Abstracts from Themes BW and CW

Biomedical Work in Progress

Clinical Work in Progress

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BW-01 C9ORF72 patient specific iPSC-derived lines as ALS *in vitro* model

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Keywords: iPSCs, C9ORF72

Background: Amyotrophic lateral sclerosis (ALS) is a fatal disorder characterized by progressive degeneration of motor neurons (MNs). Recently, a repeat expansion in the *C9ORF72* gene has been identified as the cause of 40% of familial ALS and 5–10% of sporadic cases. However, the exact role of this gene and the mechanisms by which *C9ORF72* GGGGCC repeat expansions cause neurodegeneration are still unknown. Many hypotheses have emerged, notably a loss of function of C9ORF72 protein, RNA toxicity caused by the expansions transcripts that accumulate in RNA foci and might sequester critical RNA-binding proteins (RBPs), and the presence of toxic dipeptides produced by translation from the expanded nucleotide repeats. Patient specific induced pluripotent stem cell (iPSC)-derived lines can provide fundamental insights to better understand ALS C9ORF72 pathogenesis and to develop an effective therapy.

Methods: In this study, we reprogrammed iPSCs from patients with the GGGGCC expansion and differentiated them into affected MNs. First, we characterized the pathological phenotype of the C9ORF72 lines compared with control lines, evaluating the survival of cells, the expression of apoptotic markers and RAN products, TDP43 inclusion presence, and the dysregulation of putative RBPs interacting with RNA foci. The use of antisense oligonucleotides (ASOs), DNA sequences designed to modify RNA, offers great promise for the treatment of human diseases and is now being tested in clinic. This strategy can also be exploited for C9ORF72-ALS therapy. Hence, we designed 25 ASOs with Morpholino (MO) chemistry against the expansion motif of C9ORF72. We transfected iPSC-derived MNs from C9ORF72 patients with MOs and we evaluated the effectiveness of this therapeutic strategy, analyzing any modification of the pathological markers previously identified.

Results and discussion: Our results suggest that patient specific iPSC-derived lines are a valuable tool to deepen the knowledge of C9ORF72 pathogenic mechanisms; and to validate new therapeutic strategies such as the MO-mediated approach.

Acknowledgements: Regione Lombardia (TRANS-ALS project) to GPC and Ministry of Health to GPC.

BW-02 NeuroLINCS: Identifying ALS-specific signatures from iPSC-derived motor neuron using multi-omic integration

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Keywords: iPSC, omics, integration

Background: Amyotrophic lateral sclerosis (ALS) is an aggressive neurodegenerative disease impacting motor neuron survival, with death occurring 3-5 years after clinical

diagnosis.

Aims: The NeuroLINCS consortium aims to leverage induced pluripotent stem cell (iPSC) technologies, OMICS methods, and computational biology to identify molecular signatures of ALS.

Methods: In this study, we generated iPSC-derived motor neurons from ALS patients with the C9orf72 (C9) G4C2 repeat expansion. To capture these signatures, we first performed individual omics experiments (ATAC-seq, RNA-seq, and SWATH-MS proteomics) on each induced motor neuron (iMN) cell line. Next, we used ATAC-seq, which reveals regions of open chromatin, in combination with gene expression, to predict transcriptional regulators involved in ALS C9 pathology. Finally, we applied network analysis to identify disease pathways by integrating proteomics with predicted transcription factors.

Results and discussion: Our resulting network was significantly enriched for previously described ALS genes (pval=5.63E-06) and also suggests disruption of cytoskeleton formation, microtubule assembly, iMNs, and hyperactive extracellular matrix organization in C9 ALS iMNs. These approaches will be expanded to integrate lipidomic and metabolomic data, as well as whole genome sequencing, single cell imaging, and functional cellular readouts with various perturbations. To help facilitate therapeutic development, these data will be made available to the scientific community through NeuroLINCS and AnswerALS to further elucidate the pathogenic mechanisms in ALS motor neurons.

BW-03 A microfluidic co-culture system to study the neuromuscular junctions formed by human motor neurons derived from ALS patient iPSCs

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Keywords: iPSC, neuromuscular junction, microfluidic chamber

Background: Patient specific induced pluripotent stem cells (iPSCs) have the ability to differentiate into any cell type including motor neurons (MNs). We, and others, have utilized iPSC-based technology and created *in vitro* models of genetic ALS (1-4). These efforts have uncovered a series of damaging molecular pathways in patient MNs, including an activated unfolded protein response, mitochondrial dysfunction and alterations in electrophysiological excitability (1-2). In all studies to-date, MNs were examined in isolation or in co-culture with glial cells. However, a defining functional characteristic of the MN is its ability to form a synapse with muscle, and neuromuscular junction (NMJ) dysfunction is an early event in ALS progression (5).

Objectives: We hypothesize that in order to gain further insights into ALS disease mechanisms we need to study MNs under more physiologically relevant conditions. To this end we have custom built a multi-cellular model of ALS that recapitulates the spatial resolution of the MN circuit.

Results: Our custom fabricated device consists of a tri-compartment microfluidic device with an anatomical projection between MNs and skeletal muscle cells, along with biochemical communication between MNs and astrocytes. To date, our studies have successfully established conditions in which patient MNs extend their axons through channels to make contact with human myotubes, while astrocytes, cultured separately, exchange media and nutrients with the MNs. Currently underway are experiments aimed at interrogating the functional status of nascent NMJs through both optogenetic control of MN firing and pharmacological blockade of NMJs post-synpatically with d-tubocurare. Ultimately, we plan to determine if the ALS-causing

SOD1 A4V mutation affects the ability of iPSC-derived MNs to form and sustain functional NMJs.

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Acknowledgements: Funding was provided by the Northwestern Institute for Cellular Engineering Technologies Seed Project Grant program.

BW-04 miRNA profiling of ALS iPSCs and iPSC-derived motor neurons: Molecular and therapeutic implications

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Keywords: microRNA, iPSCs, motor neurons

Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal disorder characterized by progressive degeneration of motor neurons (MNs). The mechanisms underlying the disease are almost unknown, even though dysregulation in RNA metabolism, including microRNA (miRNA) processing, has already been associated with ALS. Indeed, different ALS-linked genes, such as TDP-43 and FUS, can affect miRNAs expression. Since miRNAs are highly expressed in the central nervous system and are required for the survival of specific types of MNs, they may play important roles in the aetiology or progression of neurodegenerative diseases such as ALS.

Aims and methods: Here we aim to investigate miRNAs dysregulation in human iPSCs and iPSC-derived spinal MNs from ALS subjects compared to healthy controls. We reprogrammed patient and control fibroblasts in iPSCs and subsequently we differentiated them into spinal MNs. We performed Next Generation Sequencing (NGS) analysis on our lines in order to identify dysregulated miRNAs and their biological targets. Moreover, we also investigated the expression profile of miRNA contained in extracellular vesicles isolated from both iPSC and iPSC-derived MN culture media. Data obtained will undergo bioinformatic analysis and will be validated by molecular and proteomic studies both *in vitro* and *in vivo*.

Discussion: This approach can increase the chances of modifying complex disorders such as ALS, by targeting the entire gene network. Moreover, the identification of miRNAs implicated in the disease can lead to the discovery of new disease biomarkers and therapeutic targets.

BW-05 MicroRNA-183-5p couples cell stress sensing and cell death programming in the development of amyotrophic lateral sclerosis

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Keywords: microRNA-183b-5p, cell stress, PDCD4

Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the death of upper and lower motor neurons. A fundamental pathogenesis of ALS is prolonged cell

stress in motor neurons, which is caused by either accumulation of protein aggregates or reactive oxygen species. Much progress has been made in stress-induced cell death, however, the mechanisms underlying the link between stress sensing and cell death in ALS remain undefined.

Methods: In previous studies, we investigated the miRNA expression profiles in Chinese sporadic ALS (sALS) patients using peripheral blood mononuclear cells (PBMCs) by microRNA microarray to explore new strategies for diagnosis and therapy of ALS. We found that *miR-183-5p* was significantly downregulated in patients with sALS and provided high diagnostic accuracy for sALS. Here, we extended to identify that *miR-183-5p*, a significantly down-regulated miRNA in ALS patients, coupled the cell stress sensing and cell death programming in the development of ALS.

Results and discussion: We found that *miR-183-5p* was dramatically induced in response to either hydrogen peroxide or tunicamycin in both primary neuronal cultures and NSC-34 motor neuron-like cell lines ($P<0.01$), indicating that *miR-183-5p* was a specific neuronal sensor to oxidative stress and ER stress. Furthermore, we showed that overexpression of *miR-183-5p* by transfection of *miR-183-5p* mimics increased cell survival under stress conditions, whereas its inhibition by transfection of *miR-183-5p* inhibitors promoted cell death ($P<0.05$). Moreover, we found that *miR-183-5p* directly targeted the death executor programmed cell death 4 (PDCD4), and thus protected cells from death under stress conditions. Furthermore, the consistent reduction of *miR-183-5p* in a mouse model of ALS, with $SOD1^{G93A}$ mutation ($N=8$, $P<0.01$), enhanced the notion that *miR-183-5p* was the coordinator of stress sensing and death programming in motor neurons.

Conclusion: Taken together, our work identifies a missing link between cell stress and cell death in motor neurons, and provides novel targets for improving clinical therapy of ALS.

BW-06 Early gene expression profiling of spinal motor neuron vulnerability pathways in a mouse model of ALS

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Keywords: lower motor neurons, transcriptomics, selective vulnerability

Background: Although ALS typically presents in mid to late-life, there is increasing evidence for a protracted preclinical period of motor neuron vulnerability and damage before diagnosis. This preclinical period in ALS may span years or even decades, potentially dating back to the perinatal period of life (1).

We hypothesize that motor neuron vulnerability is induced in the perinatal period critical for early motor neuron development and maturation, reflected by transcriptional dysregulation. Importantly, these early gene expression signatures may point towards relevant and meaningful therapeutic clues for ALS.

Objectives: The goal of this study is to identify the earliest gene expression patterns in lower motor neurons that drive selective neuronal vulnerability at key developmental ages in a mouse model of ALS.

Methods: We have implemented novel transgenic $SOD1^{G93A}$ mice, with a lower motor neuron fluorescent reporter, to unambiguously isolate spinal motor neurons at key very early ages in development for transcriptomic profiling using RNA sequencing, bioinformatics, functional pathway analysis and target validation.

Results: Our preliminary studies reveal the earliest mechanisms underlying motor neuron degeneration can be reflected by

gene expression profiling studies. We have identified differentially expressed genes that could determine motor neuron susceptibility at very early age. Expression of these genes is evident in the subset of motor neurons that are destined to degenerate. Subsequently, these gene targets could potentially trigger degeneration of motor neurons by activation of stress pathways identified in the disease process downstream of mutant SOD1. Our data define these gene candidates as an early determinant of ALS pathogenesis that occurs in the final stages of the disease.

Discussion and conclusions: Data obtained from this transcriptomic study will yield lower motor neuron gene candidates for future target validation and intervention studies in mouse models of ALS. Our findings have the potential to reveal insights into the incipient molecular mechanisms that confer motor neuron vulnerability and therefore may highlight relevant gene targets and pathways for effective intervention in MND.

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Acknowledgements: Australian National Health and Medical Research Council, MND Research Institute of Australia and Stafford Fox Medical Research Foundation.

BW-07 Humanising the mouse TARDBP gene

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Keywords: TDP43, BAC, mouse model

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by degeneration of upper and lower motor neurons showing the presence of protein aggregates in the cytoplasm. Mutations in the TARDBP gene, encoding the TAR DNA-binding protein (TDP43), are causative of ALS. A common feature in almost all cases of ALS, both sporadic and familial, is the depletion of wild type TDP43 from the nucleus, with accumulation of truncated ubiquitinated/ hyperphosphorylated TDP43 in the cytoplasm inside aggregates (1). TDP43 is a highly conserved RNA/DNA binding protein, mainly located in the nucleus and involved in multiple molecular mechanisms (2). Thus, there is an urgent need to develop accurate animal models able to recapitulate the biochemical and molecular mechanisms by which TDP43 turns into a pathological protein leading to the development of ALS.

Objectives: We are creating a knock-in humanised TDP43 mouse, replacing the genomic region of mouse TARDBP, from the first coding codon (ATG) until the stop codon, with the corresponding sequence from the human orthologos, including human TARDBP introns 2 to 5. Thus, the mice produced will express, under the mouse endogenous control, a fully humanised TDP43 protein.

Methods: We chose to use human and mouse Bacterial Artificial Chromosomes (BACs) as sources of DNA sequences for our targeting strategy. Using BAC recombineering and homologous recombination, we will target mouse embryonic stem cells generating a mouse carrying a fully genomically humanised TDP43, together with the mouse untranslated regions (5' and 3' UTRs).

Results: We have established a gene targeting strategy using six steps to create our mouse model. The gene targeting strategy involves the use of two BAC clones, containing respectively, human and mouse genomic DNA, which are used to create (following several cloning steps) a final targeting vector carrying long homology arms to perform homologous

recombination in mouse embryonic stem cells. To date, we have finished the sequencing of our human BAC clone, and are sequencing the mouse BAC clone. We have also completed three of the six steps included in our gene targeting strategy. We are currently performing sequencing analysis of the first targeting construct created via BAC recombineering which will be used to target and humanise mouse TARDBP inside the mouse BAC clone.

Discussion and conclusions: Our humanised mouse may recapitulate the normal human TDP43 expression *in vivo* under physiological conditions becoming an important starting tool for understanding how TDP43 contributes to the development of ALS and for future studies of the pathological effects caused by mutation in the human protein.

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BW-08 Mitochondrial dysfunction associated with a SOD1-ALS knock in model

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Keywords: SOD1, mitochondria, suppressor

Background: Many neurodegenerative diseases such as ALS, Parkinson's disease, and Huntington's disease have been associated with defects in mitochondrial morphology and function. A growing body of evidence has suggested that these mitochondrial defects are a central contributor to the ultimate loss of motor neuron function in familial amyotrophic lateral sclerosis (fALS) linked to mutations in the antioxidant enzyme SOD1 (1-3). Studies in overexpression models of mutant human SOD1 have demonstrated a range of mitochondrial defects in neurons, such as altered axonal transport, changes in fission/fusion dynamics, abnormal distribution, ultrastructural differences, and bioenergetics (4-10).

Method and results: In a Drosophila mutant dSOD1 knock-in model where the endogenous levels of SOD1 are maintained, we have also detected defects in mitochondria. We have identified several genetic suppressors of the dSOD1-ALS model, and we are exploring how the observed defects in mitochondrial morphology and possible changes in mitochondrial function associated with mutant dSOD1 respond to genetic suppression.

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BW-09 Nuclear pore complex composition in the mammalian CNS: Regional and cell type specific differences

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Keywords: nuclear pore complex, neuron, glia

Nuclear Pore Complexes (NPC) are large molecular structures that span the entire nuclear envelope and form the main gateways between the nucleus and cytoplasm. They not only directly control the exchange of protein and RNA into and out of the nucleus, but also serve transport-independent functions such as regulating genome organization and gene expression. The proper functioning and biogenesis of these large channels are critical for cell homeostasis and survival. NPCs consist of 30 different proteins called nucleoporins (NUPs) that are organized into five distinct anatomical regions of the NPC. Increasing evidence shows that each of these NUPs play very unique and specific roles. For instance, NUP50 serves a critical role in nuclear import, XPO1 plays an essential function in nuclear export, GLE1 plays a significant part in mRNA export, and NUP93 is part of the NPC scaffold and functions as an adaptor to anchor other NUPs located in the central channel of the NPC.

