ABSTRACT BOOK

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Session 1: Neuro-immunology of the Peripheral Nervous System

RISK OF NEW-ONSET MYASTHENIA GRAVIS FOLLOWING COVID-19 INFECTION AND VACCINATION: A POPULATION-BASED CASE-CONTROL STUDY

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Background: The potential link between myasthenia gravis (MG) and COVID-19 infection or vaccination remains unclear. This study aimed to evaluate the relationship between these factors and new-onset MG.

Methods: A case-control study was conducted using Clalit Health Services` database. We applied a machine learning algorithm to reduce diagnostic misclassification. The study examined adults with new onset MG, aged 18 or older between January 2020 and December 2022 for COVID-19 infection (Cohort I) and between January 2021 and December 2022 for Pfizer-BioNTech COVID-19 vaccine (Cohort II). For each new MG case, three controls matched by age and sex were selected. Prior exposure to either infection or vaccination was assessed within 90 and 180 days for cases and controls.

Results: In cohort I, 253 new MG cases were identified. A multivariate logistic regression model showed an odds ratio (OR) of 1.44 (95% CI 0.708–2.92) within 90 days post-infection and 1.67 (95% CI 0.98–2.84) within 180 days. In the cohort II, 177 new MG cases were detected, with an OR of 1.76 (95% CI 1.049–2.95) within 90 days post-vaccination and 2.45 (95% CI 1.51–3.95) within 180 days.

Conclusions: This study suggests no significant increased risk of new-onset MG following COVID-19 infection, but Pfizer-BioNTech vaccine appears to be associated with a higher risk of developing MG, particularly within 180 days of vaccination.

IMMUNE CHECKPOINT DOWNREGULATION AND NEGATIVE CORRELATION OF TIGIT EXPRESSION WITH ADL SCORES IN MYASTHENIA GRAVIS

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Background: Myasthenia Gravis (MG) is an autoimmune neurological disorder characterized by impaired transmission at the neuromuscular junction leading to muscle weakness and fatigue. Recent studies indicate that immune checkpoint inhibitors play a significant role in MG, as their use has been associated with the worsening or onset of the condition.

Methods: We analyzed the mRNA expression levels of immune checkpoints (CTLA-4, PD-1, LAG-3, and TIGIT) in peripheral blood mononuclear cells (PBMC) of 28 untreated MG patients and 33 healthy controls (HCs) using RT-PCR. We correlated these findings with the annualized ADL-MG score, clinical and demographic information.

Results: The expression of LAG-3, PD-1, TIGIT, and CTLA-4 were significantly decreased in MG patients compared to HCs. We found a significant negative correlation between TIGIT expression and their MG-ADL score. No correlation was found between the mRNA expression of immune checkpoint receptors and age, gender, disease duration, and seropositivity.

Conclusions: Our findings of significant downregulation of LAG-3, TIGIT, PD-1 and CTLA-4 in MG patients compared to HCs suggests that these pathways might be involved in MG pathogenesis. The negative correlation between TIGIT expression and MG-ADL scores emphasizing its potential as a biomarker. In conclusion, these findings open avenues for targeted therapies aimed at restoring immune checkpoint function to modulate the autoimmune response in MG.

BRONCHIECTASIS IN MYASTHENIA GRAVIS: A CLINICALLY RELEVANT COMORBIDITY DEFINING A HIGH-RISK TRIAD WITH THYMOMA

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Background: Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction that causes fluctuating muscle weakness, which may involve respiratory muscles and, in some cases, progress to a myasthenic crisis. Comorbid respiratory disease may increase this risk. Bronchiectasis (BE), a chronic airway disease with a prevalence of 234 per 100,000 in Israel, has been described in association with thymic tumors and Good syndrome. However, its prevalence and clinical relevance in MG remain undefined.

Methods: We conducted a retrospective cohort study of 238 patients with MG followed at Tel Aviv Sourasky Medical Center. Demographic, clinical, and immunological data were systematically abstracted from medical records, and high-resolution chest CT confirmed the diagnosis of BE. For comparison, we evaluated a cohort of 111 patients with thymoma but without MG to determine BE prevalence. Group-level differences were assessed using Fisher's exact test. Multivariable logistic regression models were fitted to estimate the independent and combined effects of MG and thymoma on BE risk, including formal interaction testing. Associations are reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

Results: BE was more frequent in patients with both MG and thymoma (19.6%) compared to MG without thymoma (5.9%, OR 3.9, 95% CI 1.6–9.8, $p = 0.0047$), thymoma without MG (3.6%, OR 6.5, 95% CI 1.9–22, $p = 0.0016$), and the general population (0.23%). When compared with the general population, odds ratios for BE were markedly elevated across all subgroups: 104.0 (95% CI 51.5–210.0, $p = 7.2 \times 10^{-17}$), 26.6 (95% CI 14.3–49.7, $p = 1.9 \times 10^{-12}$), and 15.9 (95% CI 5.8–43.6, $p = 1.5 \times 10^{-4}$), respectively. Bulbar symptoms were not associated with BE ($p = 0.500$). Both MG and thymoma independently increased the risk of BE, but a negative interaction term ($\beta = -1.41$, $p = 0.043$) suggested overlapping mechanisms rather than additive effects. Clinically, BE was associated with a higher risk of myasthenic crisis (30.4% vs. 6.7%, OR = 6.1, $p = 0.0017$), especially in the presence of thymoma (60% vs. 8.3%, OR = 16.5, $p = 0.020$).

Conclusions: Bronchiectasis is an underrecognized but clinically relevant comorbidity in MG, particularly with thymoma, forming a triad associated with a high-risk disease phenotype. Its presence may reflect an autoimmune-mediated form of BE linked to the MG-thymoma spectrum.

TEMPORAL DYNAMICS OF PERIPHERAL NERVE EXCITABILITY FOLLOWING COMPLETE FREUND'S ADJUVANT-INDUCED INFLAMMATION IN MICE

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Background: Inflammation plays a critical role in the pathogenesis of pain and peripheral neuropathies. This study investigated how Complete Freund's Adjuvant (CFA)-induced local inflammation alters peripheral nerve excitability over time and examined associated immune responses.

Methods: Adult male ICR mice received unilateral hind paw injections of CFA or saline and were assessed at 1, 3, and 7 days post-injection. Nocifensive behavior and thermal hypersensitivity were measured. *Ex vivo* sciatic nerve recordings evaluated large fiber excitability. Systemic inflammation was assessed by measuring serum levels of C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α). Immune cell infiltration in the sciatic nerve was quantified using CD45 immunofluorescence. Thrombin activity was measured in skin. Schwannoma cells stimulated with lipopolysaccharide (LPS) were analyzed for expression of complement and coagulation-related genes.

Results: CFA produced a biphasic shift in large fiber nerve excitability: initial hypoexcitability at day 1, followed by hyperexcitability at day 7. Increased pain behaviors and thermal hypersensitivity paralleled these physiological changes. Systemic inflammatory markers were transiently increased, whereas thrombin activity in skin remained elevated. CD45 immune cell infiltration was demonstrated in CFA-nerves. LPS treatment of Schwannoma cells *in vitro*, altered the expression of complement receptors and thrombin-related transcripts.

Conclusions: These results demonstrate that peripheral inflammation is associated with temporally distinct changes in nerve excitability, coinciding with systemic and local immune responses. The observed patterns suggest that inflammation may influence the progression of excitability changes over time. These findings provide a foundation for further investigation into immune-related modulation of peripheral nerve function in inflammatory conditions.

REAL-WORLD OUTCOMES OF EFGARTIGIMOD IN ACHR- POSITIVE GENERALIZED MYASTHENIA GRAVIS: RESPONSE PATTERNS, PREDICTORS AND TREATMENT STRATEGIES

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Background: Efgartigimod, a neonatal Fc receptor antagonist, lowers pathogenic IgG and has shown efficacy in generalized myasthenia gravis (gMG). Real-world data on long-term outcomes, steroid-sparing, bridging strategies, and predictors of response remain limited.

Methods: This multicenter, retrospective study included 46 adult patients treated at 7 tertiary centers between April 2022 and March 2025. Primary endpoints were improvement in MG-ADL and minimal symptom expression (MSE). Secondary endpoints included corticosteroid reduction, bridging success, and safety.

