UMass Chan MEDICAL SCHOOL | UMass Memorial Health | Department of Neurology

Tenth Annual Research Celebration
May 21, 2025, from 5 to 8 p.m.

Organizing Committee

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Program Schedule

5:00 – 5:10	Welcome by AM Barrett, MD
5:10 – 5:40	Guest Speaker, David Paydarfar, MD
5:40 – 6:10	Oral Presentations by Trainees
6:10 – 7:30	Poster Presentations
7:30 – 8:00	Closing Remarks, Awards

Abstracts

1. Modification of Brain Stimulation Settings to Reduce Stimulation-Triggered Symptoms/Signs, presented by Minorvi Amin, DO

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Authors:
Minorvi Amin, DO, Michael Nozzolilo, Oguz Cataltepe, MD, Pegah Afra, MD

Objective:
To describe how stimulation-triggered symptoms/signs were reduced through modification of RNS System settings.

Background:
We report a case of a 39-year-old female with intractable left temporal FE with RNS System implantation over the right parietal area and left hippocampal depth (LHCD) and left lateral temporal strip (LLTS) leads. After RNS System-implantation, the patient had a significant decrease in seizure frequency but experienced STS with charge density (CD) of 3uC/cm2 and monopolar cathodal stim pathway. Her STS was in the form of 2-3 sharp pains at the right temple of 1 second duration. Eventually, the STS became intolerable, and she began reporting STS as auras. During an EMU admission, STS were captured via numerous push buttons (PBs) correlating to RNS stim-artifact (within 50-200 msec) without other electrographic correlates.

Design/Methods:
RNS System electrode contacts were tested via cathodal stimulation and lead to lead stimulation.

Results:
The two contacts causing STS were identified in LLTS. The current output and CD were reduced, which made STS more tolerable. The decision was then made to turn the two contacts off. Three months later, increased seizure burden prompted reactivation of stimulation at those electrodes at a tolerable, lower current output and CD setting.

Conclusions:
Adjustment of stimulation settings resulted in resolution of STS but decreased efficacy. This may have resulted from decreased “dosage” and area of stimulation. This case illustrates that adjustments in stimulation can resolve STS burden but may impact efficacy. Balancing the impact on seizure burden and stimulation tolerance should be carefully considered when determining RNS Neurostimulator settings.

2. Colitis in Multiple Sclerosis Patients Treated with B-cell Depleting Monoclonal Antibodies, presented by Agnes Bacopulos, MD

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Authors:
Agnes Bacopulos, MD, Roberto Bomprezzi, MD, PhD, Mustafa Al Gburi, MD, Idanis Berrios-Morales, MD, Carolina Ionete, MD, PhD, Molly Wilner, DO, Christopher C. Hemond, MD

Objective:
To investigate the occurrence of colitis in patients with multiple sclerosis (MS) using B-cell depleting agents.

Background:
Because of their high efficacy and overall safety, B-cell depleting agents are increasingly utilized for MS treatment. While these medications carry the potential risks of common infections and effects on vaccinations, other, rarer complications, including colitis, may be under recognized.

Design/Methods:
We queried electronic medical records for patients with diagnoses of MS and colitis. We selected patients treated with rituximab and/or ocrelizumab and who subsequently developed gastrointestinal symptoms suggestive of colitis. We recorded demographics, clinical and treatment histories, colitis workup, and neurological disability measures.

Results:
Twenty-nine patients with MS were included. Average age was 54 ± 12 years (90% female). After starting B-cell depletion, the mean interval of developing symptoms was 4.1±2.9 years. Most presented with diarrhea (86%), and 72% had a colonoscopy in their workup. 50% were diagnosed with inflammatory colitis, 21% with C. Diff colitis. Most patients (73%) improved in an average of 6.5 months. The remaining continued to have symptoms for an average duration of 50 months. 86% of patients discontinued B-cell depletion, although not necessarily immediately after symptom onset. Four patients had stopped therapy over a year prior to symptoms; 12% had stopped within a year prior. Six patients (24% of discontinuers) stopped within the same cycle as their infusion, and another 6 stopped after 1 additional infusion.

Conclusions:
Colitis is a rare complication of B-cell depleting therapies, but it is likely under recognized and under reported in MS patients.

3. Identification of Disease Associated Epitopes in Alzheimer's Disease Using Unbiased Antibody Profiling, presented by Nathaniel J. Barton, BS

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Authors:
Nathaniel J. Barton, BS, Qi Wang, PhD, Rebecca L. Best, PhD, Michael Jhatro, PhD, Kathy Kamath, PhD, John Shon, MD, MS, Diego F. Mastroeni, PhD, Elaine T. Lim, PhD, Ben Readhead, Rigel Y. Chan, PhD

Objective:
To identify disease-associated epitopes in Alzheimer's disease (AD) using unbiased antibody profiling, with a focus on potential viral and autoantigenic targets in cerebrospinal fluid (CSF).

Background:
AD is characterized by complex immune interactions, but the role of antibody-mediated responses remains unclear. Advances in high-throughput epitope screening provide an opportunity to identify epitopes implicated in AD pathogenesis. Our previously developed computational pipeline enables detection of disease-associated epitopes, which we applied to CSF samples to explore antibody responses in AD.

Design/Methods:
We performed IgG epitope profiling on CSF samples from 625 individuals, including 359 AD patients, 97 mild cognitive impairment (MCI) controls, and 158 cognitively normal controls. Samples were analyzed using the Serimmune Serum Epitope Repertoire Analysis (SERA) platform, profiling IgG binding to a 12-mer bacterial display library. K-mers (k=5,6) were extracted, mapped to human and viral proteomes, and analyzed for statistical enrichment using a permutation-based approach. Epitopes were identified through peak calling, clustered using complete-linkage clustering, and assessed for disease association via an outlier sum statistic with Benjamini-Hochberg multiple hypothesis correction.

Results:
We identified 12 AD-associated viral epitopes spanning multiple viral families, with a significant overrepresentation of herpesviruses (e.g., HHV8P, EBVB9). Additionally, 42 CNS-expressed autoantigens were associated with AD, including ion channels (SCN1A), neurotransmitter receptors (NTRK2), and immune-regulatory proteins (PD1L1).

Conclusions:
Our findings highlight a potential role for viral infections and autoimmunity in AD pathology. Further studies are needed to validate these epitopes and assess their mechanistic involvement in disease progression.

4. Iron Concentration in Deep Grey Nuclei in Multiple Sclerosis – A Radiomics Analysis, presented by Avinash S. Bissoondial, BS

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Authors:
Avinash S. Bissoondial, BS, Manojkumar Saranathan, PhD, Christopher C. Hemond, MD

Objective:
We segmented thalamic and deep gray nuclei to determine volumes and used it to map distributional iron content based on radiomic analysis; we hypothesized that these features would improve discrimination between MS and healthy controls and reveal insight into iron pathology in MS.

Background:
Multiple sclerosis (MS) is characterized by early injury to the thalamus as well as dysregulated cerebral iron distribution. These factors may be important in disease pathogenesis and progression.

Design/Methods:
This is a cross-sectional, retrospective case-control study of 99 patients with relapsing-remitting MS and 50 healthy controls (HC). The imaging data are part of an open dataset, and include standardized T1, FLAIR, and quantitative susceptibility maps (QSM). Individual (bilateral) thalamic and deep gray nuclei were segmented using a state-of-the-art technique (THOMAS), followed by additional analysis using PyRadiomics to yield first- and second-order (texture) features for each structure, based on the underlying QSM values. This yields 105 radiomic features per nucleus. For dimensionality reduction, we used lasso (L1 Regularization) on multiple subsets of the data to capture only important features. We then used Firth's Logistic Regression to interpret which features stood out as significant to classify MS. The subsets of data were used to create 3 models. The first used age, sex, volume of individual deep grey nuclei, and entire thalamus volume. The second used everything from model 1 and first order QSM statistics. The third used everything from model 1 and second order QSM statistics.