Not only do certain NUPs share roles in general import and export, but they each have been shown to traffic unique subsets of macromolecules thus adding another layer of diversity and specificity. One can begin to imagine that cells may be able to regulate certain cellular processes, given cell type-specific constraints and context-dependent needs, by altering the composition of NPCs; and that this may provide an explanation for tissue-specific diseases that arise from mutations in various NUPs. For instance, mutations in NUP62 cause Infantile Bilateral Striatal Necrosis, the selective degeneration of the striatum in infants, and mutations in GLE1 cause Lethal Motoneuron Syndrome (LCCS1), a fetal motor neuron disease, as well as rare forms of Amyotrophic Lateral Sclerosis (ALS). It is possible that NUP62 is responsible for the trafficking of a transcription factor that is absolutely necessary for striatum viability. The same can be postulated for GLE1 and motor neurons.

Although the overall structure of the NPC is conserved across different cell types, the aforementioned data suggests that protein composition of NPCs may vary among cell types and tissues. Lastly, very little is known about NPC structure and function in the mammalian CNS and whether brain cells use unique combinations of different NUPs to create NPCs bearing distinct properties and specialized functions. To this end, we have employed a novel method to isolate and purify NPCs from specific cell types and across different tissues of the CNS and characterize the composition of these NPCs using mass spectrometry and super resolution imaging analyses. We believe these ongoing experiments will provide critical insight into NPC neurobiology, which is relatively unknown. This will in turn provide a foundation for understanding CNS nucleocytoplasmic transport, which is a new and exciting focus for neurodegeneration pathobiology.

BW-10 Developing a novel *in vivo* model of cell-to-cell protein transmission in MND

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Keywords: mouse model, protein transmission

Background: The transmission of pathogenic proteins from diseased to healthy neurons is rapidly becoming a unifying theory across neurodegenerative diseases. Most neurodegenerative diseases are characterised by the accumulation of specific pathogenic proteins in or around diseased neurons. It is now accepted that these pathogenic proteins can be transmitted between cells, and that this transmission may contribute to disease progression. In MND the spread of symptoms from region to region has long been documented, and increasingly evidence that pathogenic proteins are also transmitted between cells has been found in *in vitro* and *in vivo* disease models. To increase our understanding of the mechanisms involved in transmission, and determine if the phenomena contributes to the progression of MND, we have developed a long term *in vivo* model of disease transmission in motor neurons.

Objectives: To determine if transmission of pathogenic protein occurs following long term exposure of healthy motor neurons to an *in vivo* disease environment expressing human mutant SOD1 or TDP43.

Methods: We transplanted healthy upper and lower motor neurons dissected from foetal mice into the brains of mice expressing human mutant SOD1 or TDP43. Transplanted cells were examined using immunohistochemistry for the accumulation of proteins associated with MND or protein degradation over a time course of up to 12 weeks.

Results: We have found that after 12 weeks healthy motor neurons transplanted into a disease host expressing human mutant SOD1 accumulate ubiquitin and misfolded SOD1.

Conclusions: This experimental model provides a flexible tool to investigate the mechanisms underlying the transmission of pathogenic proteins in MND.

BW-11 Comparison of autoimmune comorbidities among different motor neuron disease subtypes: A retrospective study.

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Keywords: immunology, autoimmune diseases, epidemiology

Background: There is evidence that autoimmune diseases are more frequent in patients with motor neuron disease (MND) compared to the general population (1). However, whether specific MND phenotypes have a stronger association with autoimmune diseases than others is unknown. There is growing evidence that immune responses play a role in the pathogenesis of MND. Given its diverse phenotype, it is unclear whether immune responses are differentially affected in MND subtypes.

Aim: To estimate and compare the prevalence of autoimmune diseases among different MND subtypes.

Methods: Records of patients with MND followed at the Hospital for Special Surgery ALS clinics, from 2012 to 2017, were retrospectively reviewed. Presence and family history of autoimmune diseases and markers of autoimmunity (immunoglobulin levels, monoclonal gammopathy, ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), presence of autoantibodies) were recorded. The frequency of the above will be compared among different subgroups (primary lateral sclerosis (PLS), bulbar onset MND (B-MND) and spinal onset MND(S-MND)), using chi-square.

Results: 202 patient records have been reviewed so far. Median age at symptom onset and diagnosis was 61 and 63 years, respectively. 26 patients had PLS (12.9%), 37 (18.3%) B-MND (68.8%), and 139 S-

MND. 18 (8.9%) had history of autoimmune disease, which is higher than the general population estimate of 3.2% (2). Of those, 1 had PLS, 3 had B-MND, and 14 had S-MND. 40/103 (38.9%) patients had positive antinuclear antibodies, 4/74 (5.4%) had positive anti-Ro, and 7/72 (9.7%) had positive rheumatoid factor (RF). 2/39 (5.1%) had positive acetylcholine receptor antibodies, and 4/56 (7.1%) had positive anti-ganglioside antibodies. 4/85 (4.7%) had hypergammaglobulinemia, and 9/112 (8%) had monoclonal gammopathy. 17/46 (37%) patients had elevated CSF protein. Among different subtypes, there was no statistically significant difference in the frequency of autoimmune diseases, or autoimmune markers.

Discussion: Our data suggest that, similar to prior studies, autoimmune diseases are overrepresented in patients with motor neuron disease. However, there is no association of the above with a specific MND subtype, despite their clinical heterogeneity. This might suggest that the altered immune pathways are a common feature of these phenotypically distinct clinical syndromes, closely related to their pathogenesis. Further elucidating the immune responses and pathways involved in MND subtypes can lead to more specific clinical and translational studies in order to develop novel therapeutic targets.

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BW-12 Do chloroviruses contribute to ALS?

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Keywords: chlorovirus, DNA-sequencing, serum-antibodies

Background: The exact etiology of sporadic ALS remains unknown, yet viral involvement in the development of MND has been well documented through known infections with poliovirus, West Nile Virus and HIV. Recently proposed triggers of MND have included toxic exposure from blue green algae blooms, including cyanobacteria and BMAA (1). Chloroviruses (CVs), which infect chlorella-like green algae, have been associated with neurocognitive decline in humans, inducing cytopathic effects in macrophages leading to inflammatory expression of IL-6 and NO, with subsequent apoptosis (2). CVs have not been studied in ALS.

Objectives: To determine if patients with ALS have CVs or CV DNA sequences in deep throat swabs and/or anti-CV antibodies in their blood, compared to healthy controls.

Methods: Twenty patients with ALS and TWNETY age-matched controls provided throat swabs and blood samples to be evaluated in a blinded experiment. Throat swab samples are being evaluated for two parameters: culturable CVs and virus-specific DNA sequence signatures. The blood sera are being evaluated for specific CV antibodies (IgG). Culturable CVs will be assayed by cell lysis and plaque assayed on each of four green algal viral hosts. DNA will be isolated for large scale screening. After removing human and bacterial sequences those remaining will be compared to viral DNA sequences in *Genbank*, searching for CV DNA sequences in the subjects with ALS compared to controls. CV *Acanthocystis turfacea* chlorella virus (ATCV-1) directed PCR amplicons will be evaluated using virus-specific primers. Highly purified CV ATCV-1 will be used for high-throughput screening of human blood samples for CV antibodies. This will be followed with ATCV-1 specific epitope synthetic peptides, which do not resemble any other sequences in *Genbank*.

Results: Throat swab samples were evaluated for infectious CV on 4 algal host

types. Initial culture-based amplifications were processed after 0.45 micron filtration, then sub-cultured in individual host types. No culturable virus was detected by either cell lysis or plaque assay. Patient sera were evaluated using an indirect ELISA method with CV ATCV-1 as the target. Positive control serum (ATCV-1 challenged rabbit) and appropriate negative controls produced a strong signal and little or no signal, respectively. Patient sera were differential with moderate to low signal levels.

Discussion: Quantification of serum level antibodies and evaluation of the throat swab-derived DNA is ongoing. The results will be provided at the time of presentation.

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BW-13 Immigration study on amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia complex (PDC) of the Kii peninsula, Japan

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Keywords: Kii, ALS/PDC, immigration

Amyotrophic lateral sclerosis/parkinsonism-dementia complex is endemic in the Kii peninsula, Japan (Kii ALS/PDC). Although there is a long history of research, the cause of ALS/PDC is still unknown. We have experienced a patient who developed ALS at 76 years old after immigration, at 11 years old, to the high incidence area, from a remote area. Her father also developed ALS at 62 years old after immigration at 37 years old. She showed typical neuropathological findings as ALS/PDC, including numerous tau pathology, and her gene analysis did not show any known causative mutations regarding ALS. We will present the clinical and neuropathological findings of the index patient, review the previous migration studies on Kii and Guam, and reconsider the impact of environmental factors on the pathomechanism of ALS/PDC.

BW-14 Longitudinal ALS registries: methods, objectives, and results

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Keywords: ALS registries, natural history, databases

Objective: To establish general principles of a sustainable clinic-based multi-site international Natural History clinical data repository in ALS/MND.

Background: There is a recognized value in understanding the phenotypes and natural history of ALS and other motor

neuron disorders. Utilization of the 'registry' enrollment approach (consenting everyone attending a clinic) has the added benefit of pre-populating individual participant data from electronic health records (EHR) to enrich future participation in other investigations.

Design/Methods: Disease repositories can be constructed from comprehensive health care data sources managed by governmental or health-care institutions, from direct solicitations to the community of people living with the disease, from clinical trial datasets, or from clinic-wide EHR. Each approach may introduce certain bias as well as advantages and pitfalls, depending upon their implementations. In designing a clinic-based natural history study, we considered such approaches, and, based on experience from participating sites, have developed certain workflows and recommendations.

Results: Collaborating US-based clinics strived to consent 100% of patients into the Natural History study. The epidemiologic risks of recruiting from a clinic population alone, methods to estimate differences in phenotype and natural history based on patient advice liaison services' access to clinics, the biases introduced by enrolling prevalent and incident cases, and the potential utility of such information-gathering going forward will be discussed.

Conclusions: Regulated and compliant natural history studies may enhance our understanding of the disease phenotypes, be used in developing/refining staging systems, and allow for better modeling and accelerated enrollment in placebo-controlled clinical interventional studies.

BW-15 WITHDRAWN

BW-16 Detection of C9orf72 allele expansions in a cohort of 277 ALS patients and control subjects

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Keywords: C9orf72, genotyping, patients

Background: A hexanucleotide repeat expansion (GGGGCC) in chromosome 9 open reading frame 72 (C9orf72) is the most common genetic cause of ALS, accounting for nearly 34% of FALS and 5% of SALS in European patients (1). Yet, the pathogenesis of the mutation is poorly understood. In order to create a full and effective profile of each individual's disease, each patient must be accurately genotyped. Our program includes 277 patients of a diverse background, many of which have not had any sort of genotyping. Whole genome sequencing is performed on blood DNA, but is insufficient to detect repeat expansions.

Objectives: To identify patients harboring a C9orf72 expanded hexanucleotide repeat.

Methods: ALS patients and control subjects were recruited for blood and skin biopsy sample collection. Blood DNA was isolated using PreAnalytix PAXgene Blood DNA Kit. Blood and fibroblast DNA were purified using Zymo Universal DNA Purification kit. C9orf72 allele status was determined using a two-pronged approach combining amplicon length analysis and repeat primed PCR (RP-PCR). Amplicon length analysis reliably determines repeat sizes between 2-16; inability to detect both alleles implies that the patient may carry an expanded allele. To verify the presence of an expansion, RP-PCR was performed using a previously described protocol (2) and the Asuragen AmplideX PCR/CE C9orf72 Kit. RP-PCR products were analyzed by capillary electrophoresis using an Applied Biosystems 3730xl DNA Analyzer. The data were analyzed using GeneMarker software.

Results: Of 272 patient DNA samples tested, 171 produced reportable data, while the remaining 101 samples have to date yielded reproducibly inconclusive results. Of the reportable cases, C9orf72 repeat expansions were detected in 23 patients,

including 20 patients with expansions greater than 30 repeat units and 3 patients with intermediate expansions between 20-30 repeats.

Discussion and conclusions: We have successfully detected C9orf72 hexanucleotide repeat expansions in a subset of our patient cohort. We are currently optimizing a new method designed to improve genotyping efficiency and reproducibility. Further research will focus on accurately sizing expanded C9orf72 alleles and assessing the state of methylation of intermediate and expanded repeat regions.

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Acknowledgments: The authors would like to thank all of the patients, their families, and control subjects for their participation in this study.

BW-17 Breast cancer susceptibility in patients with spinal bulbar muscular atrophy: a case report

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Keywords: SBMA, Male breast cancer

Background and aims: Spinal Bulbar Muscular Atrophy (SBMA), also known as Kennedy's disease, is a rare, adult-onset, X-linked, neuromuscular disorder due to a CAG expansion in the Androgen Receptor (AR) gene. The mutation leads to a polyQ (poly-glutamine) expansion and consequently to the accumulation of mutant AR in lower motor neurons and muscular cells resulting in the development of muscle weakness, cramps, fasciculations and bulbar symptoms. Since AR is broadly expressed in the body, non-neural symptoms may be present as well.

Case report: We report the case of a 55 year old SBMA patient carrying 55 CAG repeats in AR gene, who was diagnosed with breast cancer. Histological analysis highlighted the presence of a ductal carcinoma *in situ* with Estrogen Receptor (ER) positivity in 95% neoplastic cells and PR (Progesterone Receptor) positivity in 60% neoplastic cells. The patient reported to be affected by bilateral gynecomastia since puberty.

Results: Male breast cancer (MBC) is a relatively rare disease, representing 1% of all breast cancers. Several studies have attempted to evaluate a potential link between the AR polyQ-related effect on the receptor function and breast cancer (1). As a nuclear transcription factor, AR plays a role in the control of cellular proliferation and differentiation in androgen sensitive tissues. In the breast, androgens would act as antimitogen. Since the length of the expanded polyQ tract is inversely related to AR transactivation function, it is not unexpected that subjects with MBC have a higher chance of carrying long AR alleles (2). Therefore, the degree of polyQ-size may represent a predisposing factor for breast cancer by modifying tumor responsiveness to androgens. Even tough MBC is not described as frequent in SBMA patients, the very long AR polyQ expansion of 55 repeats found in our patient, definitely above the usual range observed in SBMA (40–54; median value: 45), could have promoted the malignant evolution of his gynecomastia.

Conclusion: We confirm that not only AR expression, but also AR-polyQ tract, should be considered as prognostic indicators in breast cancer. From a clinical point of view, we suggest that screening for MBC may be warranted in SBMA patients with very long CAG expansions in the AR.

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BW-18 Latent cluster analysis of ALS phenotypes: identification of prognostically differing groups - work update

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Keywords: latent class cluster, phenotype, subgrouping

Amyotrophic lateral sclerosis (ALS) manifests as several different phenotypes. We have previously used latent class cluster analysis to identify subgroups of ALS based on phenotype, and tested for SNP association with subgroups at the genome wide level.

