Eastern Carolina Chapter of the Society for Neuroscience Presents:

24th Annual Neuroscience Symposium

Featuring:
David Glanzman, PhD
Distinguished Professor
Departments of Integrative Biology and Physiology,
and of Neurobiology | University of California, Los Angeles

“Is Long-Term Memory in Aplysia Encoded by Nuclear Mechanisms?”

Friday, October 28th, 2022
Harvey Hall at the Murphy Center
eccsfn.ecu.edu

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24th Neuroscience Symposium Schedule
Friday, October 28th, 2022
Harvey Hall at the Murphy Center
East Carolina University, Greenville, NC

*Costumes Encouraged*

**October 27th**
5:00PM-7:00PM **Symposium Social at Tapped** with food (provided by Sam Jones BBQ) courtesy of the Department of Kinesiology. Please RSVP by 10/26 through the symposium registration link or QR code. Tapped is located at 650 E. Fire Tower Rd., Winterville, NC 28590.

**October 28th**
8:00-3:35 **Check-In / Walk-In Registration**

8:30-9:00 **Breakfast Available for All Registrants and Guest Speakers**

And

**Chat with Keynote Speaker:** Dr. David Glanzman
(for students, postdocs, and medical students/residents)

9:00-9:15 **Opening Remarks:** Dr. Karen Litwa, ECCSfN President

9:15-10:45 **Lightning Talks by Graduate Students**
(5 min each, 3 min questions)

10:45-11:00 **Break**

11:00-11:55 **Keynote Address:** Dr. David Glanzman, Distinguished Professor, UCLA
“Is Long-Term Memory in Aplysia Encoded by Nuclear Mechanisms?”

12:00-12:30 **Lunch Available for All Registrants and Guest Speakers**

12:30-3:00 **Faculty Presentations**
12:30 – 1:15 Sarah Cohen, PhD, UNC-Chapel Hill
"Illuminating Organelle Dynamics in Development and Neurodegeneration"

1:20 – 2:05 Alessandro Didonna, PhD, East Carolina University
"The Novel Immunomodulatory Role of Ataxin-1 in Autoimmune Demyelination"

2:10 – 2:55 Todd Peterson, PhD, UNC-Wilmington
"Ex Vivo Measurement of the Glial Response to Neural Insult”

3:00-4:00 **Poster Session**

4:00-4:15 **Closing Remarks and Awards:** Dr. Karen Litwa, ECCSfN President
Is Long-Term Memory in Aplysia Encoded by Nuclear Mechanisms?

David Glanzman, PhD
Distinguished Professor
Departments of Integrative Biology and Physiology, and of Neurobiology | UCLA

Long-term memory (LTM) in Aplysia can persist following the erasure of synaptic changes induced by learning. Moreover, the persistence of LTM depends on DNA methylation. These facts raise the question of whether LTM in Aplysia is encoded by nuclear mechanisms. One possible nuclear mechanism of memory is retrotransposition. To test for a potential role for retrotransposition in memory in Aplysia, we have examined the effect of inhibitors of reverse transcriptase (RT)—the enzyme that synthesizes DNA from RNA—on serotonin (5-HT)-induced facilitation of Aplysia sensorimotor synapses in dissociated cell culture. Five spaced pulses of 5-HT (5X5-HT training) induce facilitation of sensorimotor synapses that persists for ≥ 24 h (long-term facilitation or LTF). Treatment with either the nucleoside RT inhibitor lamivudine or the non-nucleoside RT inhibitor rilpivirine blocked LTF. Neither drug altered baseline sensorimotor synaptic transmission. In addition, we tested whether either RT inhibitor altered short-term facilitation (STF) of in vitro sensorimotor synapses due to a single, brief (2-min) application of 5-HT. Surprisingly, both lamivudine and rilpivirine impaired STF. The rapid time course of the effects of the RT inhibitors on STF appears inconsistent with disruption of retrotransposition; thus, RT may be critical for a retrotransposon-independent mechanism of synaptic plasticity. Taken together, our results imply that RT plays a necessary, heretofore unsuspected, role in both short-term and long-term memory in Aplysia.
**Illuminating Organelle Dynamics in Development and Neurodegeneration**