Results:

Model 1:
- Significant predictive features are age, thalamic anteroventral and pulvinar nucleus volumes
- Negative coefficients indicate thalamic atrophy in MS

Model 2:
- QSM (iron) kurtosis values were thematically important in discriminating MS from HC
- Training accuracy was higher than model 1, but overall accuracy was similar
- AV volume remained influential but pulvinar volumes were no longer significant

Model 3:
- Small Area High Gray Level Emphasis (SAHGLE) is significant in two different regions
- Negative in accumbens, Positive in medial dorsal nuclus
- Suggests that in MS there are small, iron rich regions in the medial dorsal thalmus, whereas these are evenly-distributed in the Accumbens

Conclusions:
•Multiple sclerosis exhibits prominent thalamic and deep gray atrophy compared to healthy controls. These features alone discriminate MS from HC with high accuracy (AUC=0.91, see Figure 2)
•Although iron concentrations are higher in several deep gray nuclei in MS, the concentration, statistical distribution and "texture" of iron within these deep gray nuclei do not improve accuracy in the classification of MS vs HC beyond atrophy measures.
•This study is potentially limited by T2-hyperintense lesions being included in the deep gray structures and QSM artifacts affecting intensity values

5. Development of therapeutic oligonucleotides for the treatment of sporadic ALS, presented by Annie E. Collins, BM, BCh

Email: annie.collins1@umassmed.edu

Authors:
Annie E. Collins, BM, BCh, Jonathan K. Watts, PhD, Robert H. Brown Jr., MD, DPhil

Objective:
Design and test therapeutic oligonucleotides (ASOs and siRNAs) targeted against genes shown to be implicated in common cellular pathologies in sporadic ALS

Background:
Over 90% of ALS cases are sporadic, where there is no single causative genetic mutation. However, over 97% of patients with ALS, including sporadic ALS, share common TDP-43 cellular pathologies, making the silencing of genes involved in TDP-43 pathology, such as SYF2 and GSDME, a promising strategy for an oligonucleotide-based therapy.

Design/Methods:
We synthesized and screened oligonucleotides against the genes SYF2 and GSDME, which have been implicated in the development of TDP-43 pathology (SYF2) or resultant mitochondrial dysfunction and cell death (GSDME). iPSC-derived motoneurons (iPSC-MNs) were differentiated from cell lines from patients with sporadic ALS. iPSC-MNs were assessed for in vitro neuronal pathologies and the efficacy of oligonucleotides was assessed.

Results:
We identified potent ASOs and siRNAs directed against SYF2 and ASOs against GSDME in both immortalized cell lines and iPSC-derived motoneurons. One of three iPSC-MN cell lines from patients with sporadic ALS demonstrated pathology in culture, which was partially rescued with GSDME ASO treatment.

Conclusions:
iPSC-MNs provide a powerful tool for the identification of oligonucleotides with potential therapeutic benefit in sporadic ALS. While further characterization and validation is required, ASOs targeting GSDME may prove beneficial in the treatment of sporadic ALS.

6. Association between Parkinson's disease subtype and sex in release burst patterns during consonant production, presented by Abigail DeNike, Neha Kamireddi, BS

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Authors:
Abigail DeNike, BS, Neha Kamireddi, BS, Taylor Feaster, BA, Nitya Vishwanath, Jenny Vojtech, PhD, Kara M. Smith, MD

Objective:
To examine the association of consonant articulation patterns with sex and subtype in participants with Parkinson's Disease (PD).

Background:
Release burst patterns during plosive consonant articulation have previously been associated with clinical subtypes in people with PD, however they have not yet been rigorously evaluated for differences based on both sex and PD subtype.

Design/Methods:
A retrospective analysis was conducted examining 17 plosive consonant contexts from audio recordings of a standardized reading passage. Participants were categorized by PD subtype (tremor-dominant [TD] vs. postural instability and gait disorder [PIGD]) and matched by age and sex. Burst patterns were classified as single (typical), absent, multiple, or no stop produced (NSP). Chi-square tests and multinomial logistic regression were used to assess the effects of PD subtype, sex, and their interaction on burst pattern distribution.

Results:
Significant differences in release burst types were observed ($p<.001$) with females being more likely to produce a single burst over an NSP when compared to males. PIGD participants exhibited more multiple bursts than TD participants, with the strongest effect in PIGD females. There were significant associations between burst type, sex, and subtype, with a notable interaction effect between these factors.

Conclusions:
The findings of female PIGD patients demonstrating more articulatory imprecision underscores the importance of incorporating sex-specific analyses in PD research. Our results align with prior research and highlight the potential of release burst analysis as an acoustic marker for PD subtype classification. Future studies should explore the clinical utility of speech-based assessments for monitoring disease progression and tailoring therapeutic interventions.

7. Investigating Stress-associated RNA Regulation by TDP-43, presented by Megan E. Fowler-Magaw

Email: megan.fowler1@umassmed.edu

Authors:
Megan E. Fowler-Magaw, Martina Halleger, PhD, Daryl A. Bosco, PhD

Objective:
Identify the RNAs regulated by TDP-43 under conditions of cellular stress in physiological and disease contexts.

Background:
Transactive response DNA-binding protein 43 (TDP-43) proteinopathies are neurodegenerative disorders that exhibit TDP-43 pathology. TDP-43 pathology refers to the depletion of nuclear TDP-43 concomitant with cytoplasmic TDP-43 accumulation and/or aggregation. TDP-43 pathology is prominent in multiple neurodegenerative disorders, including most cases of amyotrophic lateral sclerosis (ALS) and a significant proportion of frontotemporal dementia (FTD) cases. Under physiological conditions, TDP-43 is primarily nuclear. Loss of nuclear TDP-43 during disease pathogenesis results in aberrant RNA splicing, including de-repression of cryptic exons and misexpression of multiple genes. However, the factors that initiate TDP-43 mislocalization and dysfunction are unclear. Intriguingly, cytoplasmic accumulation of TDP-43 is observed as a function of cellular stress, raising the possibility that neuronal stress contributes to TDP-43 mislocalization. While previous studies have identified RNAs bound by TDP-43 under physiological conditions, the RNAs bound by TDP-43 during cellular stress remain unknown.

Design/Methods:
In situ RNA editing methods and crosslinking and immunoprecipitation (iiCLIP) will identify RNA targets of TDP-43 under proteasomal inhibition-induced stress using MG-132 in human induced pluripotent stem cell (iPSC)-derived neurons.

Results:
Pilot iiCLIP studies are currently underway to identify RNAs bound by wild-type TDP-43 during control and proteasomal stress conditions. Additional studies will include neurons expressing mutant TDP-43. Multiple in situ RNA editors are being transfected into neurons to determine localization during control and stress conditions.

Conclusions:
Collectively, this research will inform on the consequences of stress-induced cytoplasmic TDP-43 translocation in both physiological and disease contexts.

8. Targeting pathogenic mutations in ALS/FTD: an allele-specific ASO therapeutic strategy, presented by Asmita Ghosh, PhD

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Authors:
Asmita Ghosh, PhD, Desiree M. Baron, PhD, John E. Landers, PhD

Objective:
Design, screen, and validate allele-specific antisense oligonucleotides (ASOs) for selective knockdown of mutant alleles in genes causing hereditary neurodegenerative disorders.

