], LONERGAN K[1,2], MURPHY L[1,2], ELAMIN M[1], HARDIMAN O[1,3], PENDER N[1,2]

[1]Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Dublin, Ireland, [2]Department of Psychology, Beaumont Hospital, Dublin, Ireland, [3]Department of Neurology, Beaumont Hospital, Dublin, Ireland

Email address for correspondence: pintogrm@tcd.ie

Keywords: cognition, language, neuropsychology

Background: Amyotrophic Lateral Sclerosis (ALS) is now recognized as a multisystem disease associated with cognitive and behavioural changes involving fronto-temporal and fronto-striatal circuits. Cognitive impairment is evident in 40% of patients with a diagnosis of ALS. Executive functioning has been broadly studied in ALS and is defined as the most common form of impairment in this population. Although language changes have been described in ALS, these have not been systematically studied. The present study aims to investigate the nature and frequency of language changes in a population-based sample of ALS patients.

Method: A sample of 50 incident ALS cases, diagnosed in Ireland since December 2014, were assessed and compared to an age-, gender-, education- and premorbid IQ - matched healthy control sample (n=50) on a battery of language tests.

Results: ANOVA analysis adjusted for multiple comparisons showed significantly lower scores on the patient sample on the Word Reading ($p=0.002$), Word Spelling ($p=0.005$) and Sentence-Picture Matching task ($p<0.0001$) from the Psycholinguistics Assessment of Language Processing in Aphasia (PALPA).

Conclusions: ALS patients performed significantly worse than healthy controls on irregular word reading, word spelling and grammatical comprehension. These changes need to be further studied in relation to executive impairment. Longitudinal studies are also mandatory to evaluate the progression of language changes in ALS.

CW14 THE ROLE OF NEUROPSYCHOLOGY WITHIN A MULTIDISCIPLINARY TEAM IN AN ACUTE CARE SETTING

MELDRUM S, KERSEL D, GORRIE G

NHS Greater Glasgow and Clyde, Glasgow, UK

Email address for correspondence: steven.meldrum@ggc.scot.nhs.uk

Keywords: multidisciplinary, neuropsychology, emotion

Background: The Neurology Standards for Scotland (1) emphasise the need for clinical neuropsychology involvement in the multidisciplinary team providing care for people with Motor Neurone Disease (MND). A network of neuropsychologists across Scotland recognised the lack of service provision in this area and developed a pathway with associated protocols aimed at embedding clinical neuropsychology more effectively in the multidisciplinary team. This pilot intervention investigates the impact of clinical neuropsychology contribution to the multidisciplinary MND team in a Regional Neurosciences Centre.

Objectives: To define the role of the clinical neuropsychologist in the multidisciplinary team at the acute stage of care; to provide a baseline of cognitive and affective functioning and identify ongoing patient need; to obtain feedback from patients and families on the usefulness of the clinical neuropsychology component.

Method: The service aimed to see patients within 4 weeks of formal diagnosis. The purpose of the assessment was multifactorial using a biopsychosocial model. A structured interview with both the patient and a family member was conducted. The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (2) which has been developed for use with MND patients was used to describe a cognitive profile and identify impairment consistent with MND-FTD. A behavioural inventory was administered to the caregiver to ascertain behavioural changes associated with FTD (3). The HADS (modified) was used to assess affective state and a brief questionnaire to determine patient satisfaction with the service was administered.

Results: A high percentage of patients agreed to the assessment process. A range of cognitive deficits were identified although no variant FTD was identified. Few patients reported symptoms indicative of affective disturbance. Patients rated the quality and usefulness of the service as very high.

Discussion and conclusions: The wider MDT reported added value from the clinical neuropsychology intervention. The provision of a neuropsychological profile of the patient provided an enhanced clinical picture of the patient and their particular needs and challenges, aided clinical planning and highlighted the bespoke support needs that otherwise may have gone unrecognised. Patient and family satisfaction with the process was high and allowed the patient and the family greater insight into their condition, a space to construct a narrative of their experience and an opportunity to process their distress.

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CW15 NEUROPSYCHIATRIC SYMPTOMS IN PEOPLE LIVING WITH MOTOR NEURONE DISEASE AND THEIR FAMILY MEMBERS

MCHUTCHISON C[1], VADJA A[3], HEVERIN M[3], STEPHENSON L[2], COLVILLE S[2], PAL S[2], SWINGLER R[5,6], CHANDRAN S[2], HARDIMAN O[3,4], ABRAHAMS S[1,2]

[1]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK, [2]Anne Rowling Clinic, Edinburgh, UK, [3]Academic Division of Neurology, Trinity College, Dublin, Ireland, [4]Department of Neurology, Beaumont Hospital, Dublin, Ireland, [5]Euan MacDonald Centre, Edinburgh, UK, [6]Ninewells Hospital, Dundee, UK

Email address for correspondence: s1264013@sms.ed.ac.uk

Keywords: behavioural impairment, neuropsychiatric symptoms, cognitive function

Background: Cognitive and behavioural changes are present in approximately 50% of people living with Motor Neurone Disease (MND), around 15% of cases meet the criteria for behavioural-variant frontotemporal dementia (FTD): (1) Behavioural changes are similar to those in neuropsychiatric disorders. Furthermore, some neuropsychiatric disorders including psychosis and suicide are reported at higher than expected frequencies in MND kindreds (2). The recently identified genetic mutation (C9orf72), which is found in up to 40% of familial MND/FTD cases (3), has been associated with an increased likelihood of psychiatric symptoms at presentation (4). Additionally, the C9orf72 mutation is associated with an increased prevalence of psychosis (5), suicidal behaviour (6), bipolar disorder (7) and schizophrenia (8) in those without MND or FTD. These findings suggest an increased vulnerability in certain families for both neuropsychiatric and neurodegenerative disease.