Sarah Cohen, PhD  
Assistant Professor  
Department of Cell Biology and Physiology  
University of North Carolina-Chapel Hill

Emerging evidence indicates that organelle dynamics and interactions are dysregulated in multiple types of neurodegenerative disease. For example, many proteins implicated in Alzheimer’s disease (AD), Parkinson’s disease (PD), or amyotrophic lateral sclerosis (ALS) mediate or localize to membrane contact sites at the interface between organelles. I will describe our work using live-cell multispectral imaging to characterize the dynamics of organelle contacts. We used multispectral imaging to visualize seven organelles throughout differentiation of human induced pluripotent stem cells (iPSCs) into cortical neurons. We are also testing the effects of mutations associated with AD, PD, and ALS on organelle morphodynamics, with the goal of identifying convergent pathways that are misregulated in neurodegenerative disease.

**The Novel Immunomodulatory Role of Ataxin-1 in Autoimmune Demyelination**

Alessandro Didonna, PhD  
Assistant Professor  
Department of Anatomy and Cell Biology  
East Carolina University  
Brody School of Medicine

The overarching goal of Dr. Didonna’s research consists in elucidating the mechanisms underlying central nervous system (CNS) autoimmunity, with an emphasis on disease progression and neurodegenerative phenotypes. A consistent part of his efforts is focused on multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE). Among others, Dr. Didonna has recently described a previously unknown immunomodulatory activity for ataxin-1, a polyglutamine protein that is classically associated with the movement disorder spinocerebellar ataxia type 1 (SCA1).
One of the major consequences of neural insult is neuroinflammation. This cascade can be both beneficial and detrimental, and there is much to be learned about the dynamics of this complicated response. It is characterized by increases in pro and anti-inflammatory cytokines, leukocyte invasion, blood-brain barrier permeability, and glial activation. Astrocytes and microglia are glial cells that are activated following injury and have been shown to regulate the immune response. I am interested in elucidating the multicellular neuroinflammatory response in hopes of developing therapeutic treatments for central nervous system damage.
Lightning Talk
Abstracts
(listed by presenting author in alphabetical order)
Interaction Between the Rho and Rab Family of Small GTPases in Neurodegenerative Disorders

Shayan Nik Akhtar¹, Wyatt Bunner², Qun Lu¹, Erzsebet M. Szatmari²

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Defects in cytoskeletal dynamics and dysfunctions of the vesicular trafficking system are widely reported to promote neurodegeneration. Studies have demonstrated that the small GTPases of Rho family are key regulators of cell cytoskeleton while the Rab family regulates vesicular sorting and transport including endocytosis and exocytosis. In this regard, the role of Rho- and Rab-GTPases in the induction and maintenance of distinct functional and morphological neuronal domains (such as dendrites and axons), has been extensively studied. Here we assess the potential crosstalk between these two important intracellular functions in healthy cells and neurodegenerative diseases. Several members belonging to these two families of proteins have been associated with many neurodegenerative disorders, ranging from dementia such as Alzheimer’s diseases (AD) to motor neuron degeneration in amyotrophic lateral sclerosis (ALS). For example, Rab8a increased activity results in activation of Rho GTPase Cdc42 through Tuba, a Cdc42 guanine nucleotide exchange factor (GEF). Rab35a activation was also shown to activate Cdc42. Intersectin (ITSN), a scaffolding protein that has Cdc42-GEF properties, is one of the most highly induced genes in AD brains. ITSN1 knockout mouse have reduced exocytosis events. Since Rab GTPase control vesicular transport, we propose the functional interactions between Rho and Rab GTPase in neurodegenerative disorders.
Evaluating Neuroprotective Effects of Sulforaphane in a VPA-Induced Autism Model

Riley Bessetti¹, Virginia Koonce¹, Carson Camacho¹, Krista McCoy PhD², Karen Litwa PhD¹

¹East Carolina University, Greenville, NC
²Florida Atlantic University, Boca Raton, FL