Background:
Amyotrophic lateral sclerosis (ALS), a progressive fatal neurodegenerative disease, is familial in approximately 10% of cases. For genes implicated in ALS pathogenesis through toxic gain-of-function mechanisms (SOD1, FUS, C9ORF72), targeted gene expression reduction strategies are under clinical evaluation. Recent molecular and genetic advances have enabled RNA-based interventions like ASO therapy, which uses synthetic DNA-like molecules to selectively bind complementary RNA sequences and modify gene expression with high specificity. Current RNA interference approaches predominantly employ non-allele-specific targeting, suppressing both pathogenic and wild-type alleles, potentially causing long-term adverse effects.

Design/Methods:
Our approach for allele-specific knockdown is based on targeting common insertions and deletions (indels) with high heterozygosity frequencies within the gene. Using patient-derived fibroblasts and NIH's iPSC neurodegenerative disease initiative (iNDI) isogenic iPSC lines, we have screened ASOs for their knockdown efficiencies. We have utilized ddPCR and RNA sequencing to confirm allele-specific expression after ASO administration. We also perform western blotting to assess the effect on total protein levels following allele-specific knockdown of the mutant allele.

Results:
Best performing ASOs were taken forward to explore if alternate chemistry would show better knockdown of the mutant allele and subsequent phenotypic rescue. Our preliminary studies have focused on TDP-43, C9ORF72, KIF5A and SOD1.

Conclusions:
Using this methodology, potential therapeutics can be developed for several causative mutations in multiple diseases such as Parkinson's disease, Alzheimer's disease, Spinocerebellar ataxias etc.

9. PPMO as a Therapeutic Option to Treat Dysferlinopathy, presented by James E. Gooding

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Authors:

James E. Gooding, Janice Dominov, PhD, Robert H. Brown Jr., MD, DPhil

Objective:

Treat a pathogenic pseudo exon inclusion even using pseudo exon skipping

Background:

Dysferlinopathy encompasses a group of muscular dystrophies resulting from mutations in the dysferlin gene (DYSF). An autosomal recessive disorder, dysferlinopathy affects 1 in 200,000 people in the United States, causing muscle weakness and loss of function, accompanied by inflammation, abnormal muscle morphology, and elevated serum creatine kinase levels. Currently lacking therapeutic options due to the gene's size, the use of antisense oligonucleotides (ASOs) emerges as a promising intervention for dysferlinopathy. ASOs target mRNA, either degrading it or modulating its splicing, and offer advantages in pharmacokinetic and molecular targeting that could be applied to many of the more than 400 mutations causing dysferlinopathy.

Design/Methods:

We identified a human pathogenic dysferlin mutation involving a splicing donor site within an intron, leading to the inclusion of a pseudoexon (PE44.1) and disrupting DYSF protein structure. We created a knock-in mouse model carrying this human DYSF mutation that accurately mimics the aberrant dysferlin splicing observed in humans. We aim to attenuate pseudoexon inclusion in mature spliced RNA, using steric blocking ASOs, thereby restoring normal splicing and generating functional dysferlin protein.

Results:

Using cell cultures carrying this PE44.1 mutation, we identified ASOs that can skip the pseudoexon and increase DYSF protein expression in vitro, utilizing candidate molecules in vivo correction was achieved in our new mouse model.

Conclusions:

This intervention corrects DYSF protein expression and function in vivo showing strong preclinical results.

10. Urine Toxicology Screening in Stroke and TIA Patients in Central Massachusetts, presented by Muhammed Enes Gunduz, MD

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Authors:
Muhammed Enes Gunduz, MD, Isabella O'Shea, BS, Brian Silver, MD

Objective:
Determine the rate of toxicology screening, disparities in testing and outcomes among patients presenting to UMass Hospital with stroke (ischemic or hemorrhagic) and TIA

Background:
The National Survey on Drug Use and Health estimated 23.9 million (8.9%) individuals in the United States used illicit drugs. The use of illicit drugs has been associated with an increased risk of ischemic and hemorrhagic strokes. However, current guidelines do not include routine screening for illicit drugs and leave the decision at the discretion of the healthcare provider. With the lack of well-defined guidelines, previous literature suggested healthcare disparities in screening based on age, race, and gender.

Design/Methods:
Patients aged 18 years and older, who were admitted with stroke including ischemic, intracerebral hemorrhage, and TIA between 01/01/2013-12/31/2023 will be included. Relevant demographic and clinical information obtained by 'Get with Guidelines-Stroke' database and charts will be reviewed to assess toxicology screening.

Results:
4436 stroke patients were identified; toxicology screening was performed in 406 patients (9.2%). 92 (22.7%) resulted positive (cocaine 29.3%, opiates 21.7%, amphetamine 9.8%, cannabinoids 63%, benzodiazepines 8.7%). 75% of patients with Utox screening were admitted to ICU level of care.

Conclusions:
We will present the comparison of characteristics of tested patients with all stroke cohorts, demographic and clinical characteristics of patients with positive drug screening, and comparison of outcomes in patients with positive vs negative toxicologies.

11. Ethics of Early Diagnosis and Treatment in Alzheimer's Dementia: Medical Futility as a Framework for Understanding Novel Advancements, presented by Katarina Hughes, MD

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Authors:
Katarina Hughes, MD, Alexander Lichtenberg, MD, Leah Richler, MD

Objective:
Our objective is to further evaluate novel Alzheimer's Dementia diagnostic testing and treatment options utilizing an ethical framework that ultimately improves shared decision-making conversations and informed consent processes.

Background:
Alzheimer's dementia (AD) is increasingly being evaluated with respect to biomarkers and a de-emphasis on clinical phenotype. Recent classes of anti-amyloid treatments are predicated on these biomarker studies for identifying potential candidates and guiding management. Utilization of these advances has changed the clinical landscape as providers are able to diagnose and treat AD at earlier stages. However, ethical issues arise with these advancements in diagnosing and treating individuals with minimal symptomatology, especially with treatments that may not alter the course of disease.

Design/Methods:
We conducted a broad literature search to understand the current landscape of ethical approaches to Alzheimer's Dementia diagnostic testing and treatment options and observed a lack of literature on the concept of futility in this literature. We paired various combinations of relevant search terms including "ethics", "bioethics", "neuroethics", "futility", "Alzheimer's", "dementia", "infusions", and "diagnostic testing". Utilizing the ethical concept of futility as it is understood within the bioethics literature, we analyzed testing and treatment options through the lens of futility, and translated this ethical analysis into concrete questions that providers may use when considering the overall effectiveness and benefit of various diagnostic testing and treatments.

Results:
Discussion: Current ethics literature has expounded on many conflicting practical and theoretical issues regarding these advances, however little has been written about the role of medical futility in understanding AD advancements. Medical futility is an ethical concept that applies to interventions unlikely to produce meaningful benefit to the quantity of life or quality of life of a patient, or represents broadly unacceptable risk-benefit ratios. Although controversial, the concept of medical futility is useful for providers in evaluating the goals of treatment compared to the utility and risks versus benefits of the treatment itself. Whether futile or useful, much of the controversy surrounding AD advancements from the providers' perspective relates to this unspoken debate on futility. Using the theoretical framework of medical futility, we provide a schema for physicians to better conceptualize the utility of novel diagnostic and treatment technologies.

Conclusions:
Careful attention to ethical issues of early diagnosis and treatment of Alzheimer's dementia can improve provider care and patient understanding of novel AD diagnostics and treatments.