Phenotypic data (age of onset of weakness, sex, ethnicity, family history of ALS, site of onset of first symptoms, diagnostic delay, physician-classified phenotypic group) were obtained from UK (1313 cases and 5431 controls), Dutch (1546 cases and 2374 controls), Belgian (388 cases and 242 controls) and Irish (468 cases and 774 controls) populations, and used to perform latent cluster analysis as previously described (1). The model was tested for clinical relevance by survival analysis of the phenotypic groupings using the Kaplan-Meier method.

Quality control was performed separately on genotyped data of each population and a genome wide association joint analysis was carried out in the four datasets. After quality control, there were 3,480 cases and 8,533 controls, and 264,528 SNPs. As a preliminary analysis, logistic regression was used to test association with the disease and principal components were used to correct for population stratification. Genotyped data were extracted for each resulting cluster and a logistic regression was performed separately. Principal components were calculated separately for each cluster.

Latent class cluster analysis showed a five-cluster model had the best fit. The five clusters had significantly differing, non-overlapping survival durations. In the joint analysis, no genome-wide association was seen. In the subgroup analysis, cluster 1 showed association passing genome-wide significance for a SNP in the C9orf72 gene, (rs3849942; OR= 1.26, p=3.65 e-08), and cluster 2, in SNPs in the KCND3 gene (rs12408551, OR = 3.76, p=1.81 e-08; rs11102355, OR=3.75, p=3.04 e-08).

We present here an update of this study confirming the latent cluster analysis as an effective method for grouping patients into subgroups that convey biological or clinical significance.

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BW-19 Mutations in the *ARPP21* gene are associated with familial and sporadic amyotrophic lateral sclerosis

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Keywords: novel gene, ARPP21, RNA

Background: The evolution of next generation sequencing has led to exponential growth in our understanding of ALS genetics. Here, we report a new candidate gene *ARPP21* identified through whole exome sequencing in a cohort of familial ALS cases. Two novel variants absent in controls are shared by several unrelated index cases for which currently known genes have yet to be accounted for. To understand the contribution of *ARPP21* in ALS, we have screened the gene extensively and modelled the identified variants *in vitro*.

Objectives: The aim is to characterise the *ARPP21* gene and variants within the gene.

Method: Direct sequencing was performed on over 2000 ALS cases and 1000 controls of UK, US and Italian origin. Immunohistochemistry was performed against the endogenous protein in human and mice CNS tissues. Disease modelling was performed in HEK239T, SH-SY5Y and primary rat cortical neurons.

Results: Both variants linked with familial ALS (p.P563L; p.P747L) are identified in a replication sporadic ALS cohort. The same p.Proline563 amino acid is found to be substituted to glutamine in two sporadic cases of UK and Italian origin. Similar to other ALS causative genes, most of the mutations cluster in the C-terminus disordered region of low complexity. *ARPP21* encodes a phosphoprotein that localises predominantly in the cytoplasm of cells and is highly enriched in the neuronal population. Cellular modelling of the ALS-associated mutants showed RNA-dependent detergent insoluble aggregates, impaired regulation of the ubiquitin-proteasome system and enhanced neuronal toxicity. A proportion of these aggregates co-localised with cytoplasmic TDP43 granules, consistent with the TDP43 proteinopathy observed in most ALS post-mortem tissues. When treated with either sodium arsenite or heat shock, ARPP21 is recruited into PABP and TIA-1 positive stress granules.

Discussion and conclusions: By combining the genetics and follow-up functional assays, we have identified *ARPP21* as a novel ALS candidate gene with a mutation frequency of 1.6% in familial cases and 0.3% in sporadic cases. Cellular studies of *ARPP21* mutants recapitulated the pathological hallmarks of ALS and highlighted the importance of RNA metabolism. Ongoing work includes elucidating the functions and how these are affected by *ARPP21* mutations.

BW-20 New FIG4 gene mutation causing fast progressing ALS phenotype: a case report

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Keywords: FIG4 gene mutations, ALS11, new phenotype

Background: FIG4 gene mutations cause several neurodegenerative syndromes including Charcot-Marie-Tooth disease type 4J, epilepsy and polymicrogyria, Yunis-

Varon syndrome and, rarely, sporadic and familiar cases of Amyotrophic Lateral Sclerosis (ALS) with autosomal dominant transmission (ALS11) (1).

Case report and methods: A 27 year old woman was referred for rigidity in lower limbs associated with progressive verbal fluency impairment and dysphagia lasting for over one year. She was adopted and family history was unknown. Past medical history was characterized by moderate cognitive retardation known from early infancy without motor deficits. As the patient came to our attention (May 2016), she presented severe motor aphasia and spastic paraplegia. Mild proximal muscular weakness was identified in lower limbs together with fasciculations. Diffuse severe spastic hypertonia with brisk reflexes and bilateral Babinski sign were present. At cranial nerves examination, a long-lasting multi-directional non-positional nystagmus was observed. Blood and cerebrospinal fluid analysis were normal as well as EMG and nerve conduction studies. Brain MRI showed diffuse cortical atrophy more evident in the temporal lobes and mild atrophy of the corpus callosum. Muscle biopsy showed initial signs of neurogenic atrophy.

Results: A diagnosis of juvenile ALS was made and genetic screening for SOD1, FUS, TDP43 and C9Orf72 performed, this was negative. Extended genetic analysis for ALS-related genes was carried out, which evidenced a composed heterozygous mutation in the FIG4 gene (c.122T>C and c.1667C>T). The first mutation is known for causing upper-motor neuron dominant (UMND) ALS. The other was never described before in humans but *in silico* studies demonstrate a probable pathogenic role in ALS. Later, symptoms rapidly worsened to a spastic tetraplegia associated with complete aphasia and severe dysphagia. The patient died after *ab ingestis* pneumonia 18 months after symptom onset.

Discussion: FIG4 gene mutations usually determine slow progressive UMND ALS phenotypes with onset in the adult age. Here we describe a novel composed heterozygous mutation in the FIG4 gene causing a juvenile fast progressive neurodegenerative disorder characterised by severe brain involvement. This report widens the spectrum of FIG4 mutations and describes an unexpected, early onset and quickly progressing phenotype. Even though a diagnosis of juvenile ALS was made, this case could represent a novel clinical entity related to FIG4 gene mutations. Further functional studies are warranted to confirm characteristics of the mutation and pathogenesis of this new clinical phenotype.

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BW-21 Facing the challenge of genetic testing in familial ALS

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Keywords: genetic counselling, genetic testing, FALS

Background: Recent advances in gene discovery have led to a pressing need to better understand the implications of genetic testing in amyotrophic lateral sclerosis (ALS) and/or frontotemporal dementia (FTD) families. Once a gene mutation that is causal of ALS/FTD is identified in a family, relatives may decide to undergo predictive genetic testing to determine whether they are at risk of developing disease and/or reproductive genetic testing to prevent mutations being passed on to future generations (currently the only means to prevent ALS or FTD). Anecdotal experience from our University multidisciplinary ALS clinic, confirmed by a review of the literature, has shown that uptake of predictive and reproductive genetic testing is low, with few studies

addressing the family's experience of familial ALS (FALS).

Methods: This 12-month mixed-methods study is being conducted from January to December 2017. Qualitative in-depth interviews with 30 individuals from FALS families around Australia explore their experience of FALS, and the factors that influenced their decisions about these genetic testing options, as well as their information and support needs. Analysis of interview data uses a general inductive approach with independent parallel coding. Economic modelling to assess the economic impact of different genetic testing and reproductive options for FALS families will also be undertaken.

Results: Preliminary results highlight that unique factors underlie each participants' decision-making about the testing options, influenced by life stage, time, attitudes to FALS and reproductive options. Facilitators of predictive testing include the need for information for children or family planning, wishing to participate in research, time to be psychologically prepared or alter life's priorities. Barriers include a lack of preventative options for mutation carriers, and the possible negative psychological impact of testing. These barriers could also be facilitators for participants considering reproductive genetic testing. Some participants had difficulty gathering accurate information from health professionals about the costs and implications of genetic testing, resulting in reluctance to pursue genetic counselling. Health economic analysis will provide insight into the resources and constraints for genetic testing of ALS genes in Australia, and compare costs and outcomes of each genetic testing option available for FALS.

Conclusion: The results will provide greater insight into what impacts an individual's experiences and decision-making about genetic testing options for FALS, and provide up to date testing uptake rates and costs in Australia. It is expected to improve patient and family experience by contributing towards best-practice guidelines for management and funding support of FALS families, and ensuring genetic counselling practice is consistent and meets the needs of FALS families.

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Theme CW: Clinical Work in Progress

CW-01 ALS PREFER initiative - a platform for patient engagement in drug development

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Keywords: clinical trials, patient-centered outcome measures, disease burden

Background: There is a rising call for rigorous patient input into key areas of regulatory consideration, such as clinically meaningful outcomes and benefit/risk calculations, as well as an emerging focus on patient engagement in determinations of value for health plan coverage and payment. Together, these developments offer a critical opportunity to use established methods to ensure that patient input is appropriately and adequately integrated into drug development.

To respond to this opportunity and need, The ALS Association is developing a patient and caregiver-driven initiative – ALS PREFER – a cross-sector collaboration to build a robust, pre-competitive solution for patient preference studies in ALS with funding support from industry and other stakeholders.

The initiative will be conducted in collaboration with the broader patient advocacy community, industry stakeholders, academic and clinical partners, and government representatives. It will draw on the community momentum behind the draft ALS Drug Development Guidance recently submitted to the FDA. The Guidance project engaged nearly 40 people with ALS and their caregivers, more than 10 ALS advocacy organizations, 45 of the world's leading ALS researchers and clinicians from 30 different institutions, 15 representatives from 9 biopharmaceutical companies, and 5 government representatives from the three centers at the National Institutes of Health and the Centers for Disease Control and Prevention.

Objective: ALS PREFER will be a research-driven platform supporting a series of patient preference studies over time and generating sharable data lodged in a common and broadly accessible data repository. The vision of the initiative is to bring the patient input into the center of ALS drug development to achieve a demonstrable impact on clinical trial design, regulatory review, payment and policy decisions. The bottom line is to make trials more attractive to patients, and ensure that positive trials produce results that are meaningful to the patient community.

Methods:1) Establishment of ALS PREFER Steering and Advisory Committees: a governance and technical support infrastructure that places patients and caregivers in a leadership role while assuring that the platform is designed and implemented with critical guidance from advocacy organizations, industry sponsors, clinicians, academics and regulatory authorities, as appropriate; 2) Generation of an ALS PREFER Data Repository; 3) Integration of two initial studies: i) a disease burden survey partnership between industry and The ALS Association, and ii) the development and validation of a multifaceted, sensitive, ALS specific patient reported outcome measure for use in ALS Clinical trials led by Dr. Chad Heatwole, at

the University of Rochester Medical Center; 4) Development of patient and caregiver engagement through ALS Association Chapters, The National ALS Registry, CReATe Consortium, Western ALS (WALS) and North East ALS (NEALS) clinical research networks.

CW-02 A pilot study of Safety of Caprylic Triglycerides in ALS

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Keywords: clinical trial, caprylic triglyceride

Background: Improved function in the electron transport chain may improve mitochondrial function and ultimately be a potential therapy for patients with ALS. Previous studies found that superoxide dismutase 1 (SOD1) G93A transgenic mice exhibited a significantly slower progression of ALS-type motor impairment and lower mortality rate when administered a ketogenic diet. These changes correlated with a significant increase of serum ketone body levels. Medium chain triglycerides in the form of caprylic acid fed to G93 transgenic mice showed similar effects causing an increase in serum ketones and slower progression of motor impairment.

Hypothesis: Will caprylic acid ingestion enhance mitochondrial function and cellular energy regulation? Indicated by the presence of ketone bodies in the blood and the amount of ketone bodies will be dose dependent. If confirmed, subsequent studies will determine if the amount of ketone bodies in the blood will slow or stop the progression of ALS in a dose dependent manner.

Methods: Single center, open-label, 16-week duration, dose escalating study to determine the safety and tolerability of AC-1204 in patients with ALS. All patients had four measurements, including at baseline, McGill Quality of Life Questionnaire (MQOL), ALSFRS-R, ALS Appel, safety labs, weight monitoring, calorimetry, Tanita body fat %, and daily urinalysis. Serum was analyzed for content of ketone bodies (acetoacetate, beta hydroxybutyrate, acetone).

Results: Following approval from the institutional review board, 10 patients were enrolled in the study from March to December of 2016. Patients' age ranged from 38-68, and included three women and seven men. Disease duration from time of diagnosis to time of entry ranged from two months to four years. Of those enrolled, eight completed all study visits from screening through last visit. Two patients were unable to complete the study, one dropped out to enroll in a stem cell study and another due to a family emergency.

Conclusion: Decreased activity of electron transport chain complex IV has been observed in the spinal cords and muscle of ALS patients. Ketone bodies, consisting essentially of D-β-3 hydroxybutyrate (DBH) and acetoacetate, are derived from fat catabolism in liver mitochondria and are inversely proportional to the levels of glucose in the blood. Ketogenic diets are high fat, low carbohydrate diets that increase levels of circulating ketones. Protective effects of ketogenic diets have been demonstrated in several neurological disorders notably in epilepsy and Parkinson's and Alzheimer's. We have previously reported the beneficial role of a ketogenic diet in improving motor function and survival of SOD1-G93A transgenic mice. This is the report of the first pilot study to look at AC1204 in patients with ALS, for ketone production in blood and urine and assess safety and tolerability for future efficacy studies.

CW-03 Biomarker supervised filgrastim (G-CSF) response in ALS patients

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Keywords: therapy, filgrastim, biomarkers

Background: Several efforts have been made to investigate the potential role of G-CSF treatment in ALS patients. No convincing response was observed so far, length of treatment and dosage were limited.

Objectives: Both G-CSF treatment effects in ALS patients as well as biomarkers potentially reflecting prognosis and the mode of action of G-CSF were investigated.

Methods: Thirty-seven (36 evaluable) definite ALS patients (mean age 52 years (yrs), 25 males (m)/11 females (f)) were treated with informed written consent on an outpatient and named patient basis from 2010 up to present, with a mean dose of 351 Mio IU / (mean treatment duration 16 months (mo)). Results were compared to the PRO-ACT database and analysed for biomarkers (monthly stem cell-, cytokine- and chemokine-markers, MRI-DTI fractional anisotropy every 3 mo, Siemens Aera 1.5 Tesla). An individual survival prediction model was constructed based upon the PRO-ACT database: observed survival data correlated significantly to estimated survival data in PRO-ACT (p<0.0001).

Results: Safety, feasibility and tolerance were excellent. Adjusted (for: age, sex, ALS-FRS-R at baseline, riluzole use, site of onset, time-lapse from diagnosis to therapy) multi parameter survival analysis revealed a significant benefit (p=0.018) with an HR of 0.58 in favour of G-CSF compared to PRO-ACT. A 'matched-pair' analysis (25 PRO-ACT points *vs* 1 G-CSF pat, bootstrapping, and leave-one-out procedure x 10^4) resulted in a significant difference with a median of 367 (PRO-ACT) *vs* 609 (G-CSF) days survival. Differences between observed to predicted survival times were significantly in favour of G-CSF (Wilcoxon/Kruskal Wallis Test, 2-Sample Test p< 0.0001*, 1-Way Test, Chi Square Approximation p<0.0001*). Biomarkers correlated to prognosis and also to G-CSF response, observed in individual patients. Individual response was significantly associated to AUC (area under the curve) of patients' own stem cell mobilization (p<0.0273 - normal approx. 2 sample test, p<0.0243 chi square approx.) Biomarkers analysis investigated a G-CSF response effect, as well as a highly responsive subgroup of ALS patients.