Objectives: This study aims to investigate the frequencies of specific psychiatric disorders and association with types of behaviour and cognitive change in people living with MND and their family members compared to the general population.

Methods: In total, 120 people living with MND will be recruited through national MND registers in Scotland and Ireland along with as many of their first and second degree relatives as possible. Additionally, 120 healthy controls and their family members will also be recruited. A detailed family history of diseases will be collected followed by a series of questionnaires measuring symptoms of neuropsychiatric disorders. A brief cognitive screen will be administered and where possible, a spouse/partner/close friend will be invited to provide information on the participant's behaviour in a semi-structured interview. In Ireland all participating relatives will also be asked to provide a blood sample for DNA extraction.

Results: To date, data has been collected from 10 individuals from two MND families in Ireland and 23 healthy controls in Scotland.

Discussion and conclusions: Findings from this research will help to determine whether specific

neuropsychiatric disorders in family members predict the level and nature of abnormal behavioural and cognitive changes in individuals with MND. This would suggest a genetic link and overlap between conditions.

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CW16 APPLICATION OF NEUROPSYCHOLOGICAL MEASURES FOR PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

PARMENTER M, LANGE D, SHAHBAZI M

Hospital for Special Surgery, New York, NY, USA

Email address for correspondence: parmenterm@hss.edu

Keywords: cognitive impairment, measurement, neuropsychology

Background: Once considered two distinct diagnoses, the overlap between cognitive impairment and amyotrophic lateral sclerosis (ALS) is now largely accepted. Research suggests that mild to moderate cognitive impairment occurs in approximately 40% of patients with ALS, with a smaller percentage (14%) meeting criteria for frontotemporal lobar degeneration (FTLD) (1). The Neary criteria is commonly used to identify FTLD. However, because the clinical presentation of ALS differs across subjects and the disease progression leads to cognitive changes within subjects, no universally accepted diagnostic criteria for less severe forms of cognitive impairment exist. Instead, a variety of neuropsychological measures, including word generation tests, are often used. While these are useful at identifying subtle abnormalities in the domain of executive function, other assessments aimed at non-executive domains (ie memory function) are also necessary (2). Comprehensive screening tools can be used in addition to or in lieu of individual assessments. However, most are not designed to accommodate patients with physical disabilities. The current study aims to better understand how general neuropsychological measures can be used in patients with ALS, as well as develop interpretive guidelines for screening tools that require a written or spoken response.

Objective: To determine whether the Hopkins Verbal Learning Test- Revised (HVLT-R) and Delis-Kaplan Executive Function System (D-KEFS) can be applied to patients with ALS. These tests are considered superior tools at measuring cognitive function in other brain-disordered populations (eg Alzheimer's disease) (3); To determine what modifications can be made to the Mini-Mental State Examination (MMSE) for ALS patients who cannot perform written or verbal tasks.

Methods: 20 patients with ALS will be recruited from an outpatient clinic from May 25 to August 5, 2016. Patients with other neurological conditions will be excluded. A battery of assessments including the HVLT-R, D-KEFS, and MMSE will be administered and scored. If a patient cannot complete a portion of a test, a written explanation will be provided.

Discussion and conclusions: Current results support the diverse clinical presentation of patients with ALS. Initial analysis shows that ALS patients' scores on the MMSE are comparable to matched healthy controls (28.52, ±1.54). Despite these findings, difficulties in the areas of total recall ($T=44$, $p<0.001$), delayed recall ($T=28$, $p<0.001$), retention ($T=29$, $p<0.001$), and recognition discrimination ($T=20$, $p<0.005$) were shown. Recommendations about modifying assessments, establishing new scoring rubrics and/or implementing pre-existing tools will be discussed.

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Acknowledgements: A special thanks to the ALS clinic at Hospital for Special Surgery

CW17 INVESTIGATING COGNITIVE PROFILES IN MOTOR NEURONE DISEASE – INITIAL FINDINGS OF THE COGNITIVE AND BEHAVIOURAL IMPAIRMENT IN ALS (CABIA) STUDY

CLARKE M[1], FRATTA P[1], MALASPINA A[2], ZAMPEDRI L[1], HOWARD R[1], SHARMA N[1], SIDLE K[1], ROHRER J[1]

[1]Institute of Neurology, University College London, London, UK, [2]Blizard Institute, Queen Mary University of London, London, UK

Email address for correspondence: mica.clarke.15@ucl.ac.uk

Keywords: cognition, dementia, neuropsychology

Background: Most studies investigating cognition in MND have highlighted the presence of prominent frontal-subcortical deficits, with around 10-20% of patients fulfilling criteria for frontotemporal dementia (FTD). However, a detailed review of the literature indicates impairments can be seen not just in executive function and social cognition but also in syntactic processing, semantic knowledge, episodic memory and other cognitive domains.

Objectives: To design a detailed neuropsychological assessment that allows characterisation of the cognitive profiles of MND, with the hypothesis that there will be specific subgroups with prominent deficits in a) executive function, b) social cognition, c) language, and d) episodic memory, as well as e) a group that fulfils criteria for FTD, and f) a group with no cognitive impairment.

Methods: A comprehensive neuropsychological battery was devised to test a range of cognitive domains encompassing executive function (and specific subdomains of inhibitory control, cognitive flexibility and working memory), verbal fluency, social cognition (emotion processing and theory of mind), language (speech output, naming, semantic knowledge, syntax, reading, and spelling), episodic memory (visual and verbal), calculation, visuospatial processing and face recognition. Alternate written and spoken versions were designed during a pilot phase to allow for impaired hand-motor function and/or dysarthria. Disease severity is measured by the ALS-FRS, and behavioural changes are assessed by a modified neuropsychiatric inventory (NPI). The study aims to recruit 40 patients with MND and 30 healthy controls, with patients tested for the presence of a C9orf72 expansion.