12. Deep Cervical Lymph Node Volume Decreases Following Ocrelizumab Therapy, presented by Nikhil S. Lele, BA

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Authors:
Nikhil S. Lele, BA, Sathish K. Dundamadappa, MD, Christopher C. Hemond, MD

Objective:
Here we aimed to assess the volumetric changes in the deep cervical lymph nodes (dCLN) in association with initiation of B-cell depletion therapy (BCDT). We hypothesize that BCDT will reduce peripheral antigenic presentation and therefore reduce the size of the lymph nodes.

Background:
The deep cervical lymph nodes (dCLN) are sites of immune presentation and maturation from the brain; they are potentially involved in initiating or propagating central nervous system inflammation. They are therefore of interest as a potential biomarkers of disease initiation, progression, or response to therapeutics in multiple sclerosis.

Design/Methods:
In a retrospective, longitudinal cohort of 10 relapse-remitting MS patients who started the B-cell depleting agent ocrelizumab, we used a semi-automatic, threshold-based segmentation of T2-FLAIR MRI scans to determine dCLN volumes at (1) more than one year before starting BCDT ("pre-baseline"), (2) just prior to starting ("baseline") therapy, and (3) at least 6 months after receiving the medication. In this way, patients act as their own control. Data were analyzed using linear mixed-effect regression models with patient-specific random effect.

Results:
We observed no significant changes dCLN volumes between their "pre-baseline" and "baseline" timepoints ($p>0.05$), but a significant decrease of 158 mm^3 in volume following initiation of ocrelizumab ($t = -3.3$, $p=0.005$).

Conclusions:
Cervical lymph node volumes decrease following B-cell depletion; these data suggest a role for the dCLN as potential pharmacological response biomarkers and open multiple areas of potential future research.

13. Kleptomania Resulting from Congenital Frontal Hamartoma, presented by Alexander Lichtenberg, MD

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Authors:
Skylar Sundquist, BS (Oakland University William Beaumont School of Medicine), **Alexander Lichtenberg, MD**, Sheldon Benjamin, MD

Objective:
Describe a case of chronic impulse control disorder in the setting of inborn frontal lobe damage.

Background:
Kleptomania (failure to resist the recurrent impulse to steal unneeded objects) is a rare disorder that occasionally occurs in the context of frontal lobe syndromes, such as behavioral-variant frontotemporal dementia, or substance use disorders. There are few reported cases related to antenatal injury.

Design/Methods:
Case report of an individual patient.

Results:
A 31-year-old female with a history of congenital intracranial hamartoma, panhypopituitarism, visual impairment, cognitive impairment, seizures, ADHD, hypothalamic hyperphagia, and impulse control disorder reported chronic kleptomania, binge eating, and skin picking. 90% of the hamartoma was resected in infancy without subsequent tumor growth. Although the patient feels remorse, she does not return the stolen items until prompted. She had not tried medication or therapy directed at this behavior. MRI brain showed a hyperintense anterior cranial fossa mass with cystic changes, mass effect on the anterior frontal lobe with associated encephalomalacia, septo-optic dysplasia, optic nerve encasement and atrophy, and an attenuated anterior corpus callosum. Previous neuropsychological testing demonstrated attention, working memory, and executive functions consistent with low average to very low average intellectual abilities with memory and ability to learn new information within normal limits to impaired. Patient was started on fluoxetine and N-acetylcysteine for management of impulsive behavior. The patient's cognitive and social skills were remarkable given the degree of frontal pathology.

Conclusions:
Frontal lobe syndrome can result from inborn cortical damage. Symptoms may include kleptomania, skin picking, binge eating, and impulse control disorder, and may mimic the presentation of frontotemporal dementia.

14. Advanced base and prime editing strategies to correct common ALS-causing SOD1 mutations, presented by Katharina E. Meijboom, DPhil

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Authors:
Katharina E. Meijboom, DPhil, Nathan Bamidele, PhD, AdityaValji Ansodaria, Jacob Eisenberg, Erik J. Sontheimer, PhD, Robert H. Brown, MD, DPhil

Objective:
Develop innovative base and prime editing therapies to achieve precise somatic gene correction for common missense mutations in SOD1.

Background:
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with no effective treatment, leading to death within five years of diagnosis. Approximately 10% of ALS cases are familial, with mutations in SOD1 being the second most common genetic cause. These mutations drive toxic gain-of-function properties in SOD1 protein, accelerating motor neuron degeneration. Our goal is to develop cutting-edge base and prime editing approaches to correct prevalent SOD1 mutations. We will optimize next-generation domain-inlaid base editor strategies with enhanced efficiency, compact size to facilitate AAV delivery, and minimized bystander editing. We will also optimize different prime editor systems with optimal editing efficiencies and low off-target editing. Additionally, we will optimize adeno-associated virus (AAV)-mediated delivery for in vivo application.

Design/Methods:
We generated SOD1 HEK293T cells via prime editing and will systematically screen base and prime editor strategies in these mutation-carrying cells. Optimized editors will then be evaluated in patient-derived fibroblasts and in vivo mouse models. The therapeutic impact of gene correction will be assessed by analyzing molecular, cellular, and motor phenotypes linked to both gain- and loss-of-function consequences of SOD1 mutations.

Results:
Preliminary data show 30% correction of the A5V mutation in patient fibroblasts and A5V-HEK293T cells using base editing, with minimal bystander editing. Additionally, prime editing achieved 15% correction of the A5V mutation in patient fibroblasts.

Conclusions:
We propose that AAV-mediated somatic gene correction using base or prime editing to target SOD1 mutations will mitigate toxic gain-of-function pathology, restore wild-type SOD1 protein levels, and rescue motor deficits. This strategy offers a promising therapeutic avenue for SOD1-ALS.

15. ASO Mediated SPTLC1 silencing as a therapeutic for HSAN1A, presented by Sushmita Nayak, MS

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Authors:

Sushmita Nayak, MS, Erinn Ives, Kenneth Gable, Alexandra Weiss, Justin Lee, PhD, Huiya Yang, Teresa Dunn, PhD, Jonathon K. Watts, PhD, Robert H. Brown Jr., MD, DPhil

Objective:

HSAN1A is a rare sensory neuropathy affecting a few hundred patients worldwide. Currently, no effective curative therapies exist for patients with HSAN1A. Our goal is to find a safe and effective therapy for these patients.

Background:

Hereditary sensory and autonomic neuropathy Type 1A is a debilitating disease characterized by loss of peripheral neurons. Patients experience loss of pain and sensation leading to painless injuries often requiring distal amputations. The disease is caused by autosomal dominant mutations in SPTLC1 and SPTLC2 genes that play key roles in the biosynthesis of sphingolipids. These mutations result in neurotoxic, atypical deoxysphingolipids that are thought to drive disease pathology.

Design/Methods:

We first developed and characterized a knock-in mouse model with a HSAN1 SPTLC1 pC133Y causative mutation. Additionally, we established human dorsal root ganglion cultures from pC133Y patient derived iPSCs and investigated mitochondrial and lysosomal turnover among other phenotypes in these cultures.

Results:

We have successfully established a mouse model and a human model for HSAN1A recapitulating key phenotypes such as increased deoxysphingolipids, demyelination in the sciatic nerve and dorsal root ganglion and aberrant mitophagy. Here, we report a novel antisense oligonucleotide (ASO1) targeting the human SPTLC1 that shows a dose dependent decrease in gene expression in patient fibroblast cultures, and at the highest dose a decrease of up to 90% in patient derived dorsal root ganglion cultures. ASOs homologous to this targeted sequence in mice showed reduction in toxic deoxysphingolipids upon intracerebroventricular delivery. We are currently analyzing tissue-specific expression level reduction and rescue of any disease phenotypes.