Discussion and conclusions: Long-time G-CSF therapy in ALS patients seems very encouraging. Biomarkers to supervise this immune modulatory and stem cell activating therapy need further validation, at best within a prospective clinical trial.

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CW-04 COMMEND: A randomized, double-blind, controlled, parallel group Ph2 study assessing FLX-787 for the treatment of muscle cramps in motor neuron disease

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Keywords: muscle cramps, TRPA1, TRPV1

Background: Muscle cramps can be painful, debilitating, and lead to reduced quality of life for patients with motor neuron disease (MND). FLX-787, a co-activator of TRPA1 and TRPV1, has demonstrated human efficacy reducing both electrically-induced cramps (EIC) and nocturnal leg cramps (NLC) in otherwise healthy subjects. Muscle cramps result from spontaneous activity arising from hyperexcitability of α-motor neurons in the spinal cord. FLX-787 is believed to dampen α-motor neuron hyperexcitability by Chemical Neuro Stimulation, a process whereby

TRPA1/TRPV1 activation in the oropharynx and esophagus leads to excitatory sensory input to stimulate brainstem nuclei and subsequently descending spinal tracts to inhibit motor neuron hyperexcitability.

Objectives: Based on the concept that the α-motor neuron circuit serves as the 'final common pathway' for muscle cramps, spasms and spasticity, FLX-787 is currently being studied in MND patients to understand if FLX-787 can affect these symptoms of hyperexcitability. While the primary endpoint of the COMMEND study is focused on the reduction of muscle cramp frequency, other endpoints will be measured such as spasticity severity, spasm frequency/severity and global patient improvement to assess clinical meaningfulness.

Methods: Data from a series of preliminary studies in healthy subjects served to inform the study design and powering estimates for COMMEND. Initial cramp inhibition, dose-responsivity and safety assessments of FLX-787 was generated using an EIC model and in subjects prone to NLC. Based on these data, COMMEND is a randomized, double-blind, controlled, parallel group study enrolling subjects diagnosed primarily with amyotrophic lateral sclerosis, in addition to primary lateral sclerosis and progressive muscular atrophy.

Results: Preliminary studies demonstrated that FLX-787 was well-tolerated and efficacious. In the EIC model, FLX-787 (29 mg) reduced muscle cramp intensity by 5-fold as measured by surface EMG relative to placebo ($p<0.001$). Increasing doses of FLX-787 were observed to decrease muscle cramp intensity up to a maximally efficacious dose of ~32 mg. In a two-part cross-over study in NLC, analyses restricted to the first cross-over periods in subjects with confirmed NLC demonstrated efficacy. An analysis combining active treatments relative to control treatments demonstrated a 23% decrease in the weekly mean cramp frequency ($p< 0.05$) and a 31% decrease in weekly mean cramp pain ($p<0.05$). The effect size of the resulting decrease in mean cramp frequency was 0.53 and served as the basis for initial powering estimates for COMMEND.

Conclusions: These results demonstrate that FLX-787 may be effective at reducing both muscle cramp frequency and pain. Taken together, these data highlight the potential utility of FLX-787 to treat debilitating muscle cramps and the general strategy of Chemical Neuro Stimulation to limit α-motor neuron hyperexcitability in neurological diseases (ALS, MS, and Charcot-Marie-Tooth neuropathy) where muscle cramping is prevalent.

CW-05 GM604 – An endogenous multiple-target regulator provides a disruptive and novel regulatory therapeutic strategy for treatment of ALS and other neurodegenerative diseases, as confirmed by consistent safety and efficacy data from pre-clinical, and Phase 2A placebo-controlled clinical, functional and biomarker data

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Keywords: systems biology, multi-target therapy, bioinformatics

Background: Amyotrophic lateral sclerosis (ALS) is a fatal heterogenous neurodegenerative disease that lacks effective treatment options. Genervon hypothesized that the traditional single-target approach to treat neurodegenerative disease such as ALS may not be effective due to the complexity of disease pathology and involvement of multiple pathways. As a

novel treatment strategy, Genervon Biopharmaceuticals has discovered and developed GM604 (GM6), a 6-amino acid peptide drug modeled upon an endogenous multi-target embryonic stage protein isolated from the developing nervous system (human motoneuronotrophic factor, MNTF). Using systems biology approach, we discovered that GM6 has multi-target effects replicating the MNTF activity spectrum, leading to improved survival of neurons in neurodegenerative patients.

Results: Through *in vivo* pre-clinical studies, we have shown that GM6 prevents functional decline and promotes neuronal lesion recovery in rodent models of neurodegenerative disease. These models have included the SOD1-G93A transgenic model (ALS), mice treated with 6-hydroxydopamine or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine Parkinson's disease (PD), and mice injected with myelin proteolipid protein Multiple sclerosis (MS). *In vitro* assays using rat cortical neurons additionally demonstrated that GM6 protected against toxic factors in cerebral spinal fluid (CSF) isolated from patients diagnosed with these diseases and increased cell survival significantly. Using DNA microarrays, we identified 1259 genes altered at least 2-fold in SH-5YSY cells, including 89, 48, 46 and 9 genes associated with ALS, AD, PD and MS, respectively. Functional enrichment analyses of these GM6-sensitive genes suggested cellular changes related to repression of the intrinsic apoptotic pathway and stimulation of mitotic/proliferation pathways.

To demonstrate the clinical significance of these findings, we recently reported results from a multi-site phase 2A randomized, double-blind, placebo-controlled pilot trial of GM6 for treatment of ALS: https://f1000research.com/articles/6-230/v1. Our phase 2A findings demonstrate clinical safety of GM6, favorable shifts in ALS biomarkers, and improved functional measures. In this study, GM6 decreased plasma levels of key ALS biomarkers (TDP43, P=0.008; Tau, P=0.037; SOD1, P=0.009). Compared to a historical control cohort of definite ALS patients, GM6 slowed functional decline based upon the ALS Functional Rating Scale (P=0.005), and we observed site-specific improvement in forced vital capacity (P=0.027).

Discussion and conclusion: These findings support the hypothesis that GM6 triggers developmental-stage cascades to ultimately encourage neuron survival to attenuate progression of neurodegenerative diseases. We are now conducting a new generation of studies to better delineate mechanisms by which GM6 may promote neuron survival (eg using high-throughput complementary DNA sequencing, RNA-seq). We have designed a phase 3 ALS randomized placebo-controlled trial planning to start in 2017.

CW-06 Pivotal phase 3 clinical trial of ultra-high dose methylcobalamin for ALS: the first trial using Awaji criteria (JET-ALS Study)

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Keywords: methylcobalamin, Awaji criteria

High-dose intramuscular methylcobalamin (mecobalamin) was shown to improve muscle power in an animal model (wobbler mouse) of amyotrophic lateral sclerosis (ALS) (1). We also have reported that it increases compound muscle action potentials (CMAPs) in ALS patients at early stage of the disease (2). It was reported to prevent glutamatergic neuro-excitatory cell death and to reduce serum homocysteine, which is related to ALS pathogenesis (3).

Based on these results, we have been developing intramuscular high-dose methylcobalamin (E0302; 25 or 50mg twice a week) as a company (Eisai Co. Ltd.) lead clinical trial. Recent phase II/III trial (761) has indicated that the regimen was effective in decreasing the symptomatic decline (changes in ALSFRS-R) and prolonging survival (death or the interval to respirator-

bound; more than 600 days in the 50mg group) in a dose-dependent manner, if it was started within 12 months after the onset. There has been no serious side effects.
We have therefore planned to conduct a physician-lead phase III trial using changes in ALSFRS-R as the primary outcome for early-onset (the protocol is a randomized placebo-controlled trial to screen ALSFRS-R for its drop of one or two for 12 weeks, and to follow the scale by dosing 50mg of E0302 or placebo intramuscularly in a double-blinded manner for 16 weeks. To facilitate entry of patients with early stage, we use the Awaji criteria, which we developed and were found to reach the diagnosis more than six months earlier than El Escorial Airlie House Criteria, for the first time in the pivotal clinical trial. The total number of 128 patients are estimated to show the efficacy according to the 761 trial, and we will finish this trial within three years aided by 13 neuromuscular centers all over Japan, each of which have more than 10 ALS patient referrals per year for EMG diagnosis.

There exists no drug ameliorating symptoms in ALS except for edaravone, which is unknown to prolong survival. We have already communicated with the Japanese authority (PMDA), who suggested we consult them for the detailed protocol and to continue its clinical development as a physician-lead trial for its possible filing for drug approval, depending on the results. Eisai Co. Ltd. has agreed to provide E0302 for this trial with technical help obtained through the 761 trial. If this study fulfills its promise, this is going to be the first drug in the world to slow the clinical deterioration and to possibly prolong the survival by more than 600 days in ALS. This trial will start in September 2017, and we will report its outline, and the progress of this novel clinical trial of ALS.

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CW-07 Blinded Post-trial Selection of Outcome Measures Increases Efficiency of ALS Clinical Trials

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Keywords: trial design, ALSFRS-R, electrical impedance myography

Background: ALS is a heterogeneous condition with variable patterns of progression. Nevertheless, ALS clinical trials typically use a uniform primary outcome measure for testing efficacy, most often the ALSFRS-R total score. We explore the benefit of using an outcome measure that is individualized to each participant's specific pattern of progression.

Objectives: To demonstrate the potential for improving efficiency of ALS clinical trials by using individualized outcome measures.

Methods: A procedure is described for selecting individualized outcome measures tailored to a participant's specific pattern of disease progression. As potential outcomes, we evaluate two classes of outcomes: ALSFRS-R domain and individual question scores, and electrical impedance myography at specific frequencies recording from different muscles. For each class of outcome, we identify measures that are optimized with respect to precision in estimating progression when using a random-slopes model in a putative 6-month trial with monthly assessments. Using the PRO-ACT database, we evaluate the degree to which individualized selection of ALSFRS-R outcomes are predictive of survival relative to ALSFRS-R total score.

Results: This work is still in progress.

Conclusions: Use of outcome measures that are individualized to each participant's specific pattern of progression can increase the efficiency of ALS clinical trials.

CW-08 Assessment of longitudinal changes in ALS using diffusion MRI

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Keywords: diffusion imaging, longitudinal assessment, disease spread

Introduction: The development of robust non-invasive biomarkers of disease progression in ALS will assist our understanding of the disease state and may prove essential in ultimately understanding the mechanism of spread of degeneration. While imaging studies have provided only limited benefit in small cohorts to date, the increasing sensitivity of emerging techniques, developed in the Human Connectome Project and other advanced protocols, offer hope that we can develop methods to track upper motor neuron degeneration, in small groups or individual persons living with ALS.

Methods: We assessed longitudinal changes in diffusion MRI (dMRI) metrics using voxel-wise statistical inference of the whole brain, based on state-of-the-art spatial normalization of high-quality dMRI data to reduce the potential of obtaining false positives. We applied these novel techniques to longitudinal assessment of corticospinal tract diffusion metrics, in people living with ALS and healthy participants, scanned at an initial visit as well as 6 and 12 months after their initial visit. We have previously published clinical characterization of this cohort.

Results: We demonstrate statistically significant longitudinal changes in diffusion metrics in multiple areas in people living with ALS over the course of one year's observation. The right cerebral peduncle exhibited decreased Fractional Anisotropy (FA) and increased Mean and Axial Diffusivities (MD and AD). The posterior limb and retrolenticular area of the internal capsule also demonstrated increased MD and AD. Increased AD was also noticed in the areas of the right external capsule and superior corona radiata. No longitudinal changes were seen in an age- and gender-matched healthy control cohort. We will correlate our dMRI findings with clinical, cognitive, and functional assessments.

Conclusions: Advanced dMRI techniques demonstrate evidence of longitudinal change in ALS in a small cohort. These techniques provide high imaging resolution and minimize the risk of false-positive findings.

CW-09 Longitudinal assessment of neurochemical changes in ALS by *in vivo* magnetic resonance spectroscopy at ultra-high field

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Keywords: biomarkers, MR spectroscopy

Introduction: MR spectroscopy (MRS) has the potential for serving as a biomarker of disease progression in ALS. Longitudinal data acquired with advanced MRS at ultra-high field can reveal the natural history of neurochemical changes in the brain and may aid the evaluation of therapeutic candidates in clinical trials. To our knowledge, we are presenting the first longitudinal ultra-high field MRS data on multiple brain metabolites in people with ALS.

Methods: Twenty people with ALS and 20 age- and gender-matched healthy control participants were enrolled in the study. After undergoing 7 tesla proton MRS scans at

baseline, 14 participants with ALS and 16 healthy controls returned for scans at six months. Of those who returned at six months, nine participants with ALS and nine healthy controls also returned at 12 months. Neurochemical profiles of the upper limb motor cortex and pons were obtained at each scan session. Clinical assessments included ALSFRS-R, ECAS, and King's staging.

Results: Linear mixed-effects model analyses of time trends indicated a decline in total N-acetylaspartate over *myo*-inositol ratio (tNAA/mIns) in the motor cortex of people with ALS (N=14, p=0.02). Between-visit paired sample analyses also revealed trends for lower motor cortex tNAA/mIns and tNAA over total creatine (tNAA/tCr) ratios after 12 months in the nine people who completed all follow-up scans (p=0.07, p=0.10, respectively). In addition, an ALSFRS-R upper limb subscale analysis showed that these tNAA/mIns and tNAA/tCr trends are primarily driven by participants who suffered functional decline in the upper limbs over the 12 months (N=5; p=0.04, p=0.07, respectively). Those who remained stable in their upper limb function (N=4) did not show longitudinal change in these ratios. No neurochemical changes over time were detected in the pons of people with ALS. Cross-sectional data on the ALS and control cohorts were recently published (1).

Discussion: Longitudinal evaluation of the ALS cohort by 7 T MRS suggests that the motor cortex tNAA/mIns ratio may be sensitive to disease progression. In particular, the tNAA/mIns ratio of the upper limb cortex appears to decline only in people with decreasing upper limb function over a one-year period. A larger sample size is needed for a thorough examination of the relationship between tNAA/mIns ratio and ALS progression. In addition, the association between motor cortex tNAA/mIns ratio and functional impairment in corresponding areas of the motor homunculus may be explored in future studies.

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CW-10 Precentral and postcentral cortical thickness and their relation to ALSFRS-R and neurophysiological biomarker MUNIX in ALS

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Keywords: cortical thickness, neuroimaging, MUNIX

Background and objective: In this study precentral and postcentral cortical thinning - as detected by structural MRI - were observed in context to ALSFRS-R and the neurophysiological biomarker MUNIX during progression of ALS patients.