Results: The patients received 197 cycles at a mean interval of 9.8 weeks. 40 (86.9%) patients achieved a ≥2-point improvement in MG-ADL and 20 (43.5%) patients reached MSE after the first cycle, while 24 (52.2%) achieved MSE at any point. Overall 36 (78.3%) patients maintained a ≥2-point improvement in MG-ADL, with response patterns ranging from cyclical benefit to sustained remission, although 14 (35.9%) patients discontinued treatment due to insufficient efficacy. The prednisone dose was reduced in 17 of the 29 (58.6%) treated patients (from a mean of 30.9 to 16.8 mg/day, p=0.001), with a shorter disease duration independently predicting success. Bridging therapy was successful in a subset of 5 patients, particularly among the those receiving azathioprine or mycophenolate (OR=15.0, p=0.040). Adverse events were mild and occurred in 10 (21.7%) patients.

Conclusions: In real-world practice, efgartigimod was effective and well-tolerated in AChR-positive gMG. Distinct response patterns, a steroid-sparing effect linked to shorter disease duration, and successful bridging therapy in the presence of immunosuppressant support its role in personalized treatment strategies. Prospective validation of its use is warranted.

Session 2: Aging and Neuroimmunology

EARLY NEURONAL-GLIAL REPROGRAMMING AND CELL CYCLE RE-ENTRY SHAPE THE ALZHEIMER'S DISEASE CASCADE

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by synaptic dysfunction, neuronal loss, and dementia. Large-scale efforts to map the cellular cascade in human brains have revealed coordinated glial responses, emerging early in disease and may drive its progression. Yet, the nature of neuronal reprogramming, its dynamics across subtypes, and its coordination with glia remain poorly understood.

Methods: We applied non-negative matrix factorization (NMF) to 1.7 million single-nucleus RNA profiles obtained from 437 human prefrontal cortex samples spanning healthy aging to AD. This approach enabled us to decompose transcriptional variation into biologically interpretable programs. We next aligned these programs to disease progression and validated the findings in independent datasets, including snRNA-seq cohorts, proteomics, and targeted ELISA assays. Comparative analyses against alternative brain aging allowed us to distinguish AD-specific molecular changes from those associated with alternative aging.

Results: This analysis uncovered diverse neuronal and glial programs dynamically regulated along the disease cascade. Neurons exhibited an early coordinated shift across subtypes, validated in independent datasets. Two major neuronal trajectories were identified: one associated with oxidative stress and apoptosis, and another with DNA damage response and cell cycle re-entry, the latter linked to increased survival.

Mapping programs along progression clarified the temporal sequence of changes. We observed an early, global decline in glial homeostatic programs, accompanied by a rapid decrease in neuronal mitochondrial–ribosomal gene expression and a slower modulation of synaptic programs. Alignment across cell types revealed that synaptic dysfunction in neurons coincides with reduced neurotransmitter transport in astrocytes and synaptic pruning in microglia. Comparing AD to alternative aging highlighted AD-specific foam-lipid metabolism in microglia, stress responses in astrocytes, and myelin and cholesterol impairment in oligodendrocytes. These later changes mark the onset of a synchronized phase of neuronal and glial stress and accelerated synaptic loss.

Conclusions: Together, our findings define coordinated neuronal-glial programs as key drivers of AD progression. By resolving the temporal order of molecular changes and distinguishing AD-specific signatures from alternative aging, this study provides a framework for understanding how neuronal reprogramming and glial states interact to drive disease.

HPG AXIS DYSREGULATION IN AGING IMPACTS BLOOD-BRAIN BARRIER INTEGRITY AND ALZHEIMER-LIKE DISEASE PATHOLOGY

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Background: Age-related dysfunction of the blood-brain barrier (BBB) is increasingly linked to Alzheimer`s disease (AD) pathogenesis. In addition, women exhibit higher AD susceptibility at the post-menopause stage, a phenomenon which is often associated with dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis and elevated levels of the gonadotrophins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Here we investigated the direct role of FSH in modulating the BBB integrity as a potential mechanism linking age-related dysregulation of the HPG axis to AD vulnerability.

Methods: BBB structural integrity was evaluated with Western blot and immunohistochemistry of key endothelial regulatory and junctional proteins, while functionality was analyzed using trans-endothelial permeability assays.

Results: We show that aging in mice was associated with increased levels of circulating FSH and that FSH levels negatively correlated with endothelial expression of activin-like kinase 1 (ALK1) and Endoglin, the junctional proteins VE-Cadherin and Occludin. Notably, these age-related vascular changes occurred in female but not in male mice. In vitro, FSH treatment downregulated the expression of ALK1, Endoglin, VE-Cadherin, and Occludin in primary brain microvascular endothelial cells as well as compromised their permeability to high molecular weight dextran molecules. Mechanistically, FSH impaired the canonical ALK1 signaling, evidenced by reduced SMAD1/5 phosphorylation in response to its ligand BMP9.

Conclusions: Our findings identify FSH, a key indicator of HPG axis dysregulation in female aging, as a potent negative regulator of BBB integrity. Our study may thus highlight a novel hormonal mechanism potentially underlying the heightened female vulnerability to AD via cerebrovascular pathology following menopause.

CHARTING THE IMPACT OF GLYCEMIC STRESS ON CEREBROVASCULAR VULNERABILITY

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Background: Transient hyperglycemia resulting from metabolic demands and various stressors has been associated with poorer outcomes in ischemic stroke and long-term effects on vascular patency. But how does blood glucose fluctuation affect the brain's delicate vasculature?

Methods: Using real-time multiphoton imaging and ultrashort laser pulses in awake mice, we model microvascular injury under controlled glycemic conditions.

Results: We show that both chronic and transient hyperglycemia significantly worsen vascular damage—exacerbating serum leakage, thrombosis, microaneurysm formation, and impairing microglial clearance. Extending our analysis to arterioles and capillaries, we also explore the role of oxidative stress, nitric oxide depletion, and altered blood cell phenotypes in this heightened vulnerability.

Conclusions: Our platform offers a powerful tool to unravel how metabolic stress shapes cerebrovascular pathology—laying the groundwork for glucose-monitoring strategies to protect brain health.

Session 3: B Cells and CNS Demyelinating Diseases

REDUCED TOLEROGENIC FACTOR sCD83 IN NMOSD AND RELAPSING MOGAD: A POTENTIAL NEW THERAPEUTIC PATHWAY

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Background: Neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are autoimmune disorders of the central nervous system whose immune mechanisms remain incompletely understood. CD83, a molecule known to play a pivotal role in the induction and maintenance of immune tolerance, may represent an important factor in shaping disease activity and treatment response. This study aimed to evaluate CD83 expression in NMOSD and MOGAD and to explore its potential role as a disease severity biomarker.

Methods: RNA extracted from PBMCs of patients with MOGAD, NMOSD, multiple sclerosis (MS, and healthy controls (HCs) was analyzed to quantify CD83 expression. Soluble CD83 (sCD83) concentrations were measured in CSF and serum by ELISA. In addition, the effects of therapeutic agents commonly used in CNS demyelinating diseases on sCD83 levels were examined. The study included 231 untreated participants: 64 MOGAD, 56 NMOSD, 47 MS, and 64 HCs.

Results: NMOSD patients exhibited significantly reduced sCD83 levels compared to MOGAD and HCs. In both NMOSD and MOGAD cohorts, lower sCD83 levels were associated with greater disease severity. Treatment with IVIG led to a significant increase in serum sCD83 in MOGAD patients, and in vitro exposure to immunosuppressive drugs also elevated sCD83.

Conclusions: Our findings demonstrate lower sCD83 levels in NMOSD and relapsing MOGAD patients, with therapeutic interventions leading to marked increases. This suggests that sCD83 may function both as a prognostic biomarker and as a indicator of treatment response, while also highlighting its promise as a potential therapeutic target in CNS demyelinating disorders.

A PREDICTIVE MODEL FOR TRIPLE NEGATIVE OPTIC NEURITIS PATIENTS: IDENTIFYING THE SUBSET OF PATIENTS WITH FAVORABLE OUTCOMES

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Background: A subset of optic neuritis (ON) patients remains seronegative for AQP4-IgG, MOG-IgG, and CSF oligoclonal bands (OCBs), complicating diagnosis and management. This study aimed to characterize these triple-negative ON (TNON) cases and compare them to MS, MOGAD, and NMOSD.

Methods: We retrospectively analyzed 103 patients with a first ON episode tested for AQP4-IgG, MOG-IgG, and OCBs, classifying them into MS (n=26), MOGAD (n=25), NMOSD (n=13), and TNON (n=39). TNON was further divided into evolving MS (evMS) and idiopathic TNON. A support vector machine (SVM) was used to classify TNON based on onset data.

Results: TNON patients showed less optic disc edema and radiological involvement than MOGAD and responded more poorly to steroids. However, TNON had lower relapse rates and less need for chronic treatment than MS or NMOSD. SVM analysis revealed that most evMS cases clustered with MS, while idiopathic TNON aligned more closely with MOGAD.