Results: Data collection is ongoing. Preliminary results obtained from the first six patients (one of whom met criteria for FTD; mean (standard deviation) age = 60.8 (3.3); female:male 1:5) and sixteen controls (57.6 (6.6); 9:7) show that the battery is well-tolerated and that patients with motor and speech deficits are able to complete it. Significant differences were seen between the patients and controls in tests of cognitive flexibility (Wisconsin Card Sorting Test categories sorted = 6.0 (0.0) in controls, 4.0 (2.3) in patients, Mann-Whitney U Test p = 0.003), verbal fluency (category fluency 23.9 (5.5), 16.5 (7.4), p = 0.04), emotion processing (Ekman facial emotion recognition task 12.1 (1.0), 10.0 (2.4), p = 0.02), naming (noun naming task 19.9 (0.3), 19.0 (1.3), p = 0.02), syntax (PALPA55 sentence comprehension task 23.7 (0.6), 21.7 (1.6), p = 0.004), visual memory (Recognition Memory Test for Faces 43.8 (5.4), 36.2 (6.8), p = 0.01), verbal memory (Camden Paired Associate Learning Test 18.5 (3.2), 12.0 (5.0), p = 0.008) and face recognition (Benton Face Recognition task 49.4 (3.2), 44.3 (3.7, p = 0.01).

Discussion and conclusions: The detailed battery designed for this study is well-tolerated by patients with MND. Preliminary results show cognitive deficits in multiple domains. Further analyses will investigate the presence of different cognitive profiles in MND.

CW18 COGNITIVE IMPAIRMENT IN AMYOTROPHIC LATERAL SCLEROSIS (ALS): SCREENING TOOLS, EXPERIENCES AND PROGNOSIS IN NORWAY

TAULE T, MORLAND AS, ASSMUS J, TYSNES OB, REKAND T

Haukeland University Hospital, Bergen, Norway

Email address for correspondence: tina.taule@helse-bergen.no

Keywords: cognitive impairment, screening tools, evaluation

Background: Cognitive impairment in ALS is scarcely explored in ALS-specific outpatient clinics in Norway. It has significant implications to patients, carers and health-care professionals involved in whether the patient can retain their driving license or how to manage life-prolonging treatment.

Objective: We aim to present a protocol for validated introduction of cognitive evaluation. Four sub-studies are linked together to gain knowledge and validated tools for cognitive impairment in ALS. The purpose of study I is to translate, adapt and validate the Edinburgh Cognitive and

Behavioral Amyotrophic Lateral Sclerosis Screen (ECAS) (1) into Norwegian. Study II is to collate evidence of psychometric qualities of cognitive tests used in ALS-clinics. Study III is to explore, from the perspective of persons with ALS and their carers, perceptions to cognitive changes and consequent expectations for health-care early after being diagnosed. Study IV investigates if the scores on the ECAS can be used to identify patients who are not eligible for driving due to cognitive impairment in ALS.

Methods: The protocol for evaluation of cognitive impairment has been developed. Both qualitative and quantitative methods are defined for implementation, and statistical evaluation has been performed in order to achieve reliable results. Ethical aspects are discussed with the Data Privacy Unit.

Results: The protocol and preliminary results will be presented. The ECAS will be translated and validated in accordance with international guidelines. This includes pilot testing (n=10) and psychometric testing of participants (n=56). Age- and education-adjusted norms for verbal fluency in Norway will be calculated (n=560). The systematic literature review will be in accordance with the PRISMA guidelines and by using a meta-analysis if possible. The patients' and carers' perspective will be explored by using a qualitative interview design relying on interpretive description (n=20). A prospective blinded case-control study will be used to identify if the ECAS may be used to single out patients who are keeping ability for driving or not (n=56).

Discussions and conclusions: The Norwegian version of ECAS will be established and validated. The characteristics and clinical use of ECAS will be explored.

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Acknowledgements: Initial financial support is from the foundation ALS Norwegian support group, Oslo, Norway; the research group of movement and function, Bergen University College, Bergen, Norway; the Norwegian union of Occupational Therapists, Oslo, Norway; the Quality improvements funds, Haukeland University Hospital, Bergen, Norway.

CW19 ALS TESTING THROUGH HOME-BASED OUTCOME MEASURES (THE AT HOME STUDY)

SHEFNER J[1], MACKLINE E[2], NARAYANASWAMI P[3], RUTKOVE S[3]

[1]Barrow Neurological Institute, Phoenix, AS, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Beth Israel Deaconess Medical Center, Phoenix, AZ, USA

Email address for correspondence: jeremy.shefner@dignityhealth.org

Keywords: home based outcomes, clinical trial methodology, ALS progression

Background: Clinical trial outcome measures in ALS have two sources of variability: inherent subject variability due to differences in disease progression or other physiological factors, and variability of measurement despite best efforts to ensure evaluator training and performance. One way to reduce measurement variability is by frequent sampling; a slope derived from many interval measurements will be more reliable than if only two measurements are made. However, the extent to which measurement variability can be reduced by frequent sampling is unknown. An equally important problem faced by ALS realists is that of subject access to trials; most trials limit enrollment to subjects living in proximity to study sites. This results in slower subject accrual and recruitment biases with respect to ethnicity, socioeconomic class, and location. The AT HOME study was designed to evaluate both of these significant clinical trial limitations.

Objectives: a) To determine whether home based trial endpoints measured on a daily or biweekly basis reduces error of measurement and can be performed reliably; b) to determine whether a remote consenting process and enrollment can improve access to trials to subjects for whom geographic location limits such access; c) to determine whether greater subject diversity can be achieved by home based selection and assessment.