Methods: The sample included 17 spinal onset ALS patients compared to 17 age-matched healthy controls. ALS patients were treated by standard riluzole and additional long-time G-CSF (filgrastim) on a named patient basis with written informed consent. Cross-sectional *entire* group analysis included cortical thickness of atlas-based dorsal and ventral subdivisions of the precentral and postcentral cortex, ALS-specific functional rating scale revised (ALSFRS-R) and neurophysiological assessment of MUNIX in the left and right *m. abductor digiti minimi*. Cross-sectional group analysis was followed by examination of individual variability of cortical thinning between patients and a very long time monitoring of cortical thickness, ALSFRS-R and MUNIX in four patients.

Results: Cortical thinning in ALS patients was observed to primarily affect the precentral cortex, especially the ventral segment. Precentral ventral cortical thinning was correlated to ALSFRS-R. ALSFRS-R was significantly correlated to neurophysiological MUNIX, which in addition allowed differentiation between arm and leg onset patients. Cortical thinning of the precentral and postcentral cortex was age dependent and highly variable across patients compared to age-related controls. Individual very long-term monitoring of cortical thickness, ALSFRS-R and MUNIX in four patients across a time course of more than 18 months revealed important insights into different dynamics between subjects as well as between biomarkers.

Discussion and conclusions: The combination of cortical thickness analysis with clinical and neurophysiological biomarkers in both cross-sectional group analysis, cross-sectional individual analysis and individual longitudinal monitoring emphasized the potential of neuroimaging as a biomarker for disease progression in ALS.

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CW-11 Multimodal assessment of ALS using ultra-high field MR spectroscopy and diffusion MRI

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Keywords: biomarkers, multimodal imaging, longitudinal assessment

Introduction: MR imaging has considerable potential as an investigative tool for upper motor neuron assessment in ALS because it is non-invasive, safe, reproducible, and amenable to multimodal assessment of complementary pathological processes. Recent presentations and publications of multimodal imaging have emphasized these potential benefits (1,2). Here, we present data combining MR spectroscopy (MRS) and diffusion imaging at their current state-of-the-art levels of sensitivity. Combining the complementary information from these two modalities may define an imaging phenotype of ALS.

Methods: Twenty participants with ALS and 20 age- and gender-matched healthy control volunteers were enrolled in the study. Each participant underwent two MR scans: once to acquire neurochemical profiles of the motor cortex using proton MRS at 7 tesla and once to acquire high-resolution brain diffusion imaging at 3 tesla. The MRS and diffusion MR scans were acquired within one week of each other for each participant. Data quality criteria were applied for selecting high quality MRS and diffusion datasets. During data post-processing, MRS voxel masks were registered to diffusion space. Diffusion metrics including average fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were extracted from the white matter volume within each MRS voxel. Pearson's tests of correlation were performed between diffusion metrics and MRS neurochemical concentrations.

Results: High quality MRS and diffusion MR datasets were processed and analyzed for 18 participants with ALS and 17 healthy controls. The cross-sectional MRS data were recently published and revealed the following motor cortex neurochemical alterations in ALS compared to healthy controls: higher *myo*-inositol (mIns) and lower total N-acetylaspartate over *myo*-inositol ratio (tNAA/mIns) (3). No group differences were observed in the diffusion metrics extracted from the MRS voxel white matter. However, a significant positive correlation was observed between tNAA levels and mean FA in corresponding voxels in participants with ALS (r=0.56, p=0.02). tNAA also inversely correlated with mean MD, AD, and RD (all r=-0.57, p=0.01).

Discussion: Lower tNAA is correlated with lower anisotropic diffusion and higher diffusivity in all directions, suggesting that

loss of neuronal integrity may parallel white matter microstructural changes in ALS. Thus, advanced MRS and diffusion MRI may provide complementary information on neurodegenerative processes in ALS. We are currently assessing whether the two modalities combined confer greater sensitivity for discriminating people with ALS from healthy individuals than for either modality alone.

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CW-12 Chronic laryngeal nerve stimulation for swallow preservation in ALS: a preclinical feasibility study

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Keywords: dysphagia, electrical stimulation, mouse model

Background: The majority of ALS patients develop swallowing impairment (dysphagia), which is highly correlated with malnutrition and fatal aspiration pneumonia. Current treatments for dysphagia in ALS are largely palliative and limited in targeting the underlying neuro-pathophysiology. To address this clinical need, we have been developing a promising novel therapeutic for dysphagia in ALS. Our preliminary work demonstrated that *acute* stimulation of the superior laryngeal nerve (SLN) immediately improved swallowing function in end-stage *SOD1-G93A* transgenic mice. Here, we extend this preclinical work by exploring the feasibility of *chronic ambulatory* SLN stimulation for long-term preservation of swallowing function in ALS.

Objectives: The goals of this preclinical investigation are to 1) develop a surgical protocol for chronic SLN stimulation; 2) identify the optimal treatment parameters; and 3) demonstrate the safety and efficacy of chronic SLN stimulation relative to swallowing function and survival. We hypothesize this novel therapeutic will result in preserved swallowing function and longer survival.

Methods: We studied low copy number (LCN) expressing *SOD1-G93A* transgenic mice because their variable phenotype more closely resembles the neurodegenerative properties of human ALS. To characterize dysphagia over the lifespan, 40 mice (20 transgenic and 20 nontransgenic; either sex) underwent a freely-behaving videofluoroscopic swallow study (VFSS) assay developed in our lab. Next, 20 additional mice (both genotypes and sexes) were utilized to develop our surgical protocol. Another 20 transgenic mice were utilized for optimization of chronic SLN stimulation parameters. A safety and efficacy study is currently underway with a final 20 transgenic mice.

Results: Using our VFSS assay, dysphagia was identified in LCN-*SOD1-G93A* mice between five and six months of age, which helped develop our surgical and treatment protocols. Briefly, at five months, mice underwent stereotaxic surgery for chronic mounting of a headstage to the cranium. Then at five and a half months, mice underwent an anterior neck microsurgical approach to implant a nano-cuff on the SLN (to stimulate swallowing) and a micro-patch EMG electrode on the anterior digastric muscle (to detect swallowing). Electrode leads were tunneled subcutaneously and connected to the skull-mounted headstage. At six months, mice underwent a four-week (5X/week, 1 hour/day) treatment protocol in which the headstage was connected to an external electrical stimulator and bioamplifier for simultaneous SLN stimulation (40 Hz, 0.5 ms biphasic pulses, 0.2-0.7 mA) and EMG recording. This treatment protocol resulted in a

markedly delayed dysphagia onset and significantly extended survival in one of our three treated mice to date.

Conclusions: Based on our preliminary results, the therapeutic potential of chronic ambulatory SLN stimulation for ALS-induced dysphagia is indeed promising. If similar beneficial outcomes (ie preserved swallowing function and extended survival) continue to emerge from our ongoing study, this pioneering work will provide the scientific premise for using an implantable SLN stimulator for long-term treatment of dysphagia in ALS patients.

CW-13 A novel dynamic neck brace for ALS patients: Characterizing EMGs during synchronized neck motion

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Keywords: neck brace, head drop, EMG

Background: The neck extensor muscles of ALS patients progressively become weaker and they suffer from head drop. All available neck braces are static. These immobilize the head and limit human activity. Static braces further deteriorate the neck muscles due to disuse. Our group at Columbia Robotics and Rehabilitation (ROAR) Laboratory has developed a dynamic neck brace that can be used for measurement, assistance, or training of the head/neck motion in three dimensions. The motion measurements of the neck brace have been validated against a Vicon motion capture system in previous human studies (1).

Objectives: The goal of this study is to characterize the surface EMGs of primary neck muscles during dynamic movements of the neck for subjects with ALS and compare these with those of age and sex-matched healthy subjects. While the dynamic neck brace allows general 3-dimensional motion, we will also study uniaxial motions of the head, such as flexion and extension, lateral bending, axial rotation. Our hypothesis is that there will be significant differences in the muscle activity patterns of the two groups in terms of (i) percentage of maximum contraction of the individual muscles during the neck motion; and (ii) temporal patterns of the EMG activity during repeated cycles of motion.

Methods: Our ongoing study consists of 20 ALS patients and 20 age and sex matched healthy controls. The kinematics of the head were determined by sensors mounted on the neck brace. Muscle EMGs were measured from six neck muscles, left and right Sternocleidomastoid (SCM), left and right Splenius Capitis, and left/right Trapezius. The head movements consisted of flexion/extension, lateral bending, axial rotation, and spatial rolling. Each motion was repeated five times. Each muscle EMG data was normalized with respect to the peak EMG value recorded during the session. The data from each motion was segmented into a cycle from 0 to 100%.

Results: At this time, 10 healthy subjects and six ALS patients have completed the experiment. Preliminary analysis of the results shows that patients with ALS use a higher percentage of their maximum muscle activity to perform the neck motions compared to healthy subjects. The temporal characteristics of the muscle patterns are also different between the two groups and are being further analyzed.

Discussion and conclusions: The dynamic neck brace can be used to characterize synchronized motion of the head/neck and muscle activity of patients with ALS. The amplitude and temporal characteristics of the different muscles during neck movements provide new insights into the nature of the disease and how it progresses over time.

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CW-14 Impairment of cortico-muscular communication in motor neuron disease

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Keywords: cortico-muscular coherence, motor networks, biomarker

Background: While the traditional understanding of amyotrophic lateral sclerosis (ALS) is based on the focal involvement of the Upper and Lower Motor Neurons, there is ever increasing electrophysiological evidence of a broader network involvement. It is therefore of interest to characterize these motor and non-motor networks for a better understanding of the underlying disease mechanism. Separate recordings of electroencephalogram (EEG) (1) and electromyogram (EMG) (2) time-series analysis, has proven to be useful in quantifying the level of functional/effective communication between brain regions at rest and quantifying synchronous synergistic motor drives to muscles during functional motor tasks. However, the central-peripheral communication in the motor system remains one of the lesser studied areas in ALS.

We hypothesize that Cortico-muscular coherence (CMC) between EEG-EMG can inform on these specific alterations in cortico-muscular communications. To test this hypothesis, we study CMC during functional motor tasks, as a potential tool for assessing the network disruption in selected motor subsystems in ALS.

Objectives: To characterize the potential disruption of neural communication in motor networks due to neurodegeneration in ALS, using Cortico-muscular coherence during functional isometric motor tasks.

Method: High-density 128-channel EEG and 8 bipolar surface electromyographic (sEMG) recordings from both extrinsic and intrinsic hand muscles, including APB, ADM and FDI muscles were performed in ALS and PLS patients and healthy controls in an experimental paradigm of isometric precision grip tasks.

Results: Preliminary analysis of data shows that CMC can be present in both healthy controls and in PLS; frequency bands, locations and intensity of coherence have the potential to demonstrate difference between the groups.

Discussion: This ongoing study of cortico-muscular communication is expected to further reveal the altered sensorimotor function in motor subsystems affected in ALS. By combining EMG/EEG we aim to closely reflect affected physiological systems in ALS patients. These electrophysiological signatures will help us to better understand the underlying disease mechanisms, provide new patient stratification perspectives, and facilitate the development of diagnostic and prognostic biomarkers.

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CW-15 Investigation of dysfunction in cognitive brain networks in ALS by localisation of the sources of mismatch negativity

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Keywords: electroencephalography, mismatch negativity, cognitive networks

Background: Structural imaging (1) and neurophysiological (2) studies have provided extensive evidence that ALS is a neural network disorder extending beyond the motor system. Such non-motor pathology is evident from the impaired cognitive function identified in approximately 50% of non-FTD ALS patients (3). Prefrontal networks are widely implicated in the generation of cognitive functions (4), therefore changes in their function should be explored during cognitive tasks in ALS to identify which prefrontal networks contribute to cognitive symptoms. Mismatch negativity (MMN) is a well-described electroencephalographic (EEG) response generated by prefrontal network activity during involuntary attention shift (5). It can therefore be used to quantify cognitive network function. We have previously identified significant increases in MMN average delay in ALS, indicative of functional change in networks required for involuntary attention shift; however, the limited association of sensor space EEG to brain regions provides little information about the location of contributing networks. Source analysis of MMN is required to localise such networks with high temporal resolution.

Objectives: To localise and quantify the neural activity of the cognitive networks functionally affected in ALS, using an MMN paradigm as a specific measure of cognitive dysfunction.

Methods: 128-electrode spectral EEG was recorded from 150 ALS patients and 19 healthy controls during an auditory oddball paradigm. 3-tesla MRI was obtained for 89 of these ALS patients. Linearly Constrained Minimum-Variance (LCMV) beamforming was used (FieldTrip Toolbox) to localise network activity changes during the MMN response, 170 to 250ms post-stimulus.

Results: Preliminary results from the mean activity of 19 patients (mean age 56, range: 29-79, 5 bulbar, 14 spinal, with individual MRI scans) and controls (mean age 61, range: 30-75) identified MMN sources in both temporal lobes and prefrontal areas in both groups, consistent with previous source localisation studies (5). Activity during MMN differed in ALS patients in the right dorsolateral, ventrolateral and anterior prefrontal cortex compared to controls (top 20 percentile of the maximum differences).

Discussion and conclusions: The identified functional changes in the right dorsolateral, ventrolateral and anterior prefrontal cortex in ALS groups implicate these regions in our previous findings of delayed MMN response. Analysis of the remaining dataset will allow for a highly-powered statistical comparison of cognitive network activity during involuntary attention switching. This is expected to improve the understanding of specific brain networks functionally affected by ALS, and contribute to a new dimension in patient characterisation.

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CW-16 Detection of hand movement from EEG in ALS-patients and healthy individuals

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Keywords: EEG, brain-computer interface, movement related cortical potentials

Background: Brain-computer interfaces (BCIs) use brain signals to control external devices without the conventional means of nerve and muscle communication. Movement-related cortical potential (MRCP) extracted from electroencephalography (EEG) signals can be used for BCI control. The MRCP is a slow negative drift that commences two seconds prior to movement onset and contains features that differ between different types of movement, making it an ideal signal modality for multi-dimensional BCI control (1).

Objective: In this ongoing study we investigate whether the MRCP can be applied in BCI systems to assist ALS patients.

Case study: This work is a case study which presents the results of a pilot experiment.

Methods: Three male ALS patients (age 49, 61 and 68 years) and five healthy subjects (age range 22-43 years) participated in the study. Nine EEG channels were recorded using an active electrode system and g.USBamp amplifier (gTec, GmbH, Austria) from F3, FC1, FC5, Cz, C3, C7, CP1, CP5 and P3. Both healthy participants and ALS-patients were asked to execute hand opening or closing based on a visual cue that consisted of five phases: focus, preparation, execution, hold and rest. Following a random duration of focus time, the preparation phase started by showing a text to the participants indicating the type of hand movement. At the same time, a ramp appeared on the screen with a moving cursor. Participants were asked to execute the hand movement when the cursor reached the upward turn of the ramp and hold it for two seconds followed by a rest period. Two blocks consisting of 30 trials of random movements were separated by a two-minute break time. EEG data were band-pass filtered from 0.05 to 10 Hz by a 2nd order Butterworth filter and then MRCP trials were obtained in the time interval [-3±3] s with respect to the movement onset. The amplitude and time of peak negativity, the MRCP slopes obtained by linear regression, the MRCP variability and the mean amplitude of the MRCP were extracted and used for classification of movement type.

Results: The output of the Support Vector Machine (SVM) classifier revealed that the classification accuracy between hand movements was 76±10.5% for healthy participants and 68.3±2.9% for ALS-patients. There was no significant difference between healthy participants and ALS patients (Mann-Whitney U Test, $p>0.05$).