In the last decade, U.S. Autism Spectrum Disorder (ASD) diagnoses have increased. Pregnant women are commonly exposed to environmental factors that can increase the likelihood of offspring developing an ASD. A potential avenue for reducing the adverse effects of environmental contaminants is to enhance the body’s own detoxification and antioxidant pathways, ultimately reducing cellular oxidative stress. NF-E2-related factor 2 (Nrf2) is a transcription factor that promotes the expression of cytoprotective and antioxidant genes. The phytochemical, sulforaphane (SFN), potently activates the Nrf2 pathway by decreasing Nrf2 proteasomal degradation mediated by Keap1 (Kelch-like ECH-associated protein 1). Our investigation aims to test the hypothesis that SFN will protect developing neural circuits from the detrimental effects of environmental contaminants. We generated a human fetal brain model of chemically-induced autism by exposing either neural progenitor cells or human cortical spheroids (HCSs) to the anti-epileptic drug valproic acid (VPA). Fetal exposure to VPA has been linked to an increased risk of developing ASD in humans and autism-like behavior in rodents. At a molecular level, VPA functions as an inhibitor of histone deacetylases and is known to increase oxidative stress. In neural progenitor cells, our data show that VPA treatment produces a dose-dependent increase in cellular oxidants. In HCSs, either VPA or SFN alone impairs synapse formation. Whereas in combination, they restore synapse formation. Nrf2 nuclear translocation is increased by both VPA and SFN. Based on these findings, we are currently testing the hypothesis that synapse formation requires a delicate balance between oxidative stress and antioxidant buffering. Our data support that sulforaphane can restore synapse formation and oxidative homeostasis in the presence of environmental stressors.
A central question in the field of aging research is identifying the cellular and molecular basis of neuroresilience. One of such factors is the small GTPase, Rab10. Reduced level and activity of Rab10 lead to retaining of normal cognitive function in the face of dementia (“cognitive resilience”). Here we used Rab10+/- mice to identify novel molecular mechanisms by which reduced Rab10 level guards the aging brain. We found that physical attributes and brain morphology are normal in Rab10+/- mice compared to their Rab10+/+ littermates. Brain expression analysis of 880 genes involved in neurodegeneration showed that Rab10+/- mice have higher activation scores of pathways associated with neuronal metabolism; structural integrity; neurotransmission and neuroplasticity compared to their Rab10+/+ littermates. Lower activation scores were observed for pathways involved in neuroinflammation and aging. We identified several differentially expressed genes (DEG) including Stx2, Stx1b, Vegfa, Lrrc25 (downregulated); and Prkaa2, Syt4 and Grind2d (upregulated). Transcriptome profiling was validated at DNA level by qPCR and at protein level using Western Blotting. Finally, behavioral characterization showed that Rab10+/- mice perform better in a hippocampus-dependent spatial task (Object in Place Test), while their performance in a classical conditioning task (eye blink conditioning; EBC) was significantly impaired. Therefore, our findings indicate that Rab10 differentially controls the brain circuitry of hippocampus-dependent spatial memory and higher level behavior that requires intact cortex-hippocampal circuitry. Transcriptomic and biochemical characterization of these mice strongly suggest that Glutamate Ionotropic Receptor NMDA Type Subunit 2D is a potential mediator of Rab10+/- behavioral phenotypes. We conclude that Rab10+/- mice described here can be a valuable tool to study the mechanisms of resilience in AD model mice on reduced Rab10 background and to identify novel therapeutical targets to prevent cognitive decline associated with normal and pathological aging.
Social Regulation of the Posterior Tuberal Nucleus in Zebrafish (Danio rerio)