Methods: The AT HOME study will remotely consent and enroll up to 250 subjects with ALS and 30 control subjects. Enrolled subjects will receive a digital handgrip meter, the PiKO-6 dynamometer, the Skulpt Chisel EIM device, and a wrist worn actigraphy device. After web based training and certification, they will perform measures daily for 3 months, and twice weekly for 6 months. EIM and actigraphy data will be automatically uploaded for analyses, while subjects will enter their respiratory and handgrip data onto the study web portal. ALSFRS-R will also be assessed twice weekly. A clinical liaison will contact subjects by text and/or

phone if data are not entered in a timely fashion. As we expect interest in this study to exceed the enrollment target, we will select subjects to represent the geographic, ethnic, and socioeconomic diversity of the United States. At the end of 9 months of study, we will assess subjects' experience through a specially designed questionnaire.

Results: Enrollment will begin in August, 2016. We will describe details of the ongoing study, present interim demographic data, as well as compliance data to date.

Discussion and conclusions: AT HOME tests the hypotheses that frequent performance of home based outcome measures will reduce variability of assessment of rate of progression, and that such a home based approach will allow a more diverse community of ALS subjects potentially to be involved in future therapeutic trials.

Acknowledgements: Study funded by ALS Finding a Cure Foundation.

CW20 THE ALS EARLY RECOGNITION TIMELINE (ALERT) PROJECT: METHODS FOR A WORK IN PROGRESS

NICHOLSON K[1], HALEY K[1], CASTRO V[3], GAINER V[3], MURPHY S[3], SCHOENFELD D[2], FERGUSON T[4], ATASSI N[1]

[1]Department of Neurology, Neurological Clinical Research Institute, Massachusetts General Hospital, Boston, MA, USA, [2]Biostatistics Center, Massachusetts General Hospital, Boston, MA, USA, [3]Information Systems, Partners Healthcare, Charlestown, MA, USA, [4]Biogen, Cambridge, MA, USA

Email address for correspondence: knicholson@partners.org

Keywords: diagnosis, algorithm, scale

Objective: We aim to develop early diagnostic tools to shorten the diagnostic timeline for people with ALS.

Background: The median time from symptom onset to diagnosis in ALS is 11.5 months, an outrageous delay that is a significant portion of disease duration for most patients. The average time from symptom onset to first physician evaluation is 4 months, with an average 7 months from first doctor visit to eventual ALS diagnosis. Early identification of ALS symptoms could assist with faster referral and more timely diagnosis for earlier treatment and improved outcomes for people with ALS. Researchers are unable to target people in the early stages of the disease, impeding early identification of biomarkers and enrolment in therapeutic trials when chances of drug efficacy may be higher. Characteristic ALS signs and symptoms were defined at a 2011 meeting of ALS specialists, and termed "ALS Red Flags". US Medicare analysis of ALS patients and controls identified muscle weakness, lack of coordination, and speech/swallowing difficulties as early ALS symptoms with the highest prevalence ratios.

Methods: The Partners Research Patient Data Registry (RPDR) includes longitudinal clinical data for nearly 4 million patients within Partners Healthcare. ICD-9 codes were used to identify ALS subjects. A retrospective analysis was used to identify patients (both with and without a subsequent ALS diagnosis) with an ALS Red Flag prior to an index date. In addition, natural language processing (NLP) of providers' clinic notes will be run on this cohort adapted from the ALS red flags. Machine learning will be used to find the most predictive combination of coded and NLP ALS red flags for early diagnosis. Retrospective algorithm development is currently underway. In August 2016 prospective algorithm application will ensue. The algorithm will query the Partners EMR to identify people at risk for early ALS every 2 months. An ALS physician will review identified cases and promptly refer appropriate patients for timely diagnostic evaluation. An educational module regarding ALS diagnosis will be shared with the ALS clinic referral base. Diagnostic timelines using the red flags will be compared with historical timelines from our population, and an ALS Red Flags Scale will be developed from the prospective data collected.

Results: Feasibility of algorithm development reliant on the presence of EMR notes prior to ALS diagnosis was first explored. Approximately 50% of 3,316 patients diagnosed with ALS have coded data present within the EMR in the 2-60 months prior to initial diagnosis from 2005-2015.

Conclusions: The ALERT project is a work in progress, with potential to identify an early diagnostic scale that can be validated at different centers in future studies.

Acknowledgements: This project is funded by ALS Finding a Cure and Biogen.

CW21 FEASIBILITY AND RELIABILITY OF MODIFIED OCULOBULBAR FACIAL RESPIRATORY SCORE (MOBFRS) IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND SPORADIC INCLUSION BODY MYOSITIS (SIBM)

GEBERT N, WENCEL M, RAI S, TIERNEY P, MOZAFFAR T, GOYAL N

University of California, Irvine, Department of Neurology, Orange, CA, USA

Email address for correspondence: naraujo@uci.edu

Keywords: bulbar, dysphagia, reliability

Background: ALS and sIBM are neurodegenerative disorders that result in progressive facial, bulbar, respiratory and limb muscle weakness. The leading cause of morbidity and mortality in both diseases are secondary to bulbar and respiratory insufficiency (1). Reliable patient reported outcome (PROs) measures are used in both disorders ((ALS functional rating scale (ALSFRS-R) (2) and IBM functional rating scale (IBMFRS)) (3) that estimate the degree of facial, bulbar, and respiratory involvement in these patients. However, we lack objective scores that can quantitate disease related deterioration in bulbar, facial and respiratory functions in these diseases that would serve as an important prognostic factor for these patients. At this point, these diseases are untreatable and the usual course is relentless progression (rapid for ALS and moderate for IBM).

Objectives: We intend to test the feasibility of using the modified oculobulbar facial respiratory score (mOBFRS) (4) in these diseases. This objective scoring system was developed for use in and then validated in immune myasthenia gravis. We have routinely employed this tool in our clinic not only for myasthenia gravis but also for patients with bulbar ALS and IBM and find it a useful clinical marker (5). We now intend to evaluate if changes in mOBFRS in IBM and ALS: 1) can be reliably measured in these disease populations on a serial basis; 2) parallel changes in other objective measures of facial, bulbar and respiratory weakness (muscle strength testing, timed drinking of 80 oz. of cold water, etc); 3) correlate with the facial, bulbar and respiratory sub-scores of the existing IBM and ALS functional rating sales; and 4) changes in this score occur in a linear, predictable fashion that can be used as a potential outcome measure in future clinical experimental therapeutic trials in ALS and IBM.