Conclusion: The results confirm that it is possible to differentiate hand movements in ALS patients, thus paving the way for the design of BCI systems to control robotic assistive devices for upper limb in these patients.

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CW-17 Cortical unresponsiveness in bulbar onset motor neuron disease

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Keywords: cortical excitability, transcranial magnetic stimulation, electromyography

Background:
Cortical dysfunction appears to be an intrinsic process across the MND phenotypes. A high incidence of abnormal MEPs in MND has been shown previously using electrical stimulation of the cortex.

Aim: Investigate cortical excitability in patients with bulbar onset MND (B-MND) using TMS.

Methods: Four patients diagnosed with bulbar onset MND (B-MND) in accordance with revisited El-Escorial criteria and followed at the hospital for special surgery ALS clinics were retrospectively reviewed. Patients with focal brain lesions (as strokes, neoplasms) were excluded. All patients have normal strength throughout proximal and distal muscles of arms and legs without evidence of atrophy. Cortical stimulation using transcranial magnetic stimulation (TMS) was performed recording from *abductor pollicis brevis* and *abductor digiti minimi* muscles. Motor evoked potentials were recorded.

Results: TMS studies showed absent motor evoked potential, which indicates significant reduction of cortical motor activation in B-MND patients.

Discussion: Studies have shown before that swallowing related cortical activation, in healthy subjects, is spread extensively in primary and secondary motor and sensory areas in both hemispheres, which is mainly observed. Interestingly, cortical swallowing activity, though lower in levels of activation in MND patients, is focused on the central area of the primary motor cortex, without involving more mesial areas or the secondary sensorimotor cortex. The present data demonstrates a reduction in the cortical activation in B-MND patients, using transcranial magnetic stimulation (TMS). This reflects a disturbance of the swallowing network which can be mainly explained by the degeneration of the upper motor neuron.

CW-18 Maladaptation of intracortical processes underlies development of exercise-induced fatigue in ALS

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Keywords: fatigue, exercise

Background: Fatigue is a common and debilitating symptom of ALS. Despite this, the underlying mechanisms are seldom investigated. Previous studies using threshold-tracking transcranial magnetic stimulation (TTTMS) have established 'cortical hyper-excitability' (a reduction in short-interval intracortical inhibition, SICI) as a hallmark feature of ALS (1). In healthy volunteers, maximal sustained voluntary contractions are known to down-regulate SICI (2), however, it is unclear whether SICI is similarly affected by submaximal and intermittent contractions.

Objectives: To investigate modulation of SICI in healthy volunteers and ALS patients during and after development of fatigue following 4 different exercise protocols: 1) two-minute maximal sustained contractions; 2) two-minute submaximal sustained contractions; 3) two-minute maximal intermittent contractions; and 4) two-minute submaximal intermittent contractions.

Methods: Cortical excitability studies were undertaken in 17 healthy volunteers and 4 ALS patients using established TTTMS techniques via a 90-mm circular coil. TMS studies were conducted at baseline, immediately after three sets of fatiguing exercises involving the right thenar muscle, and at 10, 30 and 45 minutes after the last voluntary contraction. Each participant

performed four different exercise sessions on four different occasions separated by at least five days. SICI at interstimulus intervals of 1, 2, 2.5, 3, 3.5, 7 and 10ms were recorded. SICI between 1 and 7ms were averaged and compared across different time points and between exercise protocols.

Results: SICI declined progressively following both maximal and submaximal sustained isometric contractions and remained depressed up to 45 minutes (-38% and -42% respectively; $p<0.013$). In contrast, there were no significant differences in SICI following intermittent contractions at either maximal or submaximal intensities. In ALS patients, SICI increased following both maximal and submaximal sustained isometric contractions for up to 10 minutes before returning to baseline. In contrast, SICI was reduced immediately after intermittent maximal contractions and remained depressed for 10 minutes.

Discussion and conclusions: Given that SICI is mediated by inhibitory GABAergic intracortical circuits acting via $GABA_A$ receptors (3), a reduction in SICI inferred that sustained isometric contractions but not intermittent contractions specifically down-regulate the efficacy of inhibitory cortical interneurons to maintain motor output during the development of fatigue. In ALS patient, SICI was increased transiently following sustained isometric exercises, which suggest a maladaptation of cortical processes most likely related to progressive degeneration of GABAergic inhibitory interneurons.

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CW-19 Symptom monitoring application in real time for ALS (SMART-ALS): A pilot study using the Beiwe smartphone application

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Keywords: mobile health, outcome measures, digital phenotyping

Background: Digital phenotyping describes the use of technology to monitor patients' functioning, often remotely. It provides a new paradigm for gathering outcome data for ALS clinical research. Data collection might use active data gathering (asking participants to perform a task at intervals) or passive data monitoring (sensor-based data collected without participant effort). These methods could be used to assess subjective functional data (ALSFRS-R) frequently and/or provide frequent or continuous objective data about patient functioning to supplement traditional outcome measures. The Onnela Lab at the Harvard T.H. Chan School of Public Health has developed a smartphone research platform (Beiwe) which captures data from numerous smartphone sensors while running in the background and can administer scheduled surveys and voice recordings.

Objective: We are carrying out a pilot study using Beiwe, installed on smartphones, to gather passive and active data from a cohort of people with ALS to assess potential endpoints that might reflect function and supplement traditional clinical endpoints.

Methods: At an in-person visit, participants enroll for the study and provide

demographics, disease history, vital capacity, ALSFRS-R, and ALS-CBS. Throughout the study, in-person outcomes are collected at 3 and 6 months (ALSFRS-R, vital capacity, ALS-CBS) and ALSFRS-R is collected at 6 weeks, and participants are asked if they would like to stop or continue participation at 3 months. The Beiwe app (Android or iOS) runs in the background, collecting data. Passive smartphone data includes: accelerometer, GPS, Bluetooth, Wi-Fi, screen on/off events, and communication logs (metadata). Active smartphone data includes ALSFRS-R, voice recordings, cough recordings, and a dexterity measure using an on-screen slider.

Conclusions: We are implementing the Beiwe smartphone app to collect passive and active data in a small cohort of people with ALS and supplement this data by monitoring traditional ALS outcomes. We will present data from this cohort to address feasibility and possible analyses to make use of these data.

CW-20 Prize4Life: Infrastructure and resources for ALS Research

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Keywords: resources, digital health, clinical database

Prize4Life (P4L) is a non-profit organization dedicated to accelerating the development of effective treatments and a cure for ALS. P4L was founded and managed by ALS patients who assumed responsibility for fighting the disease and affecting the destiny of future patients. P4L works by offering significant prizes for measurable achievements that solve critical problems for ALS research and by creating infrastructure to support ALS researchers, advance research and encourage collaboration.

The Pooled Resource Open-Access Clinical Trial database (PRO-ACT): The largest-ever ALS clinical database (www.alsdatabase.org), containing data of over 10,000 ALS patients collected during 23 ALS clinical trials. Data was de-identified, standardized and harmonized to create a unified, easy-to-use database. The database includes longitudinally sampled data, providing rich and detailed information of the progression, antecedents and consequences of ALS. PRO-ACT is an open-access database freely available to researchers worldwide. The database was created and managed by Prize4Life in collaboration with the Neurological Clinical Research Institute at Massachusetts General Hospital.

The ALS Research Forum (www.alsresearchforum.org): Online resource for the ALS research community, providing researchers with relevant information to support and advance their research efforts, as well as reliable up-to-date ALS news coverage. This unique web portal is freely available to researchers and is specifically and exclusively targeted to ALS. Some of the features available on the Forum include: research and drug development news briefs and analyses, updated listings of professional resources, including funding opportunities, jobs and scientific meetings and an exclusive database of current industry drug development efforts. The Forum was established by Prize4Life and is funded and managed by Prize4Life and The ALS Association.

The ALS Mobile Analyzer (www.alsanalyzer.com): A novel accessible and accurate tool for tracking ALS disease progression. P4L is developing a smartphone-based application that monitors patients in their natural environment to collect objective, ongoing, comprehensive daily-life data. The app collects data through a phone's built-in sensors and evaluates patients' functional abilities (such as speech, breathing, walking and writing) by tracking their performance of a few specifically-designed simple tasks. The app is an easy-to-use monitoring tool, freely available to all ALS patients worldwide. It

will enable large scale functional data collection that will be made available to researchers worldwide via a central repository. The app will advance ALS research, facilitate individually-tailored and responsive clinical care for ALS patients and will enable faster, smaller and more efficient ALS clinical trials.

Prize4Life awards large prizes to attract the attention of top research talents to the most critical problems in ALS research and drug development; and to help bridge the gap between academic research and the pharmaceutical industry. By leveraging the resources devoted to ALS and by rewarding results, Prize4Life speeds up the identification of novel treatments and cures that ALS patients desperately need.

CW-21 Augmentative communication: Proactive preparation of low tech tools and message banking in collaboration with people with MND

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Keywords: augmentative communication, message banking, proactive

Loss of speech and motor function for physical access to technology and low tech tools is expected for a vast majority of people with MND yet there is little clinical focus on introducing augmentative communication tools and strategies early. Most often it is presumed that the information will be 'too overwhelming' for a person diagnosed with MND. Our clinical practice reveals that many people with MND are anxious to collaborate early in the disease process to understand communication options, learn strategies and direct system creation and design.

This presentation will quickly detail multiple early strategies and tools, people with MND should be introduced to at a time when they may easily direct the process. Further, simple low tech tools that have been born from patient and family collaboration but have also been powerful tools throughout the course of the MND disease, including in the last days of life, will be discussed. Web based templates will also be provided. Finally, the latest outcomes with our message banking model and the ability to integrate it with voice banking projects to minimize patient effort, will be discussed.

CW-22 Merging clinical work and research to improve care of patients with ALS/MND and calculate cost of care

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Keywords: clinical research, multidisciplinary ALS/MND clinics, cost of care

Background objectives: There is a significant difference in the standards of practice among individual ALS/MND centers, which leads to differing levels of care. Some centers (1) report that the cost of necessary care does not bring in revenue that allows for a sustainable business model. Clinical work and clinical research are often treated as separate entities, preventing the innovations of one from contributing to the other. By merging these entities, and applying validated scales to real-time clinical care, and designing a model to improve individual care, we can potentially slow down disease progression, assist in the discovery of a cure, and gather necessary data to propose changes to the overall framework of insurance payments for care.

Methods: We collected key ALS clinical information, disease milestones, vital signs, and validated clinical research scales; to calculate outcome measures and visually

display them in real-time, to guide patient care plans for present and anticipated needs. Additionally, we obtained data on patient revenue collections for every visit. We obtained aggregated data to evaluate disease severity, monthly progression, and the cost of care for the entire group.

Results: The data collected represents our first 14 ALS/MND patients. The cohort contained eight men and six women, with an average age of 69, seen an average of every three months. Nine were diagnosed with Definitive ALS, three with Probable ALS, and one Probable ALS with additional Electrophysiological support. The average age of onset was 65, with a disease duration of 45 months and an average delay to diagnosis of 21 months. Ten patients displayed symptoms of limb onset, while four displayed bulbar onset. The average score received on the ALS FRS-R scale at first visit was 29, with an average decline of two points per month. Eleven patients used augmented mobility, three used a PEG, four used augmented communication (ACC), and eight used non-invasive ventilation. For the individuals that required the use of support devices, the average delay between diagnosis and the necessary use of augmented mobility was 27 months, 61 months for a PEG, 24 months for an ACC, and 40 months for an NIV. The average baseline BMI, SVC, O_2 levels and MIP remained stable for the duration of the study.

The reimbursement paid to the hospital for these services was $7,127. The cost in salaries for six ALS clinics was $20,802.

Conclusion: Clinical work and clinical research can be merged to establish benchmark information on standards of care in patients with ALS/MND and create a robust database for clinical research. This study provides evidence that there is a significant loss of profit in this field, and that changes to the reimbursement model for ALS are necessary for sustainability.

CW-23 Retrospective study of nursing staff's use of electronic records for ALS patients at a teaching hospital in Japan

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Keywords: electronic health records, ALSFRS

Background: Electronic health records have been recommended and promoted by policy since 2001. The prevalence of their usage became 77.5% among large hospitals (more than 400 beds) in Japan. The record enabled the sharing of important patient information with multidisciplinary health care professionals in each hospital. ALSFRS-R (revised ALS Functional Rating Scale) has been seen as a good evaluation tool for the condition of patients with ALS. However, we could not find any report on amount and smoothness to get the information on the electric records.

Aim: We evaluated how many nursing staff can record each ALS patient's condition via the electric record retrospectively, and evaluated the problems.

Methods: We retrieved electronic records of patients with ALS, who were admitted to the hospital during April 2011 to March 2017. We focused on records by nurses and checked the following points: how much, how easily and where on the record, staff can take 12 items of ALSFRS-R, anxiety and pain. We set easiness to get information via three grades.

Results: The total number of patients with ALS was 72 (totaling 109 admissions) and 39 of them were registered to the Japanese

Consortium for Amyotrophic Lateral Sclerosis research (JaCALS). There were some cases that had some difficulty to identify each item of ALSFRS-R only on the electronic records, but all cases registered to JaCALS were identified ALSFRS-R. Only clinicians recorded ALSFRS-R and it was difficult to evaluate ALSFRS-R from only the electronic records. The description by the nurses was dispersed in two types; one where it was easily confirmed and the other was in a difficult place to find in the electronic record.

Discussion: This study revealed some issues for sharing the information of patients with ALS by using the electronic medical records by nurses. Low mortality and a high rate of transfer to another hospital, may be related to the character of a teaching hospital.

CW-24 Does activation of brown adipose tissue participate to hypermetabolism in ALS patients?

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Keywords: weight loss, hypermetabolism, brown adipose tissue

Background: Weight loss is an independent negative prognostic factor for survival in ALS (1) and elevation of resting energy expenditure (REE) of unknown origin has been reported in about 50% of ALS patients (2). Increase of REE seems paradoxical because skeletal muscle mass, which accounts for a large proportion of energy consumption and heat production, is decreased in ALS patients. Brown adipose tissue (BAT) is another important organ for basal and inducible energy expenditure and thermogenesis. In humans, BAT is primarily found in infants and young children. However, a recent study using 18F-FDG positron-emission tomographic (PET) scans showed that depots of functional BAT were present in about 5% of adult humans (3). It has been estimated that, if present, 50g of maximally stimulated brown tissue could represent up to 20% of REE expenditure in an adult human (4). In an autopsy series (5), depots of BAT were found in 19/20 ALS patients. In this study we aim to investigate if the presence of functional depots of brown adipose tissue could participate in the increase of REE and subsequent weight loss observed in ALS patients.

Objectives: The primary objective of this pilot study is to identify and quantify potential depots of functional BAT in ALS patients. Secondary objectives will be to correlate the amount of detectable BAT with measured REE, clinical and biological parameters.

Methods: This study is currently underway and will include five ALS patients with 'unexplained' (ie not explained by severe dysphagia) loss of 10% or more of normal body weight in the last 6 months. Five ALS patients without weight loss will be included as controls. Measurement of REE will be performed by indirect calorimetry. The volume and activity of BAT will be determined using 18F-FDG PET whole body scans. Activated BAT will be identified as areas of tissue > 4 mm in diameter with the CT density of adipose tissue, associated with a high 18F-FDG uptake (3).