Faith K Heagy, Miranda C Setneska, Katie N Clements, Fadi A Issa

Biology Department, East Carolina University, Greenville, NC, USA

Aggression is an important behavioral feature that facilitates the formation of stable dominance relationships. Aggressive animals are recognized as dominants and have priority to resources, while those that display submissive behavior are recognized as subordinates, therefore having less priority to resources. Despite its social benefits, persistent aggression is stressful psychologically and physiologically. Although the effects of social stress have been investigated, little is known of how it induces morphological plasticity of brain nuclei involved in regulating motor circuits. Here we investigated the effects of socially induced stress on the morphological plasticity of hypothalamic posterior tuberal nucleus (PTN) using adult male zebrafish as a model organism. The PTN is an integration center of multimodal sensory social cues, and its dopaminergic neurons project their axons caudally into the spinal cord to regulate the Mauthner-mediated startle escape and swim behaviors. We hypothesized that the PTN is prone to socially induced morphological plasticity that would influence the modulation of motor behaviors in a social status-dependent manner. To test this hypothesis, we measured the sensitivity of the startle response and spontaneous swimming activity in dominant and submissive fish. We found the sensitivity of startle escape was significantly enhanced in submissive animals compared to dominants or communals (control); while swimming was significantly reduced in submissive animals compared to dominants. Histological analysis using Tg[DAT:eGFP] transgenic line with targeted eGFP expression in dopaminergic neurons, showed a significant reduction in the number of PTN cells in submissive animals compared to dominants and control groups after 14 days of social interactions. There were no differences between dominants and controls cell number at Day 14. Digital rendering and volumetric analysis of PTN Type 1 soma size showed no significant difference among the three social groups. The result suggests that chronic social stress induced neuronal loss that correlates with differences in motor activity. We are conducting time course experiments to quantify PTN cell number during the first two weeks of interactions to determine whether differences in PTN cell number are a result of social stress rather than being innate differences. Additionally, we are using PSD-95 to assess whether socially induced neuronal loss is accompanied with loss in synaptic density. The results improve our understanding of how social stress induces morphological plasticity of social decision-making networks.
The Novel Function of PUF-9 RNA-Binding Protein in C. elegans Parkinson Model

Mariah Jones¹, Savannah Lipski², Myon Hee Lee¹,²

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Neurodegeneration refers to a significant loss of functional neurons, which is present in neurodegenerative diseases such as Alzheimer’s (AD) and Parkinson’s disease (PD). Despite considerable progress in our understanding of neurodegeneration, how to integrate this information to gain fundamental insights into the molecular mechanism is still severely lacking.

The long-term research objectives are to identify key regulators of neurodegeneration using the nematode C. elegans as a model organism. Although the C. elegans is an invertebrate, they contain a well-studied nervous system. Its nervous system has extensively been characterized and found to be similar in structure and function to mammals. Their nervous system has been completely mapped, laying out the various neurons and their interactions within the animal. Specifically, PD is a neurodegenerative disease that is the result of dopaminergic neuron cell death. In addition to this loss of DA neurons, there is an accumulation of Lewy bodies. Lewy bodies are classified as clumps of protein such as aggresomes. Lewy bodies are a common phenotype in neurodegenerative disorders in humans. In PD, α-Synuclein (α-Syn) has been identified as the primary protein that Lewy bodies are comprised of. α-Syn proteins are mainly expressed in the brain at presynaptic terminals, but it is not naturally expressed in the C. elegans. Notably, overexpression of α-Syn in C. elegans dopaminergic neurons mimics key symptoms of PD patients, including neurodegeneration and abnormal behaviors. Using this model animal, we have identified PUF-9 RNA-binding protein as a potential regulator of PD. PUF-9 protein is a conserved post-transcriptional regulator, but its role in neurodegeneration has not yet been reported.

Using multiple approaches, we found that puf-9(ok1136) mutation significantly delays α-Syn-induced neurodegeneration during aging. Expression analysis using CRISPR/Cas9-puf-9::gfp worms reveals that PUF-9 is highly expressed in the intestine and hypodermis, but not highly expressed in dopaminergic neurons. These preliminary findings led us to test the hypothesis that PUF-9 may induce PD phenotype non-cell autonomously. Our ongoing genetic experiments will elucidate the novel function of PUF-9 in α-Syn-induced neurodegeneration. Since PUF-9 is highly conserved in most eukaryotes, a similar mechanism may control neurodegeneration (e.g., PD) in other organisms, including humans.
Inhibiting the Classical Pathway of Complement: A Structure-Guided Approach to Fragment-Based Drug Design

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The classical pathway of complement plays a critical homeostatic role within the body by driving and priming immune responses against pathogens, cellular debris, misfolded proteins and apoptotic cells. Within the brain, these processes take on the additional role of mediating synaptic pruning and remodeling of inactive synapses during the early stages of development and adult plasticity. While endogenous regulators are fine-tuned to control complement activation, dysregulation or aberrant activation is present as a driver and/or mediator of an ever-growing list of neurodegenerative diseases, such as multiple sclerosis, stroke, traumatic brain injury, and Alzheimer’s disease, implicating the classical pathway as an important player in disease pathogenesis through its targeted proinflammatory cascade and cytokine milieu. Recent studies have demonstrated that deficiencies in key complement components, such as C1q and downstream C3, have promoted neuroprotection in Alzheimer’s mouse models. Accordingly, the classical pathway-initiating serine protease, C1r, is a promising therapeutic target for drug development due to its upstream location within the complement cascade.