Conclusions:

We report ASO1 as a potential therapy for HSAN1 patients harboring mutations in the SPTLC1 gene.

16. TDP-43 mutation renders ALS/FTD mice deficient in their CNS response to traumatic brain injury, presented by Kennedy O'Hara

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Authors:
Kennedy O'Hara, Melissa Rotunno, PhD, Megan E. Fowler-Magaw, Jianjun Zhong, MD, PhD, Elenore Wiggin, Debra Cameron, Karly Stallworth, James Bouley, Nils Henninger, MD, PhD, Oliver King, PhD, Daryl A. Bosco, PhD

Objective:
We used an ALS/FTD mouse model of mutant TDP-43 to investigate how expression of dysfunctional TDP-43 modulates the acute and chronic phases following a mild, concussive TBI (mTBI).

Background:
A major risk factor for developing an array of neurodegenerative diseases including ALS, FTD, and CTE is incidence of traumatic brain injury (TBI). A hallmark of these diseases is TDP-43 pathology and cytoplasmic accumulation, which can also be caused by TBI, suggesting that TDP-43 dysfunction is intricately involved in TBI-induced neurodegeneration.

Design/Methods:
Wild-type and ALS/FTD (Q331K) mice were subjected to mTBI, after which brain tissues were extracted and analyzed using several omics, biochemical, and histological assays.

Results:
During the acute phase following mTBI, our results revealed that Q331K mice exhibited heightened neurological deficits relative to wild-type mice. In addition, TDP-43 cytoplasmic translocation was observed in several brain regions in both Q331K and WT mice following TBI. Furthermore, TDP-43 dysfunction caused changes in gene-splicing, leading to both gain of function and loss of function phenotypes, which will be probed in situ. Notably, RNAseq analyses indicate that Q331K mice are inherently deficient in proteostasis-related processes, resulting in aberrant gene expression profiles in response to TBI.

Conclusions:
These outcomes provide insight into the consequences of TBI in vivo and indicate that expression of dysfunctional TDP-43 predisposes animals to worse neurological outcomes following head trauma. Next, we next aim to leverage these results to identify parallel effects in human cases of chronic traumatic encephalopathy (CTE) and in relatively more severe mouse models with repetitive TBI model.

17. Human Cytomegalovirus Induces AD-like Biomarker Accumulation in Dissociated Cerebral Organoid Cells, presented by Adrian R. Orszulak, BS

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Authors:

Adrian R. Orszulak, BS, Anne Mirza, BS, Nathaniel J. Barton, BS, Pepper Dawes, BS, Timothy Kowalik, PhD, Rigel Y. Chan, PhD, Elaine T. Lim, PhD

Objective:

This work's goal is to determine whether Human Cytomegalovirus (HCMV) infection induces Alzheimer's disease (AD)-like biomarker expression in dissociated, induced pluripotent stem cell (iPSC)-derived cerebral organoid cells (dcOrgs) similarly to observations during Herpes Simplex Virus-1 (HSV-1) infection. The resulting work will identify whether there exists common underlying biology between herpesviruses infection and AD-like biomarker expression.

Background:

AD is a progressive, neurodegenerative disease notably characterized by a neuroinflammatory signature, extracellular deposition of amyloid Beta (Aβ) and intracellular phosphorylated Tau (pTau) as neurofibrillary tangles. Despite its prevalence, the mechanisms of disease onset and progression are not clearly understood. AD's neuroinflammatory status propelled researchers to investigate the role microbial agents play in AD. Previous studies and our lab's work have shown that HSV-1 infection induces increased Aβ and pTau expression whereas influenza A infection does not. However, it is unclear whether other related herpesviruses produce the same biomarker increases.

Design/Methods:

IPSCs were cultured, aggregated, and differentiated into cerebral organoids. After 3 months, cerebral organoids were dissociated into 2D and allowed to recover for 1 month. DcOrgs were treated with either mock or HCMV infection at an MOI of 2. Following 3-day incubation, dcOrgs were harvested and stained for biomarker expression using flow cytometry.

Results:

HCMV infected dcOrgs show increased aggregated Aβ, pTau-181, and pTau-217 species expression. HCMV infected dcOrgs show no increase in monomeric Aβ and pTau-205 species expression.

Conclusions:

HCMV infection induces similar AD-like biomarker expression increases as HSV-1 infection. HCMV infection appears to promote aggregation of existing Aβ species over processing and production. There is a clear, underlying biology between herpesvirus infection and AD-like phenotypic changes.

18. 12 versus 24 h bed rest after acute ischemic stroke thrombolysis or thrombectomy treatments: A Retrospective Cohort Study, presented by Isabella O'Shea, BS

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Authors:
Isabella O'Shea, BS, Muhammed Enes Gunduz, MD, Brian Silver, MD

Objective:
This study compares discharge outcomes in acute ischemic stroke patients who followed bed rest protocols of either ≥24 hours or ≥12 hours post-thrombolysis and/or thrombectomy. We hypothesize that the ≥12 hour cohort will have similar favorable discharge outcomes but lower NIH Stroke Scale scores (NIHSS) and Modified Rankin Scores (mRS) at discharge compared to the ≥24 hour cohort. Additionally, we expect the ≥12 hour cohort to have fewer complications related to prolonged immobility and shorter hospitalizations.

Background:
Potential benefit of reduced best rest duration has been suggested in acute ischemic stroke patients who received intravenous thrombolysis, but clinical outcomes among patients who adhered to bed rest protocols of ≥24 hours or ≥12 hours following thrombolysis and/or thrombectomy are unknown.

Design/Methods:
Adult patients diagnosed with acute ischemic stroke treated with thrombolysis and/or thrombectomy from 1/1/2005 to 12/31/2024, identified from an existing dataset of patients from UMass Memorial Medical Center, are included. This study compares discharge outcomes and associated complications of patients admitted before 2020, who followed a ≥24-hour bed rest protocol, and patients admitted in 2020 or later, who followed a revised ≥12-hour bed rest protocol. The primary outcome is favorable discharge location (defined as home, home with services, or acute rehabilitation). Secondary outcomes include: NIHSS and mRS at discharge, pneumonia and venous thromboembolism during hospitalization, length of hospital stay, and readmission within 30 days.

Results:
Preliminary results available in May.

Conclusions:
Study results may help verify previously observed potential benefits of reduced bed rest and establish a post-reperfusion protocol that maximizes favorable discharge outcomes.

19. AAV Gene Therapy for LMNA Associated Laminopathies, presented by Monique Otero

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Authors:

Monique Otero, Simon Wentworth, Oliva Morales, McKenna Watson, Tyler Mola, William Callahan, Ananya Uppalapati, Eleonora D'Ambrosio, MD, Ignacio Pérez de Castro, PhD, Ana Rita Batista, PhD, Miguel Sena-Esteves, PhD

Objective:

We used a "silence and replace" approach with a dual-function AAV that encodes an artificial microRNA (miRNA) to target endogenous LMNA for silencing, and a miRNA-resistant LMNA transgene that mimics the natural alternative splicing mechanism to generate both Lamin A/C.

Background:

Laminopathies are a phenotypically diverse group of diseases caused by dominantly inherited mutations in the LMNA gene. LMNA encodes Lamin A and C, two intermediate filament proteins of the nuclear lamina formed through alternative splicing. Our focus is a severe LMNA-associated congenital muscular dystrophy (L-CMD). The challenges in developing an effective AAV gene therapy for L-CMD are the need to silence the dominant negative endogenous alleles and for balanced expression of both Lamin A/C isoforms.