Expected results: This study will be the first to investigate the role of functional BAT in ALS patients' metabolic dysfunction.

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CW-25 Dysphagia and dysarthria in Facial Onset Sensory Motor Neuronopathy (FOSMN): a case report

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Keywords: FOSMN, dysphagia, PEG

Background: Patients with facial onset sensorimotor neuronopathy (FOSMN) present slow onset of facial sensory abnormalities and subsequent development of motor deficits that lead to dysarthria and dysphagia (1). Management of dysphagia often requires percutaneous endoscopic gastrostomy (PEG) placement to avoid malnutrition. However, due to sensory abnormalities, dysphagia may not be symptomatic and silent aspiration of bolus could be highly prevalent in this population.

Objective: To observe the impact of PEG placement on dysarthria and dysphagia progression in a malnourished patient with FOSMN.

Methods: A 53 year-old man underwent speech and swallowing assessment before and one year after PEG placement. Body Mass Index (BMI) was collected. Fiberoptic endoscopic evaluation of swallowing with semisolids and liquids was performed. Dysphagia severity was rated through Penetration Aspiration Scale (PAS) and Dysphagia Outcome and Severity Scale. Presence and severity of dysarthria were investigated using the Italian version of Roberson Dysarthria Profile (2). Self-assessment of dysphagia and dysarthria related to quality of life (Swal-QOL and QOL-DyS) were completed.

Results: One year after PEG placement patient's BMI increased from 19.7 to 20.7. Swallow safety for semisolid and sequential liquid swallow remained the same while it improved for liquid single bolus (PAS 8 to 1). Robertson Profile showed mild dysarthria in both examinations. Subtest of muscular strength and diadochokinesis rate increased in the last examination. QOL-DyS worsened in speech characteristic and perceived reaction of others. Swal-QOL worsened in social activity but improved in symptoms.

Conclusion: Detection of dysphagia and malnutrition, early PEG placement and the maintenance of hedonic oral feeding had positive effects on nutritional status, dysphagia and dysarthria symptoms and related QOL at one year follow-up. Therefore, an early assessment, management and continuous review of swallowing, nutritional intake and weight seems to be useful in FOSMN patients.

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CW-26 Achieving independent lives for people with ALS connected to artificial respirators through the process of accepting care from non-family members

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Keywords: disability studies, decision-making, independent living

Background and Objective: The purpose of this study is to clarify through what sort of training non-family members learn how to

care for people with ALS connected to artificial respirators, as well as how people with ALS react to care by non-family members. Another purpose is to investigate the means by which people with ALS who are connected to artificial respirators, and do not rely upon care by family members, lead independent lives. The subjects of this research were studied by participant observation in settings where people with ALS live and by speaking with people with ALS.

Much research relating to the care of people with ALS has focused on the burden care imposes upon family, and the majority of the research is oriented towards mitigating or eliminating the burden of care for family members by elucidating what the burden is and arranging support systems. Therefore, there is a presumption that family members alone carry the burden of care for people with ALS, and there has been insufficient research from the perspective of an ALS patient into such topics as: what possible schemes there are for entrusting care to non-family members, and what effects these schemes have upon the patient's lifestyle and decision-making.

Results: Therefore, this research has focused on, analyzed and considered the process by which an ALS patient accepts care while directing the care of a non-family caregiver. The findings of the research found that a certain amount of time is required for a caregiver to learn how to provide medical treatment, such as managing an artificial respirator or suctioning phlegm. Furthermore, the findings indicate that if it is difficult for the patient to convey needs in accordance with a body that is undergoing minute changes day-by-day, then the caregiver will be unable to streamline care (ie it will be challenging for the ALS patient alone to direct the caregiver). Meanwhile, in Japan it is possible to team up with other people to train because the nursing care system that allows for long-term care and the system of medical care directed by physicians are covered by public funds.

Interviews with people with ALS showed that knowing about the patient's daily routine and making an effort at smooth communication are requirements for entrusting one's care to a caregiver. The process of an ALS patient accepting care from a non-family member is also an experiment to release family members from shouldering the primary burden of care and to create independent lifestyles for patients. In order for people with ALS connected to artificial respirators to establish and continuously lead independent lives, norms must be changed by demonstrating the existence of such lifestyles to the public and letting their examples speak for themselves.

CW-27 The importance of mealtime assessment in ALS patients

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Keywords: swallowing, assessment, mealtime

Background: The importance of instrumental evaluation of swallowing in ALS patients is highly recognized in order to assess swallowing safety and prevent pulmonary complications. However, swallowing performance during instrumental assessment may not be representative of what happens when consuming meals in everyday life. Indeed, as fatigue is a common feature in ALS patients, swallowing efficacy may progressively decline during mealtime consumption and food and liquid oral intake may not be sufficient.

Objectives: To investigate the relationship between the performance during mealtime

consumption and the efficacy of the oral and pharyngeal phase of swallowing in ALS patients.

Methods: Thirteen ALS patients, seven males and six females with a median age of 68.5 years (range 51-78) were enrolled in the study. Fiberoptic endoscopic evaluation of swallowing (FEES) was conducted testing liquids, semisolids and, where possible, solids. The Penetration-Aspiration Scale (PAS) and the Dysphagia Outcome and Severity Scale (DOSS) were used to assess the FEES. The Test of Mastication and Swallowing Solids (TOMASS) was performed. Tongue strength and resistance were assessed through the Iowa Oral Performance Instrument (IOPI). Patients completed the Eating Assessment Tool-10, a self-reported questionnaire. Typical oral intake was recorded using the Functional Oral Intake Scale (FOIS). Meal consumption was observed and scored through the Mealtime Assessment Scale (MAS); the time the patients needed to consume a meal was recorded. Correlations between MAS total score or time and PAS, DOSS, EAT-10, FOIS, TOMASS and IOPI measures were studied using Spearman's correlation coefficient.

Results: A statistically significant correlation was found between MAS total scores and FOIS (r=0.755, p=0.007), EAT-10 (r=-0.724, p=0.012), tongue strength (r=0.718, p=0.019) and TOMASS total time (r=-0.709, p=0.046). Time needed to consume a meal significantly correlated with tongue resistance (r=0.675, p=0.032) and number of discrete bites during TOMASS (r=-0.793, p=0.033). No statistically significant correlations were found between MAS and PAS or DOSS.

Discussion and conclusion: These preliminary results suggest that instrumental assessment of swallowing, especially FEES, may not be exhaustive in ALS patients as it does not predict patients' performance during meals. Efficacy of swallowing oral phase seems to be related to meal consumption more than pharyngeal phase. Therefore, our data stress the need of a comprehensive swallowing evaluation in ALS patients, including instrumental, oral phase and mealtime assessment, in order to estimate the risk of both pulmonary and nutritional complications related to dysphagia.

CW-28 Successful percutaneous gastrostomy tube placement with fluoroscopy in ALS patient requiring 24/7 ventilation

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Keywords: g-tube, ventilation-dependent, aerophagia

Background: Evidence suggests weight loss and decreased nutritional status portend a worse survival prognosis for patients ALS (1). One avenue to combat weight loss in the setting of dysphagia is by nutrition via gastrostomy (g-) tube. G-tube insertion techniques entail factors that can compromise weak respiratory function, including supine position and light sedation. Thus, diaphragm strength, represented by upright *vs* supine forced vital capacity (FVC), is considered a limiting factor for the period in which a g-tube can be inserted in an ALS patient, to prevent procedure-associated respiratory failure. Existing reports indicate g-tubes are most often inserted in ALS patients with FVC 30% (2, 3, 5), and guidelines maintain FVC >50% decreases risk of insertion-associated adverse events (2).

Aerophagia is a common result of positive pressure ventilation (6), such as non-invasive ventilation (NIV) that patients with lung disease secondary to ALS often use. Aerophagia can lead to gastric distension (6-8) which contributes to patients' cardiopulmonary function, and can be limiting to quality of life and NIV compliance.

Case study: In this case, an 82-year-old male with ALS on 24/7 ventilation, FVC

unmeasurable, with dysphagia to saliva, and aerophagia leading to severe bowel distension and recent bowel obstruction, received bowel decompression and subsequent percutaneous venting g-tube placement with fluoroscopy under general anesthesia (GA). No narcotic or paralytic agents were used. G-tube insertion and subsequent extubation to 24/7 NIV following treatment with cough assist were well-tolerated without complications. Following this procedure, lung volume recruitment increased.

This case demonstrates that insertion of venting g-tube can relieve gastric distension secondary to aerophagia, which is a common problem that can lead to altered cardiopulmonary function and patient discomfort (6-8), in patients with ALS on NIV. GA without use of narcotic and paralytic agents during g-tube insertion may aid in the following respiratory recovery. Cough assist can be considered to aid with extubation to NIV in intubated patients on 24/7 ventilation. Percutaneous g-tube placement with fluoroscopy may be completed successfully in ALS patients on 24/7 ventilation with unmeasurable FVC, which suggests new consideration be made for g-tube insertion in this population.

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CW-29 Addressing quality of life concerns that could influence survival through the innovative gadgetry of tubes and buttons that help manage the inflow and outflow

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Keywords: gastrostomy, suprapubic catheter, gastrostomy button

Background: The relationship of nutrition, fluid balance, quality of life and potential increase in survival in the ALS/MND patient continues to strengthen. Thirty percent of ALS/MND patients present with bulbar onset and 81% of advanced ALS/MND patients develop dysphagia but only 43% of patients that were recommended a PEG chose the treatment. Urinary frequency and urgency are common symptoms and negatively impact quality of life yet they are rarely addressed. The feasibility, safety and patient preference of primary button gastrostomy has been demonstrated. It has also been reported that ALS/MND patients are willing to accept the risks of suprapubic catheter (SPC) to allow better hydration, freedom and socialization.

Objective: Analyze the outcomes of patients who received both the low profile gastrostomy and suprapubic urinary catheter.

Methods: Subgroup retrospective analysis of a prospective database, at a single site of all patients, who had both low profile gastrostomy and SPC placement.

Results: Between November 2011 and May 2017, 198 ALS/MND patients were evaluated for PEG placement. Thirty patients had a PEG prior to their evaluation. Seventy-two patients had bulbar symptoms

with only 23 presenting with a PEG. One-hundred and nine gastrostomies were performed. One-hundred and six received the low profile button and 3 patients received a standard PEG. Ten patients had their PEG changed to a button. Forty-two patients choosing the button had an FVC greater than 60%. SPC screening began November 2012. Twenty-five patients, 10 female, had SPCs. Two had SPC prior to evaluation. Thirteen had simultaneous SPC and button PEG placement. Two patients had SPC only. Average age is 57 (29 to 75) years old. All were wheelchair bound requiring full lifts to transfer. There were no surgical complications. One SPC was inadvertently dislodged and one patient had a catheter blockage both required a second surgery for replacement. Urinary tract infections continue to be the most frequently reported sequelae with a frequency of one to five per year. Months of use range from 1.5 to 105. There have been no cross contamination with simultaneous PEG and SPC. Patients report benefits outweigh the risks and all would recommend SPC placement.

Conclusions: ALS patients want therapies that will improve their quality of life. The bulbar component of the disease is directly responsible for decrease in oral intake but to their detriment, many ALS/MND patients limit oral intake to decrease urination needs. Having both the button and SPC can change that paradigm. Because of the aesthetics of the button, patients will choose gastrostomy at an earlier time in their disease when placement is safer and long-term complication rates are consistent with standard PEG. The SPC is commonplace in other neuromuscular diseases. It simplifies care and eliminates burden of frequent urination. Maintaining nutrition and hydration not only improves quality of life but could influence survival.

CW-30 Suprapubic catheter in Motor Neuron Diseases: A case series

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Keywords: suprapubic catheter, quality of life, safety

Background: The incidence and impact of Suprapubic catheter (SPC) in patients with motor neuron diseases, has not been well described in the literature. In our population we identified patients who underwent SPC placement for self-reported challenges with transfers, risk of falls and impaired quality of life. However, there are no current studies to guide a clinician in selection of patients for this procedure nor of its impact on these factors in this patient population.

Objective: To characterize the MND patients with SPC placement and evaluate the indications, clinical variables and outcomes in these patients.

Method: This is a retrospective case series of five patients with MND who underwent Suprapubic catheter placement from 2014 to 2017. The data was collected and reviewed from the EMR (electronic medical records) and paper charts. The patients were analyzed for rate of disease and respiratory progression from diagnosis to time of SPC placement. Factors that could influence decision on the SPC placements were identified and evaluated. These included ALSFRS score, muscle tone, number of falls and transfers, family support and incidence of urinary tract infection (UTI). Postoperative complications were reviewed to determine safety (1). The effects on quality of life after SPC placement were evaluated on follow up visits and telephone interviews.

Patients: The study included three cases of ALS, two cases of PLS, four out of five patients were females. Patient 1: 51 year old (y/o) female (F) with ALS (ALSFRS score at diagnosis: 39), SPC placement after 11 months, (ALSFRS: 18), sustained bowel injury during the procedure that required surgical repair. Patient 2: 64 y/o male (M) with PLS (ALSFRS score at diagnosis: 23), SPC placement after 13 months (ALSFRS: 10) developed pseudomonas colonization one month after

SPC placement; Patient 3: 52 y/o F with ALS (ALSFRS score at diagnosis: 36), SPC placement after 96 months (ALSFRS: 19); patient 4: 58 y/o F with PLS (ALSFRS score at diagnosis: NA), SPC placement after 60 months (ALSFRS: NA), Patient 5: 50 y/o F with ALS (ALSFRS score at diagnosis: 43), SPC placement after 44 months (ALSFRS: 3).

This case series will present individual patient data on quality of life, safety, complications (1), challenges and indicators of SPC placement in patients with MND.

Conclusion: A decision to place SPC in a patient is highly individualized. In a limited subset of patients with spasticity, difficult transfers and dependence on care-givers, it may improve patient comfort and quality of life.

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CW-31 A trial of laryngeal exercises and diet among people with ALS

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Keywords: dysphagia, nutrition

Background: Dysphagia frequently occurs among people with ALS (1). Individuals with ALS usually require dietary modifications and an enteral feeding tube to maintain nutrition. Swallowing problems and poor nutrition intake compromise quality of life, contribute to poor muscle function and fatigue, and weight loss (2).

Conventionally, ALS patients with dysphagia are supported with symptom management and not active therapy. However, data on mouse models of ALS suggest that moderate intensity aerobic exercise delays disease onset and slows progression (3).

Additionally, a study of mice by Olivan et al (4) suggests a diet with 20% calories as extra virgin olive oil (EVOO) increases survival rate, improves motor coordination, producing a potential amelioration of endoplasmic reticulum (ER) stress, and lowering muscle atrophy.

Objectives: This research study investigates the effects of laryngeal exercises with or without a combination of a diet with 20% calories from extra virgin olive oil, on the swallowing function and weight status of patients with ALS.

Methods: Forty-five patients with ALS are currently being randomized into three groups: 1. Laryngeal exercise only group; 2. EVOO only group; and 3. Laryngeal exercise combined with EVOO group.

Participants receive baseline assessment of swallowing function, weight status, body composition, dietary intake, quality of life, and nutritional biomarkers. Additionally cost-effectiveness analysis of the intervention is also being assessed.