Conclusions: TNON is a heterogeneous entity encompassing both early MS and a distinct idiopathic subgroup. While clinical features alone could not differentiate these subgroups, our predictive model successfully stratified them at onset. Idiopathic TNON may reflect an undetected antibody-mediated process with a generally favorable prognosis.

Session 4: Clinical Neuro-immunology

UNLOCKING THE MYSTERIES OF FIBROMYALGIA SYNDROME (FMS): EXPLORING EXTRACELLULAR VESICLES (EVS) AS NEW PROMISING BIOMARKERS

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Background: Fibromyalgia (FM) is a chronic pain condition affecting 3-6% of the population, with unclear etiology involving neurological, mitochondrial, and immune dysregulation. Symptoms include fatigue, pain sensitization, sleep disruption, cognitive dysfunction ("Fibro-fog"), and frequently small fiber neuropathy, reflecting central nervous system dysregulation. Lack of a lab test delays diagnosis, highlighting urgent biomarker need.

Extracellular vesicles (EVs) are nanoscale, lipid bilayer particles released by cells, including neurons and immune cells. They mediate intercellular communication and participate in immune signaling, inflammation, and stress responses via their bioactive cargo (RNA, DNA, proteins) and ability to cross the blood–brain barrier making them promising diagnostic biomarkers.

Methods: In this study, we characterized circulating EVs in FM patients and compared their protein profile with that of healthy controls. Plasma-derived EVs were isolated using iodixanol density gradient combined with size exclusion chromatography and analyzed using nanoparticle tracking analysis, transmission electron microscopy (TEM) and western-blot analysis.

Results: Preliminary proteomic analysis of plasma EVs from FM patients shows distinct profiles versus controls, containing proteins unique to FM related to immune regulation (e.g. Complement), mitochondria (e.g., ATP5), neuronal activity (e.g. Cofilin-1), and oxidative stress (Superoxide dismutase). Our initial in-vitro studies indicate that EVs derived from Fibromyalgia patients increase secretion of pro-inflammatory cytokines (e.g., IFN-γ, IL-17A, IL-6, IL-1β) from LPS/PHA-activated human PBMCs, potentially promoting chronic pain by activating glial cells and sensitizing dorsal root ganglion neurons.

Conclusions: Investigating neuro-immune interactions and the `hidden` information within EVs in FM could reveal deeper insights into the disease mechanism. Our findings highlight their promising potential to improve both diagnostics and personalized treatment.

BACILLUS CALMETTE-GUERIN IMPACT ON ALZHEIMER'S DISEASE, POSSIBLY VIA THE UNFOLDED PROTEIN RESPONSE.

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Background: Treatment with intravesical instillations of Bacillus Calmette Guerin (BCG), in non-muscle invasive bladder cancer (NMIBC) patients, reduced the rate of Alzheimer's disease (AD) by 4-fold. Public vaccination against other pathogens has also reduced AD incidence. This implicates non-specific immunocyte activation in protecting against infections and, in the long run, against AD. Beta amyloid (considered bactericidal) appears in CNS plaques as a hallmark of AD, which may be viewed as unresolved protein aggregates, indicating a failed unfolded protein response (UPR) to endoplasmic reticulum (ER) stress. Abnormal UPR proteins reported in AD brain autopsies raise the hypothesis that the UPR insufficiency is part of AD pathogenesis, preventable by BCG via UPR signaling enhancement.

Methods: In a pilot study, we used protein extracts of peripheral blood mononuclear cells (PBMCs) from NMIBC patients treated with BCG protocols (which previously prevented AD). Immunoelectrophoresis of post-BCG proteins was compared with pre-BCG proteins of the same patients as controls, using the Abby instrument of microcapillary electrophoresis (Protein-Simple, San-Jose, CA).

Results: ER stress sensing proteins, an ER chaperone, two transcription factors, and the translation integrator of ER stress response, belonging to the main UPR pathway, responded heterogeneously to BCG treatment. The heterogeneity of the response to BCG may reflect the heterogeneity of the clinical protection against AD in humans.

Conclusions: The impact of BCG on the UPR by this pilot study is compelling, underscoring the need to expand studies in larger groups of patients and deepen the analysis biochemically for PBMCs` possible interactions with brain cells.

ANTI LGI1 ENCEPHALITIS, BEYOND THE LIMBIC SYSTEM - PERSISTENT EXECUTIVE DYSFUNCTION IN LONG-TERM FOLLOW-UP

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Background: Cognitive decline in anti LGI1 encephalitis is mostly assumed to be predominantly of short term memory. Executive deficits are often considered transient, but their persistence has not been systematically examined. Objectives: To investigate long-term cognitive trajectories in LGI1-AE, with a particular focus on executive function and its persistence over time.

Methods: A retrospective cohort study of 18 patients with LGI1-AE followed at a single tertiary center between 2015 and 2025. Cognitive function was assessed longitudinally using domain-specific subscales from the Montreal Cognitive Assessment (MoCA), including a broad Executive Index Score (EIS) assessing executive function and delayed recall.

Results: Over a median follow-up of 41.2 months, global cognition, memory, and executive function improved significantly; Median MoCA scores increased from 20 at baseline to 24 at last follow-up ($p = 0.001$) and the EIS (executive) rising from 9 to 10 ($p = 0.001$). Delayed recall increased from 1 to 2.5 ($p = 0.024$). However, executive function remained the most persistently impaired domain, particularly among older patients (65 years). At last follow-up, despite similar treatment timing, older patients exhibited more severe and persistent deficits than younger patients in total MoCA (19 vs. 26, $p = 0.016$) and EIS (9.5 vs. 12.5, $p = 0.009$).

Conclusions: Executive dysfunction is a prominent and persistent long-term cognitive deficit in LGI1-AE, challenging previous assumptions that it is predominantly transient. Additionally, patients older then 65 have worse cognitive outcomes than younger patients. These findings emphasise the need for domain-specific cognitive monitoring and targeted rehabilitation, particularly for older adults.

THE IMPACT OF COGNITIVE BEHAVIORAL AND MINDFULNESS INTERVENTION ON GUT-IMMUNE-BRAIN INTERACTIONS IN CROHN`S DISEASE

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Background: Crohn's disease (CD) is a chronic inflammatory disorder characterized by immune dysregulation, microbial imbalance, and metabolic alterations. The gut–immune–brain axis, shaped by the hypothalamic–pituitary–adrenal (HPA) axis and cortisol dynamics, has emerged as a promising therapeutic target.

Methods: We investigated the effect of a Cognitive-Behavioral and Mindfulness with Daily Exercise (COBMINDEX) intervention on immune regulation, microbiome composition, and metabolic signatures in CD. Patients were studied at baseline (T1), after 3 months of intervention (T2), and at one-year follow-up (T5). Participants were stratified into top and poor responders according to responsiveness scores.

Results: COBMINDEX led to reductions in CRP, calprotectin, and pro-inflammatory cytokines at T2, accompanied by improved cortisol regulation. Top responders demonstrated restoration of $CD4^+$ and $CD8^+$ T cell profiles and reduced pro-inflammatory cytokine networks. Microbiome analyses at T2 revealed increased alpha diversity and beta diversity shifts toward healthy-like profiles, with taxa such as Coprococcus, a key short-chain fatty acid (SCFA) producer, enriched in responders. At T5, these changes were sustained, with durable immune improvements and metabolomic signatures involving bile acids, taurine, mitochondrial pathways, and SCFAs.

Conclusions: These findings highlight the ability of COBMINDEX to induce both short-term (T2) and long-term (T5) improvements across immune, microbial, and metabolic axes in CD, supporting the development of biomarker-based strategies to predict responsiveness to psychosocial interventions.

HEAVY METAL MAYHEM: IS CADMIUM ROCKING THE MS BOAT?

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Background: Multiple sclerosis (MS) is a multifactorial disease of uncertain etiology damaging myelin sheaths around axons of the central nervous system. Myelin protects the axon from potentially harmful exogenous factors. The aetiological role of environmental exposure to heavy metals is unclear.

Objective: Identify whether urinary levels of metals differed in MS patients and healthy controls.

Methods: We recruited 49 MS patients from Ziv Medical Centre and 37 healthy controls. MS patients were evaluated according to Expanded Disability Status Scale into mild and moderate-severe conditions. Each participant provided a urine sample and completed epidemiological questionnaires. The levels of six metals (Aluminum, Cadmium, Chromium, Lead, Mercury, Nickel) and one metalloid (Arsenic) were measured in urine using inductively coupled plasma-mass spectrometry. We compared cases with controls in terms of their levels in urine of these compounds using the Mann-Whitney and Kruskall-Wallis tests.