Using a structure-guided approach for fragment-based drug discovery, we investigated the activity of a series of small-molecule compounds identified in a large-scale compound library screen and which were predicted to bind the C1r protease. Through several biofunctional assays, we identified two lead compounds that bind C1r and inhibit complement in a dose-dependent manner. Using molecular dynamics (MD) simulations, we were able to map out the favorable protein-ligand interactions and perform compound optimization through fragment replacement and synthesis. Newly synthesized analogs of our parent lead compound showed modest improvements in dose-dependent binding affinity and inhibition of the classical pathway, validating our structure-guided approach to fragment-based drug design. Additional routes of optimization will be explored to increase binding affinity and potency of our small-molecule compound with the aim that it may provide a promising therapeutic approach to classical pathway-mediated diseases.
Cannabidiol (CBD) Inhibits Neuroinflammation and Synaptic Loss Following Damage to Songbird Vocal Motor Cortex

Mark Tripson¹, Karen Litwa², and Ken Soderstrom¹

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The non-euphorogenic phytocannabinoid CBD has been used successfully to treat childhood-onset epilepsies, conditions often associated with developmental delays that include vocal communication. Translational to human speech, zebra finch song is a complex behavior learned during a sensitive period of vocal development and maintained through continued sensorimotor refinement. Therefore, the zebra finch is a promising model to understand mechanisms responsible for potential CBD-related improvement of vocal learning. A region that controls vocal production, HVC, is a pre-vocal motor cortical-like region that when partially lesioned temporarily disrupts vocal behavior. We found previously that CBD both speeds recovery and reduces the magnitude of disruptions. Given anti-inflammatory CBD activity in seizure and other models, we suspected involvement of similar mechanisms in vocal recovery. To test this, we investigated CBD modulation of post-lesion expression of inflammatory cytokines, markers of neuronal stress, microglial migration, and changes in synaptic densities within relevant song regions. Groups of 3-5 adult male zebra finches were treated with vehicle or 10 mg/kg CBD (≥ 98%) delivered IM in 50 µl QD for six days pre- and one day post-HVC microlesion. HVC was targeted unilaterally allowing contralateral internal controls. For qRT-PCR (IL-1β & IL-6, IL-10, MSK1, Arc/arg3.1 & BDNF) brain regions were micropunched and RNA extracted then amplified. Distribution of protein expression was studied by immunofluorescence with fixed, cryosectioned tissue (10 µm). Tissue was stained with antibodies against inflammatory (IL-1β & IL-6), and anti-inflammatory mediators (IL-10), as well as the superoxide indicator dihydroethidium (DHE). An anti-TMEM119 antibody was used to label microglia. Synaptic densities were measured using colocalization of excitatory pre- and post-synaptic markers (VGLUT2 & PSD-95). Results of qRT-PCR, DHE staining and IF experiments indicate CBD-improved vocal recovery is associated with reduced oxidative stress and anti-inflammatory activity. Decreased inflammation and stress marker expression was associated with reduced microglia within song regions afferent to the lesion target. As microglia are critical regulators of synaptic degeneration, we measured densities of excitatory synapses within Area X and RA, finding significant lesion-related decreases that were largely reversed by CBD. Synaptic protection was associated with BDNF/Arc/MSK1 upregulation implicating mechanisms important to homeostatic synaptic scaling.
An Inflation Sensation: Initial Swim Bladder Inflation in Larval Zebrafish is Mediated by the Mechanosensory Lateral Line

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Larval zebrafish achieve neutral buoyancy between 3-4 days post-fertilization by gulping air from the water's surface to inflate their swim bladders. We define this behavior of swimming to the air-water interface as “surfacing.” Little is known about the sensory basis for this underappreciated behavior of larval fish. A strong candidate is the mechanosensory lateral line, which is a hair cell-based sensory system that detects hydrodynamic information from sources like water currents, predators, prey, and surface waves. However, the influence of the lateral line on the larval behaviors that mediate swim bladder inflation remain unexamined.