The intervention groups occur for four weeks, and include: laryngeal exercises three times per week with a speech pathologist and uses surface electromyography (sEMG) biofeedback; weekly support from a dietitian, and includes guidelines to include EVOO in the diet. All baseline assessments are re-assessed after 4 weeks of intervention, and quality of life and weight status again after 3 months of follow-up.

Results: Recruitment and assessment to this study are currently underway and will be presented. We will provide information about the swallowing and dietary intervention, and preliminary results of swallowing function and weight status.

Discussion: This is a pilot study of a potential new therapy provided by a speech

pathologist and dietitian for people with ALS. If shown to be feasible and the pilot data reports improved swallowing function and weight status, this research will be further trialed in a larger study. This work has the potential to improve quality of life among people with ALS.

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CW-32 Patient-reported outcomes in ALS: Evaluation of physical therapy, occupational therapy and speech-language therapy from the patient perspective

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Keywords: multidisciplinary treatment, patient perspective, patient-reported outcomes

Background: The provision of multidisciplinary treatment (MT) including physical therapy (PT), occupational therapy (OT) and speech-language therapy (SLT) is a key element in the symptomatic and palliative treatment in people with ALS. The subjective experience of PT, OT and SLT is little explored.

Objectives: Patient-Reported Outcomes (PRO) employed in MT are intended to reveal the significance of MT over the course of treatment.

Issue: What is the patient perspective on individual therapies in MT?

Methods: The care network Ambulanzpartner organises MT as part of its case management via a digital management platform. It offers a rating option for individual therapies by means of a Likert Scale. The scale is the basis for the Net Promotor Scores (NPS) and illustrates the likelihood of a patient recommending a certain type of therapy. Clinical data such as age, sex, duration of the disease and severity of ALS (ALSFRS-R) were captured and allocated to the various groups.

Results: In the evaluation period, 324 ALS patients performed an evaluation of individual therapies. 137 patients evaluated PT, 66% of whom were highly likely to recommend this therapy, 23% were likely to do so and 8% would rather not or not at all issue a recommendation to this effect. The results for OT (evaluated by 106 patients) were as follows: 62% were highly likely, 21% were likely to recommend this therapy and 10% would rather not do so. Of the 81 patients who rated SLT 73% were highly likely, 17% were likely to recommend this therapy and 5% would rather not or not at all do so.

Conclusions: MT in ALS has gained great significance in the symptomatic treatment of the disease thanks to extensive prescription practices. Patients are predominantly satisfied or highly satisfied with the individual therapies. Of the three therapies analysed, SLT has the highest rate of recommendation which sets it apart from PT and OT. In the context of a palliative treatment concept, the subjective experience of MT is crucial to the patients' quality of life. Further distinction and identification of specific supportive factors in MT is required to establish patient-oriented treatment standards.

CW-33 – WITHDRAWN

CW-34 How can family members keep working while providing care for ALS/MND patients?

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Keywords: family members of patients, keep working, financial security

Background: This presentation reports on methods by which family members can keep working while providing care for ALS/MND patients. Because of the national insurance and recommendations by doctors or family members (1, 2), in Japan, the ratio of ALS/MND patients who use Tracheostomy Positive Pressure Ventilation (TPPV) is relatively high compared with other countries. However, this does not mean that Japanese patients have no trouble in maintaining their daily lives with TPPV.

One of the most difficult issues is that some family members of patients have to stop working to provide care for them. This occurs because the national insurance does not guarantee 24-hour care and family members have to take over when there are no care workers. If family members stop working, however, the family can become financially distressed. That is why some patients, with their family's interests in mind, do not choose to go on living using TPPV, even though they themselves would prefer survival (3). In other words, patients and their families are forced to make a choice between the patient's life and the family's financial security. It is therefore necessary to find a way for family members to continue working while care is being provided.

Methods: The authors have been interviewing both family members who continue working and those who stop. The former set of interviews reveals the conditions that encourage family members to keep working, although such family members are few. The latter set of interviews, on the other hand, indicates factors that prevent family members from working. The authors will make a report on these case studies and share it with other patients and family members who face the same problem and would like to know how to handle it.
In addition, our poster will compare these family members and investigate some of the main conditions that influence their choices about working. To identify such key factors, the authors will adopt qualitative comparative analysis (QCA), because this approach can treat qualitative data in a reproducible fashion and find complicated combinations of conditions that influence the outcome, ie continuing to work.

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CW-35 Behavioural subphenotypes in Amyotrophic Lateral Cclerosis and their contribution to caregiver burden

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Keywords: caregiver wellbeing, cognitive and psychological assessment, therapeutic symptom management

Introduction: ALS is a clinically heterogeneous neurodegenerative disorder associated with cognitive and behavioural impairment. The aim of the present study was to delineate the impact and relationship between specific clusters of behavioural change in ALS, and the burden experienced by caregivers. It is well-established that behaviour change contributes to caregiver burden, however, less is known about the relative contributions of specific behavioural phenotypes in ALS.

Methods: A cross-sectional population-based research design was applied to examine cognitive, behavioural, and psychological data from ALS patients (n=133) and their identified primary caregiver (n=133). Patients were screened for the *C9orf72* repeat expansion. Patient-caregiver dyads completed a battery of measures investigating cognitive status, psychological wellbeing, and the Beaumont Behavioural Inventory (BBI) was used.

Results: Data analysis is ongoing; however, preliminary results indicate that elevated scores on the BBI, consistent with the literature, correlate with caregiver burden. Secondary analyses are underway to investigate the relative impact that distinct behavioural sub-phenotypes have on ALS caregivers. Furthermore, cognitive correlates of behavioural sub-phenotypes are also being investigated.

Conclusion: By defining and addressing the complex issues facing caregivers of people with MND/ALS, it is expected that psychologically tailored interventions can be designed, developed, and disseminated to alleviate burden faced by caregivers. This research is an essential progression to understanding the profile of cognitive and behavioural changes in ALS, and to the challenges faced by caregivers.

CW-36 Changes in the event-related auditory potentials in Amyotrophic Lateral Sclerosis patients with spinal onset

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Keywords: event-related potentials, cognitive functions, frontal deficit

Background: It has become apparent that nerve cell degeneration in ALS/MND is not restricted to motor neurones, but also extends to involve extramotor areas of the cerebral cortex: early findings from *post-mortem* studies converge with recent advances in neuroimaging, neurogenetics and neuropathology in demonstrating that ALS/MND is, in fact, a multisystemic neurodegenerative disorder (1). The widespread pattern of brain neurodegeneration in ALS/MND has been proposed to account for the cognitive derangements that can be observed in a subset of ALS/MND patients (2): one of the best documented cognitive symptoms in ALS/MND is the impairment in executive functioning. Recent years have witnessed an increasing interest in the event-related potential (ERP) analysis for the study of cognition in ALS/MND patients: we combined the assessment of motor performance by using the ALS-Functional Rating Scale (ALSFRS) with the ERP recording, over time.

Methods: Our pilot study enrolled six subjects (three men and three women, mean age ± SD: 64.2 ± 13.8) suffering from spinal-onset clinically probable/definite ALS (according to the El Escorial criteria). Patients underwent (at three months apart) two auditory cognitive potentials (to detect P_{300} and other relevant waves).

Results: We have shown that most patients have increased latencies of P_{300} and mismatch negativity waves in the second recording, as compared to the first one, significantly ($p<0.05$) correlated to the worsening of motor syndrome.

Conclusions: We think that our preliminary data give support to the concept of ALS/MND as a multisystemic disorder. Moreover, it might seem that progression of cognitive deficit somehow parallels that of motor functioning.

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CW-37 Longitudinal changes in cognition and behaviour in ALS

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Keywords: cognition, behaviour, longitudinal

Background: Longitudinal studies of cognition and behaviour in ALS have found mixed results as to whether these symptoms decline with disease progression (1,2,3). However, large-scale studies have suggested that cognitive performance may relate to ALSFRS-R decline, particularly in bulbar functions (4), and may only affect a subset of patients (5). Longitudinal studies of cognition suffer from variable proxies of disease progression, small sample sizes, the presence of practice effects caused by repeated administration of the same cognitive tests, and high rates of attrition. The latter is of real concern as data is therefore collected from only the few most physically and cognitively able participants. However, recent advances in clinical assessment have provided a standardised measure of disease progression (The King's Clinical Staging) and neuropsychological profile (The Edinburgh Cognitive and Behavioural ALS Screen; ECAS). Furthermore, alternate versions of the ECAS have recently been developed for the longitudinal assessment of cognition and behaviour in ALS.

Objective: The aim of the present study is to utilise these advances to explore whether cognitive and behavioural status changes over the course of the disease as patients transition through disease stages. The results will be presented and discussed in line with potential clinical implications.

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CW-38 Cognitive-behavioral assessment and disclosure practices across the Northeast Amyotrophic Lateral Sclerosis (NEALS) Consortium

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Keywords: cognitive-behavioral, assessment, disclosure

Background: Up to 50% of patients with ALS exhibit cognitive impairment and up to 15% will meet diagnostic criteria for frontotemporal dementia (1). The impracticality of comprehensive neuropsychological testing, but importance of addressing cognitive-behavioral change in the clinic setting, has led to recent efforts to develop valid, reliable, and feasible ALS-specific assessments (2,3). However, the frequency with which cognitive-behavioral assessments are performed, the instruments used, and the practices of healthcare providers in discussing the results of these assessments in multidisciplinary ALS clinics are unknown.

Objectives: 1) Describe the current use of cognitive-behavioral assessments in NEALS Consortium members' ALS centers; 2) Describe current cognitive-behavioral discussion and disclosure practices across the NEALS Consortium.

Methods: A cross-sectional survey examining current cognitive-behavioral assessment and disclosure practices was sent to all NEALS Member Sites' medical directors and nurses via email. Follow-up invitations are planned. One response per site was requested. Responses were collected using NEALS' SurveyMonkey® account. Descriptive statistics were utilized to summarize findings.

Results: Of 118 NEALS Member Sites surveyed, data were available from 23 respondents following the initial email invitation. 96% reported assessing for cognitive changes and 83% reported assessing for behavioral changes in clinic. The most frequently utilized cognitive assessments were the ALS Cognitive Behavioral Screen (ALS-CBS) (46%), Montreal Cognitive Assessment (MOCA) (32%), and Mini-Mental State Examination (MMSE) (27%). The most frequently utilized behavioral assessments were the ALS-CBS (50%), informal clinical assessment (44%), and Edinburgh Cognitive and Behavioral ALS Screen (ECAS) (22%). Lack of time was the main barrier cited for not performing in-clinic assessments. All respondents reported discussing the comorbidity of cognitive-behavioral changes some (50%) or all (50%) of the time, with these discussions first occurring either at the time of diagnosis (38%), only upon the emergence of symptoms (29%), or at the time of cognitive-behavioral assessment (24%). When cognitive-behavioral assessments were administered, sites reported returning results some (19%) or all (81%) of the time.

Discussion and conclusions: Assessing and discussing cognitive and behavioral changes with patients, families, and caregivers appears to be commonplace across the NEALS Consortium. However, the methods by which Member Sites are reportedly assessing for such changes vary. While these findings underscore the lack of consensus regarding the assessment of cognitive-behavioral changes in the contemporary literature, they provide an opportunity to identify and establish best care practices. The main limitation of this study is that a minority of ALS centers responded, making it uncertain whether the practices documented here reflect practices in most centers, or only those with the highest level of interest in cognitive-behavioral dysfunction. Input from more centers is needed and further studies assessing patient and caregiver preferences may help to further inform and refine these practices.

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CW-39 Frequency of cognitive impairment in first and second degree relatives of patients with Amyotrophic Lateral Sclerosis (ALS)

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Keywords: cognition, ECAS, relatives

Background: Over 40% of patients with ALS develop cognitive impairment (1), 30% have behavioural impairment (2) and an additional 14% develop frontotemporal dementia (FTD) (1). Executive dysfunction and co-morbid FTD are negative prognostic indicators in patients with ALS (3). Cognitive impairment in ALS patients is also associated with an increased risk of dementia in relatives (4).

Objectives: To determine whether global cognitive decline and ALS specific cognitive impairment is present in relatives of patients with ALS.

Methods: The cognitive profile of first and second degree relatives of ALS patients was assessed using the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS), using validated cut-offs normalized to the Irish Population (5). The results were compared with those from controls previously assessed as part of a population study examining cognitive impairment in ALS. The results of DNA samples from relatives, tested for the presence of C9orf72 repeat expansion, are pending. No participants had clinical evidence of ALS or FTD.

Results: 40 first and 26 second degree relatives from 10 familial ALS kindreds and 134 controls were assessed. Relatives of patients were significantly younger than controls (m = 44 v 61 years old, p =0.000). There was no significant difference in years of education between both groups.

Global cognitive deficits were found in 20% (13/65) of relatives of ALS patients compared to 7% (9/132) of controls (p=0.006). ALS specific cognitive impairment was found in 21.5% (14/65) of relatives compared to 9% (12/132) of controls (p=0.015). There was no significant difference in incidence of ALS non-specific cognitive deficits between groups. The frequency of cognitive change in relatives carrying the C9orf72 variant will be compared with those of non-carriers and healthy controls.

Discussion and conclusions: First and second degree relatives of ALS patients demonstrate a significantly higher incidence of cognitive deficits compared with healthy controls, both globally and in ALS specific cognitive domains. Cognitive deficits, particularly executive dysfunction have been identified as a shared endophenotype for schizophrenia, autism and obsessive compulsive disorder (6,7). The presence of cognitive impairment in ALS specific domains in relatives of ALS patients suggests the presence of cognitive endophenotypes.

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CW-40 Depictions of people with ALS in Canadian newspaper coverage of assisted death

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Keywords: MaiD, media, EOL

Background: After diagnosis, people with ALS and their family members commonly seek additional information from traditional media and the internet (1,2). In the context of biomedical breakthroughs, and experimental treatments like stem cell therapies, stories are framed as hopeful (3), which may lead people with ALS to seek out unproven therapies (4). In contrast, the framing of the medical aid in dying (MAiD) debate in Canada depicted the experience of ALS negatively. People with ALS, including Sue Rodriguez and Gloria Taylor, were central to the court cases that ultimately led Canada to pass legislation allowing MAiD on June 17, 2016 (5) amidst intense media scrutiny. The legislation has triggered changes in clinical communication about end-of-life (EOL) decisions for Canadians with terminal illness, including ALS. Attitudes of people with ALS towards MAiD are complex (6). Health care providers will require communication strategies based on an understanding of the spectrum of information available to people with ALS and caregiver's outside the clinic.

Objectives: We conducted a quantitative media analysis of Canadian print news media of MAiD to identify dominant portrayals of people with ALS over time.

Methods: We used a standardized strategy to search for Canadian newspaper articles about MAiD in Canadian Newsstand from January 1, 1997 to April 2, 2017. We identified 16,935 relevant articles. The automated content analysis on articles on MAiD and people with ALS to identify positive and negative sentiments (7) as well as hope and hype (8) is underway.

Discussion and conclusions: Based on pilot data we hypothesize that the depiction of people with ALS in the context of newspaper coverage of MAiD will be more negative than positive. Our analysis provides evidence to develop guidelines that help people with ALS, their families and healthcare providers navigate this challenging environment and effectively communicate clinically complex and emotionally sensitive issues related to EOL care and MAiD.

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