Results: Urinary cadmium and mercury levels were higher in MS patients than controls (p0.01). Cadmium levels were higher in moderate-severe MS patients (n=24) than in mild MS patients (n=25) (p=0.003).

Conclusions: Urinary Cadmium and mercury levels were higher among MS patients than controls. Cadmium levels correlated with disease severity, suggesting a potential role in disease progression. Further studies are needed to explore potential causal pathways between these metals and MS pathogenesis. Studies will involve laboratory experiments with an animal model to explore the potential effect of these compounds on the pathogenesis of MS focusing on promising diagnostic and therapeutic implications.

Session 5: CNS Repair

TRIACK A NOVEL IRREVERSIBLE HIGH POTENCY THROMBIN PATHWAY MODULATOR IN EYE DROPS PENETRARES TO MURINE AND PIG RETINA

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Background: We developed two thrombin–PAR1 modulators, PARIN5 and TRIACK (five and three amino acid sequences, respectively), with potential applications in retinal neuroinflammation. Their high potency and irreversible inhibition profile support evaluation as candidates for topical administration.

Methods: Penetration of the compounds into intact pig eyes was assessed both ex-vivo and in-vivo following topical administration. Retinal penetration was evaluated by measuring inhibition of intrinsic thrombin activity in the neuroretina, while aqueous humour penetration was assessed by inhibition of either intrinsic or exogenously added thrombin.

Results: Ex-vivo exposure of intact eyes to both compounds reduced thrombin activity in the neuroretina and the aqueous humour compared with controls (Neuroretina: PARIN5: 0.10 ± 0.02 vs. 0.20 ± 0.02 mU/ml, respectively, p0.01; TRIACK: 0.015 ± 0.009 vs. 0.27 ± 0.03 mU/ml, respectively, p0.0001, aqueous humour: PARIN5 2mM 0.003±0.002 mU/ml vs. TRIACK:0.002±0.002 mU/ml vs. 6.9±0.03mU/ml). In-vivo topical TRIACK administration conducted in healthy, intact eyes affected neuroretinal thrombin activity compared with the control eye (0.38 ± 0.04 vs. 0.26 ± 0.03 mU/ml, respectively, p0.05), with the largest effect observed in the central retina.

Conclusions: The modulators of the thrombin–PAR1 pathway demonstrated significant penetration into pig eyes and exerted measurable biological effects on the retina. These findings support their potential development as topical eye-drop therapies for retinal diseases associated with neuroinflammation and diabetes.

MOLECULAR REGULATORS OF OLIGODENDROCYTE MATURATION AND REMYELINATION: FOCUS ON WWOX

Baraa Abu-Diab[1], Carlo Manenti[2], Rania Akkawi[1], Mustafa Obeid[1], Srinivas Repudi[1], Sara Abu-Swai[1], Takwa Jbara[1], Jose Davila-Velderrain[2], Rami Aqeilan[1]
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Background: Myelination is critical for neuronal function, yet the molecular pathways regulating oligodendrocyte differentiation and myelin repair remain incompletely defined. Large-scale analyses of remyelination identified the WW domain–containing oxidoreductase (WWOX) gene as a top hit, prompting us to explore its role in oligodendrocyte biology and repair. Objective: To define the function of WWOX in oligodendrocyte progenitor cell (OPC) maturation, CNS myelination, and remyelination.

Methods: We integrated in vitro stem cell models, conditional knockout mice, and transcriptomic profiling. WWOX was depleted in human embryonic stem cell–derived oligocortical spheroids to assess its role in oligodendrocyte differentiation. In vivo, an Olig2-Cre conditional Wwox knockout was generated to delete WWOX in OPCs, followed by evaluation of developmental myelination and cuprizone-induced remyelination. Single-nucleus RNA sequencing of corpus callosum tissue was compared with single-cell RNA sequencing from chronic multiple sclerosis (MS) lesions.

Results: WWOX depletion in human spheroids disrupted the generation of mature oligodendrocytes (mOLs). OPC-specific Wwox knockout mice exhibited impaired differentiation, hypomyelination, and reduced remyelination capacity. Transcriptomic analysis revealed novel WWOX-regulated effectors controlling OPC proliferation and differentiation. In MS lesions, WWOX expression was reduced in both oligodendrocytes and neurons, supporting the translational relevance of our findings.

Conclusions: WWOX emerged from remyelination screens as a pivotal regulator of OPC maturation and repair. Our integrative studies reveal its essential role in myelination and remyelination, highlighting WWOX and its effectors as promising therapeutic targets to enhance neural repair and recovery in demyelinating disorders.

MICROGLIA DEVELOPMENT, PHAGOCYTOSIS AND IMMUNE FUNCTIONS ARE REGULATED BY PROS1

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Background: The TAM (Tyro3, Axl, Mertk) receptors are key regulators of immune homeostasis, activated by the ligands GAS6 and Protein S (PROS1). Although microglia express high levels of PROS1, its role in microglia - the brain immune cells – is unexplored.

Methods: We generated mice conditionally deleted for Pros1 expression in microglia (Pros1-cKO). Conditional knock out was driven by LysM-Cre or Cx3Cr1-Cre-ER. Microglial development and function was assessed by immunohistochemistry, gene expression and histology. The role of PROS1 in microglial response to LPS-induced peritonitis and brain inflammation was also assessed.

Results: Pros1-cKO mice had fewer microglia throughout the brain at 2 months of age. PROS1 deletion within microglia specifically abrogated certain stages of microglia development and regulates homeostatic microglia proliferation. Additionally, key microglia functions known to be mediated via TAM receptors such as Phagocytosis and regulation of inflammation are also impaired at steady state. Moreover, loss of PROS1 within microglia has altered brain homeostasis and recovery following systemic LPS challenge. Finally, microglia-derived PROS1 plays a role in regulating neurogenesis in adult mice, impacting normal brain function.

Conclusions: Using Pros1-cKO mouse models, we identify microglia-derived PROS1 to be (1) necessary for microglia development, (2) a key regulator of microglial immune functions both at steady state and following systemic inflammation and (3) involved in regulating adult neurogenesis. This study reveals the role of PROS1 in maintaining a healthy, functional immune status of the brain at steady state, and following a systemic challenge. Finally, we conclude a cell-autonomous mechanistic function to microglial-derived PROS1.

Session 6: Guided Poster Walk with Cheese & Wine

NOVEL MOUSE MODEL FOR LATE-ONSET MULTIPLE SCLEROSIS

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Background: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by demyelination and neurodegeneration. disability. Most of the treatment aims to target the relapsing remitting stages; therapeutic applications for the chronic stage are limited. Late-onset MS, in which symptoms begin at age 50 or later, is characterized by a more rapid progression compared to earlier-onset cases. Therefore, there is a crucial need for an appropriate animal model for this stage to simulate as much as possible disease at old age. Cellular senescence (CS), is a state of cell-cycle arrest following stress, associated with an increased proinflammatory phenotype that is elevated with age. Elevation of CS markers has been reported in different neurological diseases, including MS. Here, we aim to establish a novel mouse model that will assess the effect of CS in the CNS on the progression of EAE, an MS mouse model.

Methods: We generated a novel mouse model in which we can selectively induce CS at adult age in the CNS. We compared EAE progression in this model to control without the induction of CS.

Results: We found that induction of CS in the CNS led to early induction of disease, and those mice showed an exacerbated disease progression. Furthermore, the RT-PCR analysis of the brain tissue of those mice revealed elevated inflammatory markers alongside downregulation in lipid production.

Conclusions: Our model provides a novel platform to study age-related mechanisms driving late-onset MS towards assessing potential therapeutic targets.

MAPPING THE MS PRODROME: CLINICAL PATTERNS AND TIMING PRIOR TO DIAGNOSIS IN A POPULATION-BASED EHR STUDY FROM ISRAEL

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Background: A prodromal phase preceding the clinical onset of multiple sclerosis (MS) has been increasingly recognized, but its characterization across diverse populations remains incomplete. Objective: To characterize the clinical features of the MS prodrome using electronic health records from a large Israeli healthcare provider.

Methods: We conducted a retrospective nested case-control study using Leumit Health Services data, including 908 MS patients and 4,540 matched controls (1:5 ratio). Diagnoses were grouped into focal demyelinating symptoms, comorbidity-related conditions, and diffuse systemic symptoms. Temporal patterns were analyzed to determine the onset of each symptom cluster. Data included physician visits, ICD-coded diagnoses, and ATC-classified medication use. Statistical significance was assessed using Fisher's exact test with Benjamini-Hochberg correction.