Design/Methods:

The miRNAs were designed to target homologous sequences in the mouse and human LMNA gene and screened in human and mouse cells for silencing. The transgene was made miRNA-resistant through alternative codon usage in the miRNA target seed sequence. The AAV-LMNA-miRLMNA vector is driven by a muscle specific promoter (MCK7) to target that skeletal and cardiac muscle for L-CMD. We tested different vector designs, where the miRNA position within the vector genome (intron or 3'UTR) and the scaffold used was varied, as these factors can impact silencing efficacy and transgene splicing. The goal is to identify an AAV vector design with the most potent silencing of endogenous LMNA mRNA, and balanced expression of both Lamin A and C.

Results:

We identified a top miRNA that silenced LMNA by ~50% in both human and mouse cells. We cloned this miRNA into the AAV-LMNA-miRLMNA and tested in human and mouse cells to measure silencing of the endogenous LMNA allele, and expression of Lamin A/C. We identified AAV candidates that overexpressed both Lamin A/C isoforms compared to naïve and silenced the endogenous allele.

Conclusions:

Our top vectors will be packaged into a muscle specific capsid (Myo4A) for testing in the LMNAR249W/R249W mouse model of L-CMD. This model has a severe phenotype with a shortened lifespan (~6 weeks), reduced body weight and muscle weakness allowing for rapid testing of therapeutic efficacy. Successful outcomes will be significant extension of lifespan, improved in-life phenotype.

20. A muscular dystrophy misdiagnosed as ALS, presented by Maria T. Pesco, MD

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Authors:
Maria T. Pesco, MD, Eleonora S. D'Ambrosio, MD.

Objective:
Myotonic dystrophy type 1 (DM1) and amyotrophic lateral sclerosis (ALS) both lead to progressive muscle weakness, wasting, and active and chronic changes on EMG, making differential diagnosis challenging. Our objective with this presenting case is to demonstrate this challenging when diagnosing DM1 with an EMG results demonstrating unspecific changes that point to the wrong direction, and how important is the genetic testing when clinical examination and exams do not give us a clear and definitive diagnosis.

Background:
DM1 primarily affects muscles, causing weakness, myotonia, arrhythmia, sleep apnea, digestive issues, and early cataracts. ALS, however, it stems from motor neuron degeneration, leading to weakness, fasciculations, spasticity, and speech/swallowing difficulties. Symptom overlap and unclear EMG findings can complicate diagnosis.

Design/Methods:
We present the case of a 49-year-old man referred to our ALS center due to an EMG showing widespread denervation and abnormal motor unit pathology across all myotomes. However, a strong family history of sudden cardiac death, along with clinical findings such as male-pattern baldness, facial weakness, action and percussion myotonia (also present in his two children), and diffuse areflexia, suggested an alternative diagnosis.

Results:
Genetic testing revealed 1,600–2,100 CTG repeats in the DMPK gene, confirming a diagnosis of DM1.

Conclusions:
This case highlights the challenge of differentiating ALS from MD when symptoms are unclear. Clinical evaluation, family history, and genetic testing are crucial for an accurate diagnosis.

21. Community Stroke Education at the Worcester Senior Center: A Global Health Project by UMass Neurology Residents, presented by Sarah-Pearl Siganporia, MD

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Authors:
Sarah-Pearl Siganporia, MD, Corinna Vannozzi, DO, Fabiola De Varona Colon, Kajol Doshi, MD, Anindita Deb, MD

Objective:
Improve community awareness of acute stroke and long term stroke management to foster stronger physician-patient relationships, and decrease fear surrounding neurologic disease like stroke. This will promote informed, proactive healthcare engagement.

Background:
Timely recognition and intervention play a critical role in improving outcomes in stroke. Older adults, who are at higher risk for stroke, often have gaps in knowledge and misconceptions regarding stroke symptoms and the importance of early medical attention. As part of the Global Health Track at UMass Neurology Residency, we implemented a community-based stroke education initiative to target local senior centers.

Design/Methods:
Neurology trainees designed and delivered an interactive stroke education session at the Worcester senior center in Worcester, MA. The session was advertised to seniors in the monthly senior center calendar and broadcasted via local radio.

Results:
138 people signed up to attend. Multiple cultural groups were reached through this education program due to provision of live interpreters for Arabic, Spanish, Mandarin, Portuguese, and Vietnamese.

Conclusions:
This community stroke education highlighted the effectiveness of interactive, trainee-led educational sessions in improving stroke awareness among older adults while fostering physician-patient relationships. Future initiatives will aim to expand outreach to additional local senior centers, broaden the scope of educational topics to other prevalent neurologic diseases, and address barriers specific to our local community. Integrating community education into neurology training equips residents with valuable public health experience and also contributes to broader efforts in stroke prevention and neurologic disease awareness.

22. Deep Learning Segmentation of Circumventricular Tissues to Facilitate Structural MRI Analysis in Multiple Sclerosis Patients, presented by Shridhar R. Singh

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Authors:
Shridhar R. Singh, Dan Tiamzon, Niels Bergsland, PhD, Michael Dwyer, PhD, Christopher C. Hemond, MD

Objective:
We aimed to create a deep learning pipeline to segment circumventricular tissue and relate their volumes to the clinical and MRI features of multiple sclerosis and other neurological diseases.

Background:
Circumventricular areas are implicated in neuroendocrine and immunomodulatory feedback loops; volumes of these structures are shown to be associated with MS diagnosis and disease severity.

Design/Methods:
This is a retrospective case-control study of 492 patients with relapsing-remitting MS (RMS), progressive MS (PMS), non-inflammatory neurological diseases (NIND), and other inflammatory neurological diseases (OIND). A Swin-UNETR deep learning model was trained on forty patients' T1 images with manual labels of the pituitary, pineal, and choroid plexus (CP). Model inference was used to obtain segmentations for the rest of the cohort. Tissue volumes were compared between groups using regression and ANCOVA adjusted for age, sex, and intracranial volume.

Results:
PMS patients had larger CP than RMS ($p=0.01$) and NIND ($p=0.04$) patients, and EDSS was positively correlated with CP volume ($p=0.04$). CP volume negatively correlated with thalamic volume ($p<0.001$) and positively correlated with T2-lesion volume (T2-LV) ($p<0.001$). Pineal volume negatively correlated with T2-LV ($p=0.003$) and positively correlated with thalamic volume ($p=0.02$). Pituitary volume decreased with age ($p=0.009$) and was larger in females ($p<0.001$).

Conclusions:
CP volume is associated with greater disease severity in MS and worse neurological disability. Both CP and pineal volumes track with indicators of MS pathology and are structures of high interest as potential imaging biomarkers and targets of therapy.

23. Global Transcriptomic Analysis of Multiple Isogenic Patient C9orf72 iPSC-Derived Neurons, presented by Aparna Sreeram

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Authors:
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Objective:
To identify reproducible altered transcriptomic changes across multiple C9orf72 patient iPSC-derived neurons.

Background:
Amyotrophic Lateral Sclerosis (ALS) is a motor neuron degenerative disease, primarily caused by C9orf72 repeat expansions. Despite understanding the mutation, the exact neurodegenerative process remains elusive. Transcriptomic analyses offer insights into molecular pathways, aiding biomarker and therapeutic discovery. However, current studies faces challenges in 1) heterogeneity between patient iPSC models with mixed neuron-glia populations, obscuring neuronal expression; (2) difficulty identifying reproducible cellular phenotypes across patients with no isogenic controls and (3) low sequencing depth, limiting detection of novel transcriptional changes.