Methods: The subjects will have these measures administered to them as part of their routine clinic visits on a regular interval. Given the differences in rates of progression of the two diseases, ALS patients will be assessed at baseline, month 3 and month 6 (3 time points), while the IBM patients will be assessed at baseline, month 6 and month 12. Statistical analysis for power calculation as well as for study related data will be done through the BERD unit.

Results: Data is being collected and we hope to present the results at the Symposium.

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CW22 MODELLING ALS PROGRESSION USING AN ARTIFICIAL NEURAL NETWORK-BASED COMPUTATIONAL SYSTEM

UBERTI M[1], GALVANI G[1], VERDE F[2,3], DORETTI A[2], MADERNA L[2], PICCARRETA R[1], SILANI V[2,3], BORGONOVO E[1], TICOZZI N[2,3]

[1]Department of Decision Sciences, Bocconi University, Milan, Italy, [2]Department of Neurology and Laboratory of Neurosciences, IRCCS Istituto Auxologico Italiano, Milan, Italy, [3]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Email address for correspondence: n.ticozzi@auxologico.it

Keywords: progression, artificial neural networks, PRO-ACT

Background and method: This work presents the results of a research project aimed at using artificial intelligence and data mining methods to forecast the progression of the ALS disease. In particular, we present results concerning the use of artificial neural networks (ANN) trained through the ProACT database. An in-depth statistical analysis of the dataset has accompanied the construction of the model. In particular, forecasts for FVC, FRS and BMI at time t (endogenous variables), have been obtained training the ANN on Gender, Onset (bulbar, limbs), Age, the rate of change between 0 and t-1 of FRS, FVC and BMI, as well as the age, the time between onset and the visit at t-1.

Results: Training, validation and tests show that the trained ANN predictions come with very low root mean square error.

Discussion: Results are promising for building a decision support tool that can help clinicians in forecasting the evaluation of the disease in anticipation, which is especially relevant when delicate decisions concerning medical interventions (eg mechanical ventilation) are at stake.

CW23 A RETROSPECTIVE STUDY OF PATIENTS DIAGNOSED WITH AMYOTROPHIC LATERAL SCLEROSIS AND CONCURRENT CASES OF PERIPHERAL THROMBI

KAISER M, HOLZBERG S

Hospital for Special Surgery, New York, NY, USA

Email address for correspondence: kaiserm@hss.edu

Keywords: DVT, thrombus, complications

Background: Patients diagnosed with amyotrophic lateral sclerosis (ALS) have decreased mobility. Decreased muscle tone results in inadequate venous return, thus subjecting the ALS patient to an increased risk for the development of a thrombus. Swallowing impairments may decrease fluid intake, which further increases the risk of these events with resultant dehydration. Although little literature exists on this subject matter, (2) notes that when considering the occurrence of deep vein thrombosis (DVT) in patients with ALS, "immobility was significantly associated with increased risk of venous thrombosis." (3) further contributes that "clinically important VTE is common in patients with ALS," therefore routine VTE screening and prophylaxis is of utmost importance in avoiding complications.

Objectives: The objective of this study is to determine the risk for the development of peripheral thrombi in the ALS population, therefore informing the necessity of early prophylactic measures in avoiding this complication.

Method: This will be a retrospective chart review of 200 male or female patients diagnosed with ALS between the ages of 18 and 80 at the Hospital for Special Surgery Department of Neurology from January 1, 2015 to January 1, 2016. This study will involve consideration of factors such as location of thrombus, MRC scale for muscle strength of involved extremity and swallowing impairment. Results will be expressed in percentage as a whole as well as based upon specific characteristics assessed.

Discussion: If a positive relationship is evident, the necessity of considering early interventions such as prophylactic anti-coagulation, intermittent pneumatic compression devices and thrombo-embolic deterrent (TED) stockings in the home may be considered. Patient education regarding active and passive range of motion as well as physical therapy should be considered.

Early interventions to combat the risks of thrombus formation may result in decreased mortality related to complications as well as greater satisfaction when the patient is considering comfort care. Little literature exists on the occurrence of peripheral thrombus formation in patients with ALS. Further, "venous thromboembolism is a major health care problem resulting in significant mortality, morbidity, and expenditure of resources" (Bauer et al., 2016). VTE routine screening and prophylaxis as a standard of care may help to avoid such strains.

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CW24 THE DIAGNOSTIC YIELD OF LABORATORY INVESTIGATIONS IN THE WORK UP FOR A SUSPECTED DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS

MIRIAN A[1], KORNGUT L[2]

[1]University of Calgary, Calgary, Alberta, Canada, [2]Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

Email address for correspondence: ario.mirian@ucalgary.ca

Keywords: serology, diagnosis, investigations

Background: There is no single diagnostic test that can determine the diagnosis of Amyotrophic Lateral Sclerosis (ALS) (1). An extensive panel of investigations are performed to find out whether a different treatable or untreatable disease mimicking ALS is causing the symptoms and/or clinical signs (2-4). The current literature provides little data on the diagnostic yield of serological investigations with respect to patients presenting with signs of ALS.

Objectives: The aim of this study is to determine the proportion of the current serological workup administered in a tertiary care centre/MND clinic for patients presenting with signs of ALS changes their primary diagnosis and/or management of their condition. The study will also use survey methodology to determine the laboratory investigations ordered by all Canadian ALS/MND clinics to establish a necessary overview of current clinical practice and the health economic impact of the testing.