Results: MS patients showed significantly higher physician visits, including neurosurgery (OR = 9.36), neurology (OR = 4.91), pain clinics (OR = 2.81), and ophthalmology (OR = 1.71). they had increased rates of mental (OR = 1.63), nervous system (OR = 1.61), circulatory (OR = 1.52), and musculoskeletal (OR = 1.44) disorders. Symptom clusters appeared years before diagnosis with comorbidity-related appearing earliest and most significantly, although less prevalent of all (2.9%; 3.1 years; e.g., FMF, OR = 10.26). Medication use was also elevated, particularly nervous system drugs (OR = 2.38), antithrombotics, antiepileptics, and psychoanaleptics.

Conclusions: This population-based study supports a distinct MS prodrome, with increased healthcare utilization and characteristic clinical patterns years before diagnosis. Early recognition of these patterns, combined with emerging biomarkers, may enable timely evaluation and inform AI-based risk prediction models.

THE EFFECTS OF PHYTOCANNABINOIDS ON PROGRESSION OF THE ALS DISEASE AND NUEROINFLAMMATION

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Background: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by motor neuron loss and chronic neuroinflammation. Current treatments provide only limited benefits, emphasizing the need for new therapeutic strategies. Acidic phytocannabinoids, such as tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA), have shown anti-inflammatory and neuroprotective effects without psychoactive properties.

Objective: To assess the anti-inflammatory effects of THCA and CBDA in glial cells, and to evaluate the therapeutic potential of THCA in a transgenic ALS mouse model.

Methods: In vitro studies were conducted using murine microglial (BV2) and astrocyte (C8D1A) cell lines. Cells were treated with THCA or CBDA, with LPS stimulation. Nitric oxide (NO) levels were measured via the Griess assay; cytokine expression (IL-1β, IL-6, TNF-α) was assessed by ELISA and qPCR. Protein expression of iNOS, GFAP, and COX-2 was evaluated by Western blot. Immunofluorescence staining was performed on treated C8D1A cells to examine glial activation markers. In vivo, SOD1G93A transgenic mice were treated daily with THCA (i.p.) beginning at symptom onset. Neurological function was evaluated through grip strength, weight tracking, and clinical scoring. At endpoint, brain and spinal cord tissues were harvested for immunofluorescence staining.

Results: THCA and CBDA significantly reduced NO production and pro-inflammatory cytokine expression in both BV2 and C8D1A cells. Western blot analysis showed decreased expression of iNOS, GFAP, and COX-2 in cannabinoid-treated cells. Immunofluorescence confirmed reduced astrocytic activation in vitro. [il1] In vivo data collection and histological analysis of neural tissue are currently ongoing.

Conclusions: Acidic phytocannabinoids demonstrate strong anti-inflammatory effects in vitro at both molecular and protein levels. Ongoing analysis of in vivo experiments will further clarify their therapeutic potential in ALS progression. These findings support continued exploration of THCA and CBDA as candidate agents for ALS treatment.

EVALUATING THE ROLE OF CANNABINOID ACIDS IN NEUROINFLAMMATION AND MULTIPLE SCLEROSIS

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Background: Neuroinflammation is central to multiple sclerosis (MS) pathogenesis, involving glial activation, autoreactive CD4+ T cell infiltration and increased pro-inflammatory mediators e.g., nitric oxide, IL-17A, and TNFα. Cannabinoid acids, including cannabidiolic acid (CBDA) and tetrahydrocannabinolic acid (THCA), are non-psychoactive cannabis compounds with emerging anti-inflammatory and neuroprotective potential.

Methods: In vitro experiments were performed using BV2 microglial cells and primary mixed glial cultures exposed to lipopolysaccharide (LPS), followed by treatment with CBDA or THCA. Levels of NO, IL-17A, TNFα and iNOS expression were measured using ELISA and Western blot. MS in vivo model, an experimental autoimmune encephalomyelitis (EAE) mouse model, was employed. Mice were treated intraperitoneally with CBDA or THCA (10 mg/kg), and neurological scores, spinal cord histology (Iba-1, GFAP, CD4+), and splenocyte cytokine secretion were analyzed.

Results: CBDA and THCA significantly reduced LPS-induced NO production and iNOS expression in microglia (up to 90% inhibition), and decreased IL-17A secretion, while both compounds increased TNFα release in vitro (in BV2 and primary glial cells) and in splenocytes from EAE mice model. In EAE mice, treatment with CBDA or THCA improved neurological scores, reduced microgliosis and astrogliosis inflammation, and diminished CD4+ T-cell infiltration into the spinal cord.

Conclusions: These findings suggest that CBDA and THCA modulate neuroinflammatory pathways relevant to MS. Their ability to cross the blood–brain barrier and directly affect glial activity makes them promising candidates for future MS therapies.

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FUS TREATMENT FOR MS RELATED TREMOR

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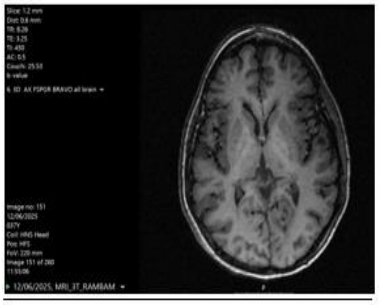
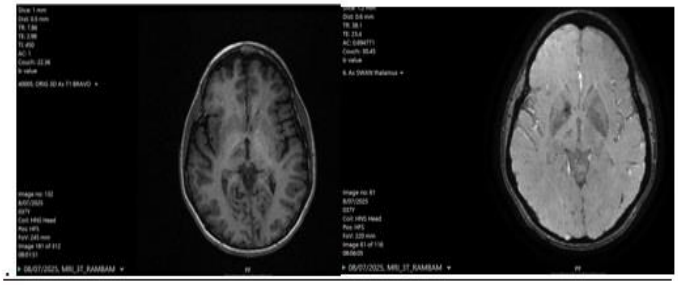
MRI scan:

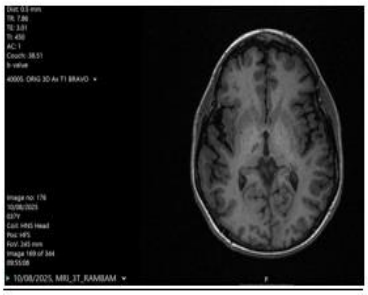
Before:



Tx day:



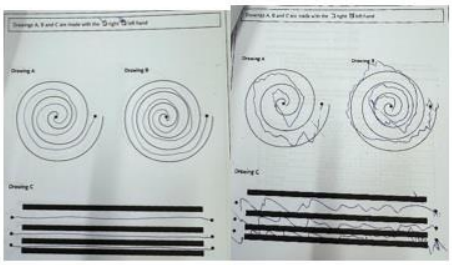
1 mo after



Spiral test:

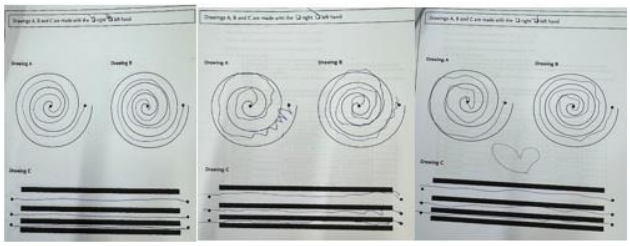
Before:

Non-treated hand Treated hand



After – 1 w, 1 m.

Non-treated hand Treated hand



Background: MRI-guided focused ultrasound (FUS) has established efficacy in tremor relief. Data regarding safety and efficacy in patients with tremor due to multiple sclerosis (MS) is sparse.

Methods: To report on the efficacy and safety of unilateral focused ultrasound treatment in the first Israeli MS patient who suffered from significant intractable tremor. The patient was evaluated with the Clinical Rating Scale for Tremor (CRST), EDSS, GCI score, QOL questionnaires, FIS and MOCA before and after FUS treatment.

Results: The patient was a 43 year-old right handed woman. CRST in the treated hand decreased from19 to 12, and overall CRST decrease from 30 to 18 immediately following treatment and was similar 1 month later. EDSS decreased from 3.5-4.0 before treatment to 2.5-3.0 after treatment. There was clear improvement in the CGI and QOL scores. No change in MOCA score was reported. Adverse events included mild ataxic gait.

Conclusions: Unilateral focused ultrasound was effective in reducing tremor in the first Israeli MS patient treated with this technology. Adverse events were mild. Follow-up is needed to evaluate long term results. FUS is a promising treatment option in MS patients suffering from severe tremor.