Design/Methods:
Using four unrelated C9orf72 patient iPSC lines and their isogenic controls, we employed neurogenin-2 transcription factor-driven differentiation to generate homogeneous neuronal cultures (iCNs). High-read depth bulk RNA sequencing (100M paired-end reads, 2x150bp; n=3/line) was performed on two lines, with top hits validated on the remaining lines through qRT-PCR, ddPCR, and cellular phenotypes were assessed by immunostaining.

Results:
We identified consistent dysregulation in pathways related to extracellular matrix/cell adhesion, synaptic signaling, and cytoskeletal regulation, with increased expression of apoptotic gene-CTSF in all patient iCNs. Additionally, a common 300–600 genes exhibited splicing aberrations, including exon 30 skipping in Filamin B (FLNB), an actin-binding protein. This alteration was validated across multiple patient iCNs and associated with changes in FLNB's nuclear-cytoplasmic localization, impacting actin density and mechanosignaling.

Conclusions:
This study addresses prior limitations by using a homogeneous and isogenic patient iPSC neurons along with high-depth RNA sequencing to enhance resolution and show reproducible transcriptomic and cellular phenotypes changes across multiple patient C9orf72-ALS iCNs.

24. The Fazekas Score Predicts Cognitive Decline and Frailty in Older Adults: Insights from the SAGE-AF Prospective Cohort Study, presented by Bahadar S. Srichawla, DO

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Authors:
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Objective:
This study examined the association between Fazekas scores, cognitive impairment, and frailty over two-years in 86 participants from the SAGE-AF observational cohort, a prospective multicentered study of older adults with atrial fibrillation (AF).

Background:
White matter hyperintensities (WMH), visualized on neuroimaging and quantified by the Fazekas score, are linked to cognitive and physical impairments. However, their relationship with cognitive decline and frailty in older adults with AF remains underexplored.

Design/Methods:
WMH severity was assessed by two independent reviewers using the Fazekas score from magnetic resonance imaging of the brain completed prior to enrollment. Cognitive and physical function was measured using the Montreal Cognitive Assessment (MoCA), and Fried Frailty Phenotype respectively at baseline as well as at 1- and 2-year follow-up visits. Participants were characterized based on the severity of their white matter hyperintensities and compared to baseline, one-year, and two-year cognitive and physical functional status. Longitudinal regression models were used to adjust for demographic, clinical, and geriatric covariates.

Results:
Fazekas scores (grades 2–3) had significantly lower MoCA scores at baseline and at 2-year follow-up and were more likely to meet frailty criteria over two years. After adjusting for confounders, higher Fazekas scores were associated with a 2.6-fold increased risk of cognitive decline ($p=0.04$) and a 2.7-fold increased risk of frailty ($p=0.02$).

Conclusions:
Higher Fazekas scores are linked to both cognitive decline and frailty in older adults with AF. WMH as measured using the Fazekas score may serve as a crucial imaging biomarker for aging-related cognitive and physical impairment.

25. Genome-wide CRISPR Knockout Screen Reveals Human Genes Contributing to Alzheimer's Disease Pathology in HSV-1 Infected Cerebral Organoids, presented by Jon Sundstrom

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Authors:
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Objective:
We aim to identify human genes involved in neuroinflammation-induced Alzheimer's disease (AD) cellular pathologies. We utilized a genome-wide CRISPR/Cas9 knockout library (Brunello) to generate mutations and sorted edited cells from herpes simplex virus 1 (HSV-1)-infected dissociated cerebral organoids (dcOrgs) based on expression intensities of AD pathological biomarkers such as Abeta42, aggregated Abeta, and monomeric Abeta.

Background:
AD is a neurodegenerative disease, causing progressive deterioration of cognitive function. There may be many contributing factors to AD pathology, including viral infections such as HSV-1 infection. AD has several biomarkers, including intracellular accumulation of Abeta42, extracellular deposits of amyloid beta plaques, and neurofibrillary tangles in the brain.

Design/Methods:
We used nucleofection to introduce the Brunello plasmid library into dcOrgs. Edited cells were then infected with HSV-1, stained with an antibody to detect Abeta42, aggregated Abeta (aducanumab), or monomeric Abeta (solanezumab), and FACS sorted based on infection status and Abeta expression within the infected population. Plasmid DNA was extracted from the sorted cells and amplified using PCR. We used next-generation sequencing to identify sgRNAs associated with the sorted groups and compared proportions of the sgRNAs within each sorted group to non-targeting sgRNA controls.

Results:
In HSV-1-infected dcOrgs, the three Abeta antibodies were positively correlated with infection. We found that genes involved in immune pathways were differentially expressed in high vs low Abeta1-42-sorted dcOrgs infected with HSV-1.

Conclusions:
Identifying human genes that can modulate Abeta expression in HSV-1-infected cells can identify therapeutic targets and biomarkers for a subset of AD patients whose pathology may be due to neuroinflammation.

26. Thrombolysis for Stroke in those with Advanced Age, Disability, and Dementia: A Case Report, presented by Michael Tokov, DO

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Authors:
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Objective:
To elucidate the risk and benefit of thrombolytic therapy in acute ischemic stroke (AIS) for those with advanced age, disability, and dementia.

Background:
AIS is one of the most common causes of mortality in the elderly. Modalities of acute treatment in AIS in the elderly present a clinical conundrum as there is often a balancing of the benefit of thwarting poor prognosis versus the risk of intracranial hemorrhage. Balancing these factors in acute stroke treatment remains an ongoing discussion in the stroke literature for this particular patient population.

Design/Methods:
We present a 99-year-old woman with dementia and cardiovascular risk factors who presented to our center with a moderate to severe AIS. The patient was a candidate for prompt thrombolytic therapy and was subsequently treated with intravenous tenecteplase. After the fact, numerous old microbleeds on MRI were detected on stroke work up. These findings were not previously known during acute intervention. Chart review and literature review were retrospectively performed to understand how this case fits into the current paradigm of acute stroke treatment.

Results:
Over the course of this patient's 10-day admission, there was demonstration of significant improvement in stroke symptomatology despite numerous microbleeds concerning for possible cerebral amyloid angiopathy.

Conclusions:
This case represents a patient who might not ordinarily be treated with thrombolysis due to her advanced age and poor functional baseline, but with careful consideration of her candidacy for thrombolysis we found that acute stroke treatment led to significant improvement in symptoms as well as preservation of quality of life.

27. Examining Cadmium-Induced Changes in Alzheimer's Disease Markers and Neuroinflammatory Pathways Using Cerebral Organoids, presented by Khanh Tran, BS

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Authors:
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Objective:
Our objective is to investigate how cadmium exposure alters molecular pathways related to neuroinflammation and gene expression regulation in Alzheimer's disease (AD). We aim to quantify and characterize inflammatory and AD-related markers using flow cytometry and ELISA.

Background:
Cadmium (Cd), a toxic heavy metal, has been linked to neurodegenerative diseases, including AD. Elevated Cd levels have been detected in the plasma and brain tissue of AD patients, but the mechanisms underlying its role in AD remain unclear. Given its environmental prevalence and neurotoxic effects, this study examines how Cd exposure alters AD-related molecular markers in a cerebral organoid model.

Design/Methods:
Human dissociated cerebral organoids were exposed to cadmium chloride ($CdCl_2$) for 24 hours, with zinc chloride ($ZnCl_2$) as a negative control. Flow cytometry was used to assess changes in AD's-associated markers, including amyloid precursor protein (APP), amyloid-beta (Aβ) species, phosphorylated tau isoforms, and cell-type-specific markers for neurons, astrocytes, and oligodendrocytes. Additionally, cytokine profiling was performed using a multiplex ELISA assay to evaluate Cd-induced changes in neuroinflammatory mediators.