Methods: A retrospective chart review is being conducted on patients from the Neuromuscular Intake Clinic, South Health Campus, Calgary, Alberta. All charts dating back to January 2000 in which the clinician queries ALS post-assessment will be reviewed for inclusion in the study. Eligibility criteria includes all living and deceased patients that underwent a workup for possible ALS with reported results of serological investigations in their chart. The proportion of abnormal results per investigation will be calculated. Each abnormal result will be assessed for whether it results in a change in clinical management by identifying a diagnosis other than ALS and/or a concomitant diagnosis. A standard survey will be sent to the clinical coordinator of all 15 ALS/MND clinics in Canada. The survey will ask each respondent if there is a standard serological workup for patients in which the clinician queries ALS and to specify the investigations included in the panel. All investigations will be reported along with the percentage of clinics ordering each investigation.

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CW25 SERIAL HIGH-DENSITY SURFACE ELECTROMYOGRAPHY (HDSEMG) RECORDINGS IN MOTOR NEURONE DISEASE: FASCICULATIONS AS A BIOMARKER OF MOTOR NEURONE HEALTH

BASHFORD J[1], WICKHAM A[2], DRAKAKIS E[2], BOUTELLE M[2], MILLS K[1], SHAW C[1]

[1]King's College London, London, UK, [2]Imperial College London, London, UK

Email address for correspondence: james.bashford@kcl.ac.uk

Keywords: fasciculations, neurophysiology, biomarker

Background: The presence of limb fasciculations is a clinical hallmark of motor neurone disease, particularly in the early stages before significant muscle weakness has occurred. Despite their almost universal presence, it is unknown whether serial measurements of fasciculation frequency, location and morphology may correlate with neurological decline. Part of the difficulty in performing serial recordings has been the lack of a suitable technique. Conventional needle EMG can be painful, so few patients tolerate repeated testing. An alternative and relatively new approach is to use HDSEMG, where non-invasive sensors are applied to the skin (1, 2). The test is painless so fasciculations can be recorded for longer periods and repeated at sequential intervals.

Objectives: 1. To determine whether it is feasible and practicable to undertake serial resting HDSEMG recordings in the same patient, at the same anatomical locations, using commercially available sensors; 2. To determine whether there is a pattern to the frequency of fasciculations in particular muscle groups and correlate this with validated clinical markers of disease progression.

Methods: We have recruited seven patients with MND and one patient with multifocal motor neuropathy (MMN). MND patients were diagnosed with probable/definite MND using the revised El Escorial Criteria. At each visit, 30-minute HDSEMG recordings are taken from four resting muscles (biceps brachii and medial gastrocnemii bilaterally) using 8x8 electrode sensor arrays and the TMSi Refa-64 analysis system. Measurements of revised ALS functional rating scale, MRC power sum score and slow vital capacity are performed at each visit.

Results: The mean age of patients is 59.8 years, with three females (two MND, one MMN) and five males. 26 (out of 48) patient-visits have been completed, equating to 52 hours of raw HDSEMG data. Using a specifically designed automated code in Matlab, the number of fasciculations detected in the right biceps of two MND patients, across multiple time-points, ranged from 721 to 3,104 per recording. This calculates a fasciculation frequency of 0.4-1.72Hz. The number of distinct fasciculation morphologies detected per recording ranged between two and four.

Discussion and conclusion: Serial HDSEMG recordings are well tolerated by patients. The quality of the raw neurophysiological data is

consistently high across sequential time-points. Our initial analysis demonstrates that HDSEMG reliably detects fasciculations and that 30 minutes is of sufficient duration to capture numerous fasciculations. The high-density nature of HDSEMG provides a sufficient resolution to distinguish distinct fasciculation morphologies, which reflect origins from separate motor units. We will expand our analysis as the pilot study continues, applying comparisons between neurophysiological and clinical parameters.

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CW26 SKELETAL MUSCLE MRI IN SPINAL AND BULBAR MUSCULAR ATROPHY – A STUDY IN AN ANIMAL MODEL AND PATIENTS

KLICKOVIC U, GRAY A, SINCLAIR C, SHAH S, REGA M, TORREALDEA F, ZAMPEDRI L, CLARKE J, HOWARD R, MALASPINA A, ORRELL R, SHARMA N, SIDLE K, HANNA M, GOLAY X, YOUSRY T, MORROW J, GREENSMITH L, THORNTON J, FRATTA P

UCL Institute of Neurology, London, UK

Email address for correspondence: uros.klickovic.15@ucl.ac.uk

Keywords: Muscle MRI, biomarkers, disease progression

Background: The development of novel therapies for motor neuron disorders (MND) requires reproducible outcome measures which can sensitively monitor disease progression. Muscle magnetic resonance imaging (MRI) is an excellent candidate due to its reproducibility and observer independence. To date, in MNDs MRI has been primarily used in amyotrophic lateral sclerosis (ALS) to evaluate the corticospinal tract and motor cortex (1), as well as in peripheral nerve disorders to measure muscle decline (2). No longitudinal studies with MRI in patients with spinal and bulbar muscular atrophy (SBMA) have been published to date.

Objectives: The aim is to evaluate the use of MRI of skeletal muscle as an outcome measure in SBMA patients, with validation in a preclinical model. Our primary hypothesis is that MRI can detect changes of muscular fat content in MND.

Methods: SBMA patients (n=12) and healthy controls (n=12) were imaged at a 3T MRI on lower limb, upper limb, and bulbar region with qualitative techniques, including T1-weighted and STIR imaging, quantitative volumetric imaging and 3-point Dixon imaging. This approach has been successfully applied in Duchenne´s muscular dystrophy (3) as well as in Charcot-Marie-Tooth disease 1A and inclusion body myositis (2).
We have also undertaken 9.4 Tesla muscle MRI imaging in a bacterial artificial chromosome (BAC) transgenic mouse model of SBMA (n=12) and controls (n=6) that reproduces the decline in muscle function observed in SBMA patients.