ASTROCYTIC RESPONSES AND THEIR REGULATORS HAVE DIVERGENT ROLES IN AGEING AND ALZHEIMER`S DISEASE

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Background: Alzheimer`s disease (AD) initiation and progression involve comprehensive changes in the cellular environment, particularly in astrocyte responses that significantly differ between AD and healthy brain ageing. The factors driving these diverse astrocyte responses, including cellular signalling and external stimuli, remain largely unknown. AD risk and progression are associated with various stressors and signalling pathways, like oxidative stress and inflammation, which disrupt astrocytic homoeostasis and may also drive their transition to pathological states that could either contribute to cognitive decline or, alternatively, neuroprotective states. Despite their importance, the molecular mechanisms regulating astrocytic responses to pathogenic stimuli remain mostly unknown.

Methods: High-throughput RNA sequencing of astrocyte-enriched primary cultures and screened various signals, including AD-associated damaging agents, cytokines and protective signalling molecules, to investigate their effect on astrocytic response to early AD pathology.

Results: Using causal modelling, we revealed modulations of astrocyte functions, each linked to specific stimuli and upstream regulators. Mapping these results to a large cellular atlas of post-mortem human ageing and AD brains, we associated the astrocytic functions and their predicted regulators to the crossroad between the progression toward AD or toward alternative brain aging.

Conclusions: These results provide mechanistic insights into how diverse cellular signals shape astrocytic functions, and their potential roles in AD progression.

POTENTIAL NEW THERAPEUTIC APPROACH FOR NEUROINFLAMMATION AND MULTIPLE SCLEROSIS: CANNABINOID ACIDS AS BLOOD BRAIN BARRIER MODULATORS

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Background: The blood-brain barrier (BBB) is a selective interface that regulates central nervous system (CNS) homeostasis by separating the brain from peripheral circulation. In neuroinflammatory and neurodegenerative diseases such as multiple sclerosis (MS), the BBB becomes compromised allowing immune cell infiltration and promoting disease progression. Phytocannabinoids, derived from the cannabis plant, are produced as acidic precursors, tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA), which convert into their neutral form (THC, CBD) by decarboxylation. While neutral cannabinoids have been shown to modulate BBB permeability, the effects of their acidic forms remain largely unexplored.

Methods: BBB Permeability was assessed in-vitro using bEnd.3 endothelial cells and C8D1A astrocytes. The effect of THCA and CBDA on BBB integrity were investigated under neuroinflammatory conditions, triggered by disrupting agents. In-vivo experiments were conducted using the experimental autoimmune encephalomyelitis (EAE) mouse model of MS. Mice were treated with THCA and CBDA (10 mg/kg i.p.), and BBB function was evaluated by neurological scoring and claudin-5 immunofluorescence.

Results: THCA and CBDA reduced BBB permeability in-vitro when it was challenged. In EAE mice, these compounds improved neurological scores and upregulate claudin-5, indicating improved barrier integrity.

Conclusions: This study provides first evidence that THCA and CBDA enhanced BBB function under neuroinflammatory conditions in-vitro and in-vivo, offering new therapeutic potential for MS and related disorders.

NEURO-IMMUNE ENGRAMS: LINKING TISSUE MEMORY AND BRAIN CIRCUITS IN SKIN INFLAMMATION

Margarita Sirotkin[1], Re'ee Yifa[2], Tehilah Marom[1], Megan Sammons[2], Tom Haran[2], Rotem Yam-Shahor[1], Merav Birk-Bachar[2], Shai Shen-Orr[2], Hilla Azulay-Debby[1], Asya Rolls[1]
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Background: Many skin disorders, including psoriasis and atopic dermatitis, have well-documented psychosomatic triggers that lead to recurrent inflammatory flares. Yet, the mechanisms by which mental states or brain activity precipitate immune reactivation in peripheral tissues remain poorly understood. Recent evidence suggests that the brain can initiate organ-specific immune responses through neuronal activation in the insular cortex (IC), giving rise to the concept of immune engrams. However, whether peripheral tissues themselves retain immune memories and how these interact with brain circuits to drive disease recurrence remains unclear.

Methods: This study aimed to investigate how immune memories are established within peripheral tissues and how they communicate with the brain. To do so, we expressed the DREADD receptor in TRAP2-Fos mice, allowing selective activation of neurons in the Insular cortex (IC) that were previously active during hapten-driven skin inflammation. To assess the molecular consequences of prior inflammation, we performed quantitative real-time PCR on previously inflamed skin to examine the expression of neuropeptide receptor genes. In parallel, analysis of microarray datasets from psoriatic patient samples to evaluate alterations in neuronal receptor gene expression associated with chronic skin inflammation.

Results: Reactivation of those neurons after the resolution of the inflammation was sufficient to trigger a renewed immune response in the skin. Complementary real-time PCR analysis revealed that previously inflamed skin exhibited upregulation of neuropeptide receptor genes, suggesting that local tissue changes enhance responsiveness to future neuronal signals. Supporting this notion, microarray analyses of psoriatic patient samples revealed similar alterations in neuronal receptor gene expression.

Conclusions: Together, these findings identify a potential brain–tissue interaction that could underlie psychosomatic triggers in recurrent skin inflammation and point toward new therapeutic targets.

EXPRESSION OF HUMAN P16 IN MOUSE CX3CR1-EXPRESSING CELLS INCREASES NEUROINFLAMMATION AND EXACERBATES COGNITIVE IMPAIRMENT IN 5XFAD MICE

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Background: Cellular senescence (CS) and chronic neuroinflammation are emerging hallmarks of Alzheimer's disease (AD). Microglia, the brain's resident immune cells, drive neurodegeneration through inflammatory responses and impaired amyloid-β (Aβ) clearance. CS markers have been identified in microglia of 5XFAD mice. CX3CR1, a chemokine receptor on microglia/monocytes, was reported to play an important role in neuroinflammation in AD. Here, we investigated the effect of p16 expression, a CS modulator, in CX3CR1+ cells on neuroinflammation and cognition in 5XFAD mice.

Methods: We generated transgenic mice expressing human p16 (hp16), under the microglial CX3CR1 promoter using a Cre-Lox inducible system, and crossed them with 5xFAD mice. Three-month-old male control and 5xFAD mice received doxycycline for 24 days, at 6 months behavioral testing. The amygdala was then analyzed for Aβ burden and macrophage/microglial reactivity. In parallel, bone marrow-derived macrophages (BMDMs) from adult female control and 5xFAD mice were treated with doxycycline in vitro and assessed for inflammation profile and Aβ uptake.

Results: We found that hp16 induction in CX3CR1+ cells impaired cognition in 5XFAD mice, as shown in nesting scores and decreased Y-maze preference for the novel arm. In the amygdala, hp16 expression increased Iba1+ cell density and neurons with intracellular Aβ, without altering plaque burden. In BMDMs, hp16 upregulated senescence markers and pro-inflammatory proteins while reducing Aβ uptake.

Conclusions: Our results suggest the importance of CX3CR1+ P16+ cells in the development of brain pathology in AD.

IMMUNE-SUPPRESIVE ROLE OF CD83 PROTEIN IN SEIZURE REGULATION

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Background: Knowledge of immune processes underlying epilepsy in humans is limited. Our group recently published data showing that soluble CD83 (sCD83) may be linked to an immune regulatory response in myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) (Rechtman et al., 2025). We are currently investigating the role of sCD83 in the regulation of epilepsy.

Methods: We obtained CSF from six patients with seizures (one patient also had MOGAD), 37 patients with MOGAD and 11 controls without immune disorders. ELISA protein assay was utilized to determine sCD83 protein concentrations in CSF.

Results: Average concentrations of sCD83 in CSF from patients with seizures was 479 pg/ml, with three having low concentrations (average 24.6 pg/ml) and three with higher concentrations (average 940.8 pg/ml). The average concentration from patients with MOGAD was 215.2 pg/ml, 172.6 in controls, and 52.2 pg/ml in the patient with epilepsy and MOGAD. Interestingly, the patients with seizures and lower sCD83 were young (average age 23.7), while the patients with seizures and higher sCD83 were older (average age 51.7) and had drug-resistant epilepsy. The patient with epilepsy and MOGAD had a low sCD83 concentration, possibly due to immune system dysfunction and reduced ability to produce sCD83, whereas the other epilepsy patients and controls had normally functioning immune systems.

Conclusions: Immune-suppressive mechanisms mediated through sCD83 may affect epilepsy, possibly being upregulated by frequent seizure activity contributing to mitigation of postictal symptoms. Low sCD83 concentrations may contribute to perpetuation of seizures and CNS dysfunction. Further studies are needed to elucidate the role of sCD83 in epilepsy.

NEUROINFLAMMATION AND BLOOD–BRAIN BARRIER DYSFUNCTION IN WILLIAMS SYNDROME: AN EMERGING AVENUE FOR TREATMENT

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Background: Neurodevelopmental disorders (NDDs) are multifactorial conditions with poorly understood pathophysiology, leading to treatments focused on addressing symptoms rather than underlying causes.