Results:
$CdCl_2$ exposure led to increased intracellular APP, Aβ species, and phosphorylated tau isoforms compared to $ZnCl_2$-treated controls. Flow cytometry revealed significant changes in neuron, astrocyte, and oligodendrocyte markers, while cytokine profiling indicated altered inflammatory responses.

Conclusions:
Cd exposure exacerbates Alzheimer's disease pathology by increasing AD-associated markers and modulating cellular and cytokine profiles in a cerebral organoid model. These findings highlight the neurotoxic potential of cadmium and its role in altering key processes implicated in AD pathogenesis.

28. Chromatin folding and transcriptome dynamics during maturation of normal and ALS C9orf72 motor neurons, presented by Ozgun Uyan, PhD

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Objective:
To investigate chromatin folding and corresponding transcriptomic changes during the maturation of motor neurons (MNs) from healthy individuals and ALS patients with C9orf72 mutations.

Background:
Motor neurons (MN) have a critical role in the central nervous system by controlling voluntary and involuntary movements in the body. Loss of motor neurons can cause several chronic and fatal motor neuron disorders, such as amyotrophic lateral sclerosis (ALS). The most common cause of ALS is the hexanucleotide repeat (GGGGCC) expansion (HRE) detected in the first intron of the chromosome 9 open reading frame 72 (C9orf72) gene.

Design/Methods:
We utilized 3C-based chromosome conformation technologies and RNA sequencing to analyze genome folding and transcriptomic profiles in two healthy and two ALS patient-derived cell lines harboring C9orf72 mutations. Analyses were conducted during reprogramming, neural differentiation, and MN maturation.

Results:
We show that MNs require long term maturation to establish proper transcriptome and genome folding. Moreover, we detect enriched interaction patterns among telomeric and centromeric regions in MNs compared to fibroblast and iPSC lines. In disease state, C9orf72 HRE mutation does not cause any alteration in fibroblast and IPSC lines. However, we observe several defects in C9-ALS MNs such as long-range and heterochromatic interaction abnormalities in genome folding, impaired pathways that are crucial for maturation and reduced expression levels of mitochondrial encoded genes in transcriptomic profiles.

Conclusions:
C9-ALS motor neurons exhibit defects in chromatin architecture and transcriptome regulation, particularly at matured state, providing insight into the molecular mechanisms underlying ALS pathology.

29. Microglial Dysfunction in Models of ALS/FTD TDP-43, presented by Elenore A. Wiggin

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Objective:
To investigate the impact of endogenous TDP-43 dysfunction on microglial function.

Background:
The RNA binding protein TDP-43 is a key pathological factor in multiple neurodegenerative disorders, including ALS/FTD. Much has been learned about TDP-43 in neurons, but less is known about the impact of TDP-43 dysfunction in immune cells. Microglia are the predominant innate immune cell in the CNS and are important for responding to traumatic brain injury (TBI).

Design/Methods:
We utilized a human iPSC-derived microglial model harboring CRISPR-induced ALS/FTD associated mutations (Q331K, M337V) to examine endogenous TDP-43 dysfunction in microglia-like cells (iMGs). Furthermore, we subjected a knock-in TDP-43 Q331K+/+ mouse model to TBI and characterized differences in response to injury relative to WT mice.

Results:
Transcriptomic analysis of TDP-43 Q331K iMGs revealed diminished myelocytomatosis (Myc) signaling and altered splicing events in targets related to replication. Immunofluorescent imaging revealed diminished nuclear size consistent with diminished proliferation. Quantitative PCR on whole-brain samples from TDP-43 Q331K+/+ mice revealed dampened homeostatic cytokine expression in mutant versus WT mice, consistent with our iMGs. Upon LPS treatment, TDP-43 Q331K iMGs secreted elevated levels of chemokine CCL5 compared to WT iMGs. CCL5 and MCP1 expression were elevated in TDP-43 Q331K+/+ mice after TBI, coinciding with heightened neurological deficits and signs of chronic inflammation.

Conclusions:
We propose a model in which the loss of homeostatic immune signaling due to TDP-43 dysfunction primes the CNS for dysregulated innate immune response after injury. This may implicate Myc signaling as a therapeutic target for ALS/FTD.

30. Thalamic and Deep Grey Nuclei Atrophy in Parkinson's Disease Progression, presented by West WJ Williams

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Objective:
The purpose of this research is to use current neuroimage processing tools and statistical analysis methods to characterize thalamic and other deep grey nuclei volumetry in Parkinson's Disease vs prodromal patients and healthy controls.

Background:
If there is a correlation found between a change in nuclei volumes and progression in Parkinson's Disease, this would provide medical caregivers with another means to identify the disease in patients at risk.

Design/Methods:
MRI image data from the Parkinson's Progression Markers Initiative database was analyzed using THOMAS, a program for accurate segmentation of thalamic and other deep grey nuclei. THOMAS provided volume data for each of the nuclei, which was standardized and compared to the patient's clinical data derived from the PPMI curated dataset from December 11, 2024. The patient's cognition data was assessed with mild cognitive impairment test scores and their Montreal Cognitive Assessment score. The patient's motor outcomes were derived from their TD/PIGID classification and their MDS-UPDRS part III and part IV scores. Patients with PD were compared to prodromal patients and healthy controls at three time points as available data allowed.

Results:
This research is still in progress, so the results are not yet collected. Nuclei will be looked at individually to determine if specific nuclei across multiple patients consistently show atrophy when PD is more progressed.

Conclusions:
The data presents the opportunity for further development of the understanding of how Parkinson’s Disease affects brain anatomy and may contribute to ongoing research for new methods of detecting Parkinson’s Disease in patients at risk.

31. Evaluating the Effectiveness of a Mobile Mindfulness Application on Quality of Life in Patients with Multiple Sclerosis, presented by Molly Wilner, DO

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Authors:
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Objective:
The aims of this current study are to assess the acceptability and efficacy of mobile mindfulness application in people with MS (pwMS), and to compare application use to a mindfulness-based course at the same multiple sclerosis center.

Background:
Multiple sclerosis (MS) is a chronic autoimmune disease commonly associated with anxiety, depression, stress, fatigue, pain, and cognitive impairment. These symptoms negatively impact patients' quality of life (QoL), and unfortunately, current pharmaceutical interventions do not address them. Given this treatment gap, there has been a growing effort focused on approaches to improve the wellbeing of pwMS as an adjunctive to pharmaceutical interventions. Mindfulness-based interventions have been shown to be effective in reducing pain, anxiety, depression, fatigue, improving QoL, and improving processing speed in pwMS. Recent studies have shown that online mindfulness-based interventions are acceptable and effective for pwMS.

Design/Methods:
We plan to assess pre and post mobile mindfulness applications changes in metrics for perceived stress, depression, anxiety, quality of life, and fatigue; compare a mobile mindfulness application to a mindfulness-based course at the same multiple sclerosis center.

Results:
During this eight week pilot, we expect adherence and acceptance of a mobile mindfulness application, and a reduction in psychological measures of distress equally, if not greater than, the reduction seen in the use of a mindfulness-based course.

Conclusions:
Mobile mindfulness applications are increasing in popularity and allow for short daily exercises. To our knowledge, no studies have explored the potential benefits of mobile mindfulness applications in pwMS, but given easier accessibility we expect it to provide benefit.