Results and discussion: We have found widespread intramuscular fat accumulation in the patient group. We also combined our imaging results with data on functional rating scales, dynamometry measurements and plasma biomarkers. As a move towards preclinical validation of muscle MRI as an outcome measure, we acquired MRI in a mouse model of SBMA and detected a marked reduction in hindlimb muscle mass. At present, clinical trials in MND rely on binary outcome measures such as number of patients surviving at a specified time point 4. Establishing biomarkers that could provide surrogate outcome measures is an important step for drug development. Muscle MRI might provide useful monitoring indices due to its non-invasiveness, reproducibility and objectivity.

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CW27 A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE DIAGNOSTIC UTILITY OF CEREBROSPINAL NEUROFILAMENTS IN MOTOR NEURONE DISEASE

AKYOL L[1], SOANE T[2,6], YEO JM[6], GREEN A[2,4], CHANDRAN S[2,5], PAL S[2,3]

[1]University of Edinburgh, Edinburgh, UK, [2]Centre for Clinical Brain Sciences, [3]Anne Rowling Regenerative Neurology Clinic, [4]National CJD Surveillance and Research Unit, [5]The Euan MacDonald Centre for Motor Neurone Disease Research; University of Edinburgh, Edinburgh, UK, [6]The Department of Clinical Neuroscience, Western General Hospital, Edinburgh, UK

Email address for correspondence: timsoane@doctors.org.uk

Keywords: CSF, neurofilament, diagnosis

Background: A number of recent studies have reported on the use of CSF neurofilaments as a potential diagnostic biomarker in MND. To date, there have been no meta-analyses or structured quality assessments performed of the studies undertaken.

Objectives: We conducted a systematic review and meta-analysis to investigate the use of CSF neurofilaments as a diagnostic biomarker in MND.

Methods: Electronic databases including Medline Ovid, Embase Ovid, Web of Science and Scopus were systematically searched in all languages using defined search terms: "Amyotrophic Lateral Sclerosis, Motor Neuron* Disease, Progressive bulbar palsy, Cerebrospinal Fluid, Intermediate filaments, Neurofilaments, Diagnosis". Studies were filtered according to strict inclusion and exclusion criteria and then assessed using The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) framework. Meta-analysis was performed using RevMan 5.3 (Cochrane Collaboration, Oxford, United Kingdom) utilising means and standard deviations directly extracted or estimated from studies, or calculated from individual patient data made available to us by study authors. Weighted mean differences (WMD) were calculated using the inverse-variance random-effects model.

Results: 13 studies met inclusion criteria for the systematic review (with data from 827 patients with MND, 237 healthy controls, and 933 with other neurological diseases). Quality assessment demonstrated most studies included basic patient demographics, and the reference standard was clearly identified. However, all avoided partial verification, differential verification and incorporation. Very few studies indicated precise patient selection criteria, or indicated if samples were blinded. A meta-analysis of: 1) Five studies comparing CSF neurofilament light chains in MND compared to other neurological diseases demonstrated a significantly higher concentrations in MND (WMD 2570 pg/mL, 95% CI (850, 4290), $p = 0.003$); 2) Three studies comparing CSF neurofilament heavy chains in MND compared to other neurological diseases demonstrated a significantly higher concentration in MND (WMD 1490 pg/mL, 95% CI (330, 2640), $p = 0.01$); 3) Three studies comparing CSF neurofilament light chains in MND compared to healthy controls demonstrated a significantly higher concentration in MND (WMD 3030 pg/mL, 95% CI (1250, 4800), $p = 0.0008$).

Discussion: CSF neurofilaments measurement (both light and heavy chain) appears to be promising in diagnosis of MND, and successfully discriminates MND from other neurological diseases and healthy controls. Further well powered, larger, prospective, and higher quality studies are required, including well characterised patients and controls before firmer recommendations can be made about implementation for clinical practice.

CW28 ISOLATION AND CHARACTERISATION OF CIRCULATING NEUROFILAMENT-CONTAINING AGGREGATES IN HEALTH AND DISEASE

ADIUTORI R[1,2], ZUBIRI I[1,2], AARUM J[1], LU C-H[1], BREMANG M[2], JUNG S[3], LEONI E[2], LIANG H-C[2], MITRA V[2], WARD M[2], PIKE I[2], MALASPINA A[1]

[1]Trauma and Neuroscience Centre, Blizard Institute, Barts and The School of Medicine and Dentistry, Queen Mary University of London, London, UK, [2]Proteome Sciences plc, Institute of Psychiatry, London, UK, [3]Proteome Sciences R&D GmbH, Frankfurt, Germany

Email address for correspondence: rocco.adiutori@qmul.ac.uk

Keywords: aggregates, biomarkers, MS-based proteomics

Background: There are currently no accurate diagnostic or prognostic tools for ALS, resulting in delayed diagnosis and poor disease stratification. Although the aetiology of ALS is still unknown, a hallmark of this neurological condition is the presence of protein aggregates within neurons (1). In addition, ALS and other neurodegenerative diseases are associated with a compromised blood

brain barrier (BBB), resulting in leakage of brain-derived proteins into plasma (2). Thus, plasma could represent a readily accessible source of diagnostic and prognostic biomarkers. We and others have shown that Neurofilaments (NFs) in cerebrospinal fluid (CSF) and plasma are a promising ALS biomarker, but suffer from high variability within and between patients. Interestingly, our data suggest that this could in part be due to epitope masking caused by protein aggregation. We propose that these circulating NF aggregates will have multiple protein components, reflecting both mechanistic and random associations. Thus, the identification of these aggregate components may provide a source of sensitive and specific biomarkers for the early diagnosis and prognostic monitoring of ALS patients.

Objectives: To develop and validate a method for the isolation of circulating blood protein aggregates and to characterise the composition of these aggregates by Mass Spectrometry (MS) based Proteomics.