Williams syndrome (WS), a rare genetic NDD caused by a heterozygous deletion of ~26 genes, is characterized by intellectual disability, hypersociability, and vascular abnormalities, with limited knowledge about the mechanisms underlying its neurological and vascular symptoms. Among the deleted genes, general transcription factor II-i (*GTF2I*) is a critical factor that may contribute to cerebrovascular (CV) dysfunction and neuroinflammation.
Based on our findings of both blood-brain barrier (BBB) disruption and persistent neuroinflammation in a *Gtf2i*-heterozygous mouse model, we hypothesize that inflammation drives BBB alteration and contributes to neurological manifestations of WS.

Methods: Using *Gtf2i*-heterozygous mice, we assessed BBB integrity via permeability assays, quantified tight junction (TJ) protein expression, and characterized endothelial properties. Neuroinflammation was characterized using immunofluorescence, cytokine profiling, and protein expression analyses.

Results: Our preliminary data demonstrate BBB hyperpermeability in *Gtf2i*-heterozygous mice compared to normal mice, accompanied by reduced TJ protein expression, microglial activation, and elevated proinflammatory cytokines.

Conclusions: Our findings establish the coexistence of vascular impairment and neuroinflammation in WS, supporting the hypothesis that neuroinflammation underlies BBB dysfunction in WS. By understanding the role of vascular dysfunction in WS pathophysiology, we aim to develop targeted therapies. Repurposing existing anti-inflammatory and BBB-stabilizing drugs may offer novel, disease-modifying strategies for WS and related NDDs.

Session 7: Microglia and Neuro-degeneration

CHRONIC STRESS ATTENUATES CNS MYELOID CELL FUNCTION AND NEUROTOXICITY IN ALZHEIMER`S DISEASE

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Background: Alzheimer's disease (AD) pathology includes amyloid-β (Aβ) deposition, gliosis, and neuronal loss. Though initially neuroprotective, CNS myeloid cells (Microglia and CNS-associated macrophages) adopt a neurotoxic phenotype in advanced AD stages. Depression in midlife is a risk factor for developing AD in late-life, and was shown to accelerate Amyloid pathology. However, its role in AD pathogenesis during late-life, and specifically its effects on microglial neurotoxicity and neurodegeneration remain unknown.

Methods: We utilized 7 months old 5xFAD mice which exhibit extensive Aβ pathology without neuronal loss, representing a late preclinical AD stage. We used a six-week chronic-mild-stress (CMS) paradigm to induce depressive behavior, after which CNS myeloid cell activation was evaluated by transcriptomic analysis, activation marker expression and oxidative function. Microglial neurotoxicity was evaluated histologically in brain cortices following CMS and an ICV injection of Zymosan, a neurotoxic microbial TLR2 agonist.

Results: Transcriptomic analysis indicated a baseline hyper-activated state of CNS myeloid cells in 7-months old 5xFAD mice. CMS downregulated multiple immune and metabolic pathways in CNS myeloid cells by markedly increasing the epithelial to mesenchymal transition pathway. CMS reduced CD68 expression and impaired microglial oxidative responses. CMS alone did not induce neurodegeneration. Rather, it abolished the microglia-mediated neurodegeneration, caused by Zymosan.

Conclusions: Chronic stress and depression attenuate CNS myeloid cells, acting as a double-edged sword: At early AD stages, CMS-induced attenuation of CNS myeloid cells reduces their ability to clear Aβ, whereas at late stages, similar attenuation reduces their neurotoxicity, thus conveying a paradoxical protective effect on the AD brain.

A HIGHLY PHAGOCYTIC ALZHEIMER'S DISEASE -ASSOCIATED MICROGLIAL POPULATION EXPRESSING HIGH TSG101 GENERATES INTRACELLULAR AMYLOID AGGREGATES

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Background: Disease associated microglia (DAM) are a transcriptomic-defined cell population, considered as neuroprotective microglia. Their functional properties, protein markers and role in Alzheimer`s disease (AD) pathogenesis are poorly studied. We classified adult 5xFAD mouse CNS myeloid cells functionally, enabling the identification and characterization of a microglial subset with highly-enhanced Aβ phagocytic capacity. We investigated its association with DAM markers and pathological protein aggregation.

Methods: We isolated CD11b+ microglia from 7-month-old 5xFAD mice, FACS-sorted them based on their Aβ phagocytic activity, and performed comparative proteomic analyses between high versus low/non-phagocytic populations. Immunofluorescence, phagocytosis assays of monomeric proteins, and image analysis were employed to assess functional phenotypes and marker expression ex-vivo and in-vivo.

Results: We found large variability in microglial Aβ-phagocytic activity, with 5% of cells displaying 8-fold higher phagocytic activity than average. This population is age-acquired in 5xFAD mice and found ex-vivo and in-vivo in peri-plaque areas.
Proteomic profiling revealed upregulation of Tumor Susceptibility Gene 101 (TSG101) in these cells. TSG101high microglia showed strong correlation with DAM markers. Aβ was not cleared from these cells, but accumulated in RAB7+ late endosomes and aggresomes. Moreover, positive staining for Thioflavin-S indicated intracellular Aβ aggregation. Cell morphology and staining for p-MLKL in some highly-phagocytic microglia suggested also necroptotic cell death.

Conclusions: TSG101+ DAM are highly phagocytic, plaque-associated microglia that emerge in the AD brain. Intracellular accumulation of monomeric Aβ in highly-phagocytic microglia is followed by aggregation and necroptotic death. Thus, highly-phagocytic, TSG101+ DAM may potentially contribute to Amyloid plaque seeding and formation in AD.

THE AUTISM-ASSOCIATED PROTEIN CHD8 REGULATES AUTISM-RELATED BEHAVIOR BY MODULATING MICROGLIAL NUMBER, TRANSCRIPTOME, AND ACTIVITY

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Background: Microglial dysfunction and cytokine dysregulation have been characterized in autism. However, the roles of autism-associated genes and how these genes can affect microglial function have not been well characterized. Mutations in CHD8 (chromodomain-helicase-DNA binding protein 8) are highly associated with autism spectrum disorders. CHD8 is ubiquitously expressed. However, there is little knowledge of its specific roles in microglia, and the comparative roles of neuronal CHD8 and microglial CHD8 in the progression of autism

Methods: We used conditional knockdown technology in mice to specifically delete CHD8 in microglia or neurons, and then determined the effects on behavior, microglial and neuronal morphology, and transcriptome. Of importance, all experimentation was performed on both male and female cohorts.

Results: We determined that adulthood deletion of Chd8 in microglia induces robust changes in behavior, including anxiety, social deficits, and depression-like behavior, in association with changes in microglial activation and robust microglial gene expression changes, including expression of cytokines. Of great interest, most of these changes were seen specifically in male mice, and not female mice. In contrast, adulthood neuron knockdown had more subtle effects on behavior, mainly on depression-like behavior in males and few effects on the neuronal transcriptome.

Conclusions: In summary, CHD8 is particularly important for microglial function in adulthood and has cellular and behavioral effects that are specific to males. Therefore, microglial dysfunction and cytokine dysregulation play a role in the genetic etiology of autism, and sex-specific regulation of microglia may play a role in the male: female bias of autism.

Session 8: Biomarkers and Diagnostics in Demyelinating Diseases

APPLICATION OF THE 2024 MCDONALD CRITERIA IN THE INTERNATIONAL ACUTE OPTIC NEURITIS

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Background: The 2024 McDonald criteria for multiple sclerosis (MS) incorporate optic nerve lesions as a fifth topography for dissemination in space (DIS), kappa free light chains (KFLC), and new MRI metrics as additional diagnostic features. We evaluated their performance in acute optic neuritis (ON) patients within the global Acute Optic Neuritis Network (ACON).

Methods: In this ongoing, prospective, multicenter study, we applied the 2024 McDonald criteria to 250 patients with a first-ever ON (August 2020 – December 2024) from 22 centers across six continents. We included 61 patients with idiopathic ON (iON), 53 with clinically isolated syndrome and 64 with MS according to 2017 McDonald criteria (2017-CIS, 2017-MS), 22 with aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder (AQP4-IgG+NMOSD), and 50 with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). We assessed the sensitivity of the 2017 and 2024 McDonald criteria using the MS ”at-risk” population (defined by criteria specific DIS or dissemination in time (DIT) using MRI). Specificity was measured using the AQP4-IgG+NMOSD and MOGAD cohorts.

Results: All 2017-MS patients (64/64, 100%) fulfilled the 2024 criteria and 33/53 (62%) 2017-CIS patients were reclassified as MS. Additionally, 18% of AQP4-IgG+NMOSD and 14% of MOGAD patients fulfilled the 2024 McDonald criteria. The sensitivity of the 2017 and 2024 criteria were 55% (95%-CI 45-64) and 83% (95%-CI 75-89); specificity was 100% (95%-CI 95-100) and 85% (74-92), and diagnostic accuracy was 72% (95%-CI 65-78) and 84% (95%-CI 76-89). VEP and OCT showed higher sensitivity than MRI for the detection of DIS using the 2024 criteria; however, MRI yielded higher specificity. Due to limited use, the impact of new MRI metrics and KFLC were not assessed.

Conclusions: The 2024 McDonald criteria enhance diagnostic sensitivity in ON-related CIS, enabling earlier MS diagnosis, but reduce specificity, especially amongst antibody-mediated ON.

BRAIN ATROPHY IN NMOSD AND MOGAD: A META-ANALYSIS OF VOLUMETRIC AND DTI BIOMARKERS

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Background: Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are demyelinating diseases of the central nervous system. Brain atrophy is well recognized in multiple sclerosis; however, approximately 50% of studies report no significant difference in overall brain volumes when comparing NMOSD patients with healthy controls (HCs). To quantitatively assess differences in brain volume and white matter integrity in NMOSD and MOGAD patients compared to HCs through a meta-analysis.

Methods: A systematic literature search of English articles in PubMed was performed through December 2024. We analysed sixty-one studies that met the inclusion criteria, providing volumetric MRI or diffusion tensor imaging data with HC comparisons. Outcomes of interest included brain volume, and DTI parameters. Standardized mean differences were computed, and random-effects meta-analyses were performed to account for study heterogeneity.

Results: The studies included data from 1,786 NMOSD patients, 376 MOGAD patients, and 1,936 HCs. NMOSD patients exhibited significantly lower total brain, gray, and white matter volumes compared to HCs. Notable atrophy was observed in several regions including the accumbens, brainstem, caudate, cerebellum, hippocampus, putamen, and thalamus. MOGAD patients have reduced brain volume compared to HCs. Furthermore, comparisons demonstrated that NMOSD patients had significantly lower brain and gray matter volumes than MOGAD patients.

Conclusions: Our meta-analysis confirms substantial brain atrophy in NMOSD patients compared to both HCs and individuals with MOGAD, indicating a more pronounced neurodegenerative impact than previously recognized. These findings carry important clinical implications by enhancing our understanding of disease-specific imaging biomarkers.

NEUROFILAMENT LIGHT CHAIN MEASUREMENTS BY CENTAUR AND SIMOA SYSTEMS IN HUMAN AND MURINE SAMPLES

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Background: Neurofilament light chain (NfL) is an established biomarker for detecting axonal injury in various neurological disorders. The Quanterix Single Molecule Array (Simoa) is the current standard; however, automated immunoassays, such as the Siemens Atellica and Centaur, may serve as alternatives. In this study, we compared NfL measurements obtained with the Centaur system to those from the Simoa-SR-X to assess their agreement and applicability in clinical practice, research, and animal studies.

Methods: NfL levels were measured in 27 human serum, 8 plasma, and 16 cerebrospinal fluid (CSF) samples, and 9 murine serum samples, by Centaur and Simoa systems. NfL levels in concomitantly drawn serum and plasma were compared in 8 human subjects. The agreement between platforms was evaluated.

Results: NfL levels measured by Centaur and Simoa systems demonstrated a strong correlation in serum (Spearman r=0.97, p0.0001) and plasma (Pearson R^2=0.95, p0.0001). Centaur measurements were higher (p=0.01) than Simoa. Most importantly, system-specific Z-score calculation corrected these differences. Serum and plasma levels measured by the Centaur system correlated strongly (Pearson R^2=0.98, p0.0001) and showed similar results. CSF levels measured by the Centaur system were lower (52% bias) than those measured by Simoa, with poor correlation at concentrations within the normal range (R2=0.32, p=0.11). Mouse serum results showed a strong correlation between systems (Pearson R^2=0.86, p0.001), with similar values.

Conclusions: The Centaur system offers an alternative to Simoa for measuring NfL in human serum, plasma, and murine serum. System-specific age-adjusted Z-scores

SERUM CALPROTECTIN AS A BIOMARKER OF INFLAMMATORY ACTIVITY AND TREATMENT RESPONSE IN RELAPSING MULTIPLE SCLEROSIS: A PROSPECTIVE STUDY COMPARED TO NEUROFILAMENT LIGHT CHAIN

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Background: Monitoring disease activity and predicting treatment response in relapsing–remitting multiple sclerosis (RRMS) remains a clinical challenge. Neurofilament light chain (NfL) is a validated biomarker of neuroaxonal damage, but it reflects downstream effects. Calprotectin, a pro-inflammatory mediator secreted by activated myeloid cells, may serve as an upstream biomarker of innate immune activity. Objective: To evaluate serum calprotectin as a biomarker of inflammatory disease activity and treatment response in RRMS, and to compare its predictive performance to NfL.

Methods: In this single-center prospective study, 60 patients with RRMS were assigned to three groups: active relapse (n=20), cladribine-treated (n=20), and diroximel fumarate–treated (n=20). Serum calprotectin was measured in all groups at baseline (pre-treatment or relapse) and at follow-up (post-treatment or remission). In addition, NfL was assessed in the treated groups (cladribine and diroximel fumarate) at the same two timepoints. The primary outcome was achievement of 2-year no evidence of disease activity (NEDA). Predictive performance was evaluated using ROC analysis and logistic regression.

Results: Calprotectin levels were elevated during clinical relapse (2.35 ± 2.00 µg/mL) and declined during remission (1.17 ± 0.76 µg/mL; p0.01). Diroximel fumarate, but not cladribine, significantly reduced calprotectin levels over 3–6 months. Among treated patients, higher post-treatment calprotectin predicted failure to achieve NEDA (Cladribine AUC=0.92; DRF AUC=0.68; combined AUC=0.80). In contrast, NfL showed weaker predictive value (combined AUC=0.62). A combined model including both biomarkers did not outperform calprotectin alone (AUC=0.83). Multivariate analysis confirmed calprotectin as an independent predictor of treatment failure.

Conclusions: Serum calprotectin is a dynamic marker of inflammatory activity and a strong predictor of treatment response in RRMS, outperforming NfL in this context. These findings support its potential utility for early therapeutic monitoring and biomarker-guided treatment strategies.

NEUROFILAMENT LIGHT CHAIN FROM SERUM-CIRCULATING NEURONAL-DERIVED EXTRACELLULAR VESICLES IN PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS PATIENTS

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Background: Primary-progressive multiple sclerosis (PPMS) is characterized by neuroinflammation/neurodegeneration. Serum Neurofilament light chain (sNfL) have emerged as a tool for assessing neurodegeneration. However, sNfL quantification may involve NfL from nonneuronal source. Extracellular vesicles (EVs) carry molecules reflecting the parental cells. NfL in serum-circulating neuronal-derived EVs (NDEV) might mirror neurodegeneration. This study aimed to assess NfL in NDEV from PPMS and healthy subjects (HS) by Flow Cytometry (FC).

Methods: PPMS patients according McDonald 2017 criteria and age-and gender-matched HS were enrolled. Serum-EVs were isolated by ultra-centrifugation, enumerated by nanoparticle-tracking analysis and characterized by atomic-forced microscopy. Total sNfL was assessed by digital ELISA.

EVs were captured by avidin-magnetic beads coated with biotinylated-anti-CD9+, CD63+ and CD81+. The score between total NfL+EVs and NfL+NDEV+ (double positive for neuronal specific L1CAM+ and NFL+) was assessed and the total sNfL was corrected accordingly.

Results: PPMS patients (n=13, 5 female, age:58.3±10.5 years) and HS (n=11, 4 female, age:59.8±5.6 years) were analyzed. sNfL concentrations were 11.5±4.9 and 6.7±3.0 pg/ml (p=0.05) in PPMS and HS, respectively. Size of EVs from PPMS and HS was 126.7 ± 64.4 and 142.5±64.1 nm, respectively (p=0.4). Concentration of EVs was 3.67*108±5.37*106 and 5.66*108±4.67*107 particles/ml in PPMS and HS, respectively (p=0.3). The proportion of NfL+NDEV was 2.7-fold higher in PPMS than HS (p=0.003). The total intensity of neuronal NfL from PPMS patients was 2.3-higher than in HS (p=0.01). The proportion of neuronal NfL and total NfL+EVs was 63.9±12.0% and 24.2±9.0% in PPMS and HS, respectively (p=0.05).

Conclusions: The higher proportion of NfL+NDEV in PPMS suggests its utility as biomarker of neurodegeneration.