Methods: In order to establish the best isolation method, a Pooled Plasma sample (PP) has been created using plasma from six Healthy Controls between 51.2-62.9 years of age and with known blood level of NF heavy chain (between 7.0 and 42.9ng/ml). Two different conditions for aggregate isolation have been evaluated, Sedimentation velocity and SeprionTM ligand interaction.

Results: Western blot (WB) showed a detectable amount of NFs in the aggregate fractions. Tandem MS data showed the presence of 651 and 1068 proteins (Protein Grouping: True; Peptide Confidence: High; Minimal number of peptides: 1) for the sedimentation and ligand methods, respectively. 380 common proteins were found between the two methods.

Discussion: We showed that sedimentation is a good methodology for isolation of aggregates circulating in blood. The detection of high molecular weight bands by WB suggests the presence of aggregates containing NFs in our pellets. Also, from proteomics data it is clear that these two methods isolate cytoskeletal and other intracellular proteins, potentially allowing the detection of CNS derived material. Further analysis is ongoing to evaluate the best methods for isolation and analysis.

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CW29 MICROGLIA CELL-TYPE SPECIFIC NF-KB NETWORKS IN AMYTROPHIC LATERAL SCLEROSIS MOUSE MODEL

BÉLAND L-C, BOUTEJ H, KRIZ J

CRIUSMQ, Université Laval, Québec City, Québec, Canada

Email address for correspondence: louis-charles.beland.1@ulaval.ca

Keywords: microglia, proteomics, inflammation

Background: Amyotrophic lateral sclerosis (ALS) is a non-cell autonomous disease (1), meaning that not only neurons, but other cell types are involved in the neuropathogenesis; cell types such as oligodendrocytes, astrocytes or microglia. Our study focuses on the latter. Microglia are known to acquire a pro-inflammatory phenotype with the progression of ALS. A recent study from our group has shown that microglia are altered before onset of the disease in mice and that the microglial inflammatory phenotype can change the course of the disease (2).

Objective: With this project, we aim to understand the mechanisms of ALS in microglia by studying its proteomic signature in mice lumbar spinal cord. Also, we want to compare the proteomic signature at different stages of the disease, namely at presymptomatic (50d), early symptomatic (135d) and late symptomatic (158d) stages.

Methods: To do so, we generated and characterized a mouse model for cell-type specific microglial molecular profiling. This model expresses a fusion protein, mRPL10a-eGFP-Flag under the monocytic promoter CD11b. We crossbred this Ribotag mouse with the ALS mouse model expressing hSOD1G93A. This model was used to immunoprecipitate microglial ribosomes and peptides in translation. Peptides were eluted and sequenced through mass spectrometry. Results were analysed on the application ClueGO on the program Cytoscape to generate interactomes and study regulation of proteins and pathways.

Results: We are able to identify proteins and pathways linked to inflammation through different stages of ALS. As preliminary results, we did a qualitative experiment on presymptomatic mouse

lumbar spinal cord microglia to test the model and pinpoint pathways such as the response to the IL-4 or TNFα - NFκB signaling pathways which were studied later on. Then, through a quantitative experiment we showed that the most upregulated biological functions change through the course of the disease. Functions linked to RNA processing were more upregulated at the beginning (50d) and at the end of the disease (158d) while we found functions linked to inflammatory response to be more upregulated in the middle of the disease (135d). We then proceed to check the protein regulation in the two pathways previously identified. Interestingly, we show that proteins such as G3bp2, heat shock proteins or 14-3-3 proteins are differentially regulated throughout the disease.

Conclusion: We suggest that by studying and modulating the regulation of microglial proteins linked to inflammation in ALS, we should be able to change the course of the disease. Our mouse model, will allow us to identify possible treatments and biomarkers, both much needed in the field of amyotrophic lateral sclerosis.

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CW30 HIGH-AFFINITY VITAL STAINING OF NEUROMUSCULAR JUNCTIONS FOR CONFOCAL ENDOMICROSCOPY

ROESL C, JONES R, DISSANAYAKE K, GILLINGWATER TS, SKEHEL P, RIBCHESTER R

University of Edinburgh, Edinburgh, UK

Email address for correspondence: richard.ribchester@ed.ac.uk

Keywords: neuromuscular junction, confocal endomicroscopy, vital staining

Diagnosis of MND/ALS is normally based on a combination of clinical judgements, supplemented by electromyography (EMG). Neuromuscular junctions are among the first components of the motor neurone that become dysfunctional and degenerate in ALS but motor point biopsy is now rarely performed, for ethical reasons.

Thus, we are seeking new ways of visualising neuromuscular junctions *in situ*, using a combination of vital staining and fibre-optic confocal endomicroscopy (CEM). Although we have shown in principle that the technique can readily be combined with EMG recording in transgenic thy1.2-YFP16 mice, which express fluorescent protein in motor neurones, a major hurdle to application of the technique to humans is the requirement for high-contrast, high intensity fluorescent vital stains that can safely be injected and will bind with high affinity to motor nerve terminals.

We have found thus far that Alexa488-alpha-bungarotoxin produces reliable staining of postsynaptic acetylcholine receptors at motor endplates in muscles from mice, rats, pigs and muscle tissue from human (non-MND/ALS) subjects; and this staining is readily visualised with a Cellvizio confocal endomicroscope fitted with a 1.5 mm diameter optical fibre probe. We have also found that a GFP-conjugate of the tetanus-toxin heavy chain produces high-contrast staining of motor nerve terminals at mouse NMJ, also readily visualised by CEM, and is thus a potential candidate for vital staining of terminals in human muscle.

We are also seeking novel high-affinity binding partners for NMJ using an alternative approach that makes no a priori assumptions about the nature of the binding sites for targeting fluorochromes. Our approach utilises the application of differential phage display, applied to NMJ-rich and NMJ-deficient regions of skeletal muscle. We will report on progress combining both of these approaches.