To explore the connection between the lateral line and surfacing behaviors, we utilize a genetic mutant (lhfpl5b/-/-) that specifically silences the lateral line from birth. We observe that approximately half of lateral line mutants over-inflate their swim bladder during initial inflation and become positively buoyant. Thus, we hypothesize that larval zebrafish use their lateral line to sense the air-water interface during the suracing behavior to regulate swim bladder inflation. We report that (i) over-inflation is caused by abnormal surfacing behaviors in lateral line mutants, (ii) lateral line defects are responsible for swim bladder over-inflation, and (iii) the lateral line is specifically responsible for surface detection during initial inflation. In summary, we reveal a novel sensory basis for achieving neutral buoyancy where larval zebrafish use their lateral line to sense the air-water interface and regulate initial swim bladder inflation.
CRY–BARs: Versatile Light-Gated Molecular Tools for the Remodeling of Membrane Architectures

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²Department of Physical Therapy, East Carolina University, Greenville, North Carolina, USA

BAR (Bin, Amphiphysin, and Rvs) protein domains are responsible for the generation of membrane curvature and represent a critical mechanical component of cellular functions. Thus, BAR domains have great potential as components of membrane-remodeling tools for cell biologists. In this work, we describe the design and implementation of a family of versatile light-gated I-BAR (inverse BAR) domain containing tools derived from the fusion of the Arabidopsis thaliana cryptochrome 2 photoreceptor and I-BAR protein domains (“CRY–BARs”) with applications in the remodeling of membrane architectures and the control of cellular dynamics. By taking advantage of the intrinsic membrane-binding propensity of the I-BAR domain, CRY–BARs can be used for spatial and temporal control of cellular processes that require induction of membrane protrusions. Using cell lines and primary neuron cultures, we demonstrate here that the CRY–BAR optogenetic tool evokes membrane dynamic changes associated with cellular activity. Moreover, we provide evidence that ezrin, an actin and phosphatidylinositol 4,5-bisphosphate–binding protein, acts as a relay between the plasma membrane and the actin cytoskeleton and therefore is an important mediator of switch function. Overall, we propose that CRY–BARs hold promise as a useful addition to the optogenetic toolkit to study membrane remodeling in live cells.
Evidence suggests that the primary consequences of Covid-19 infection are neuroinflammatory responses mediated by Bradykinin via the B1R receptor. Elevated Bradykinin termed the “Bradykinin Storm” is thought to underlie both pulmonary fibrosis and neuroinflammatory effects of the virus and has been linked to increased risk of strokes and other long term neurological sequelae in humans (Zarifkar, 2022). Several studies have reported the benefits of B1R antagonist administration in curbing neuroinflammation in animal models, but none have applied the same methodology to controlling neurological sequelae of Covid-19 infection. For example, animal studies using cryoablation as a neurological insult have shown that mice treated with B1R antagonist had less severe cerebral edema and disturbances to the Blood Brain Barrier than untreated mice (Raslan, 2010). Based on our preliminary data, we hypothesized that antagonizing the B1R receptor during infection with SARS-CoV-2 in susceptible mice would block or attenuate some of the neuroinflammation and lung fibrosis effects of the disease. Our preliminary data suggests that administering a B1R antagonist could reduce fibrosis of the lungs following COVID-19. Other additional findings indicate a potential reduction in neuro-inflammatory and cognitive response.
Differences in Dopamine Metabolite Pathways May Predict Opioid Responsiveness in Chronic Neuropathic Pain

Felicia Branch, Dylan Marshall, Jacob Yow, Mandee Schaub, Stefan Clemens, Kori Brewer

Departments of Emergency Medicine and Physiology, Brody School of Medicine, East Carolina University, Greenville, NC

The current standard to manage pain is through the prescription of opioid medications. Opioids, however, provide pain relief in only about one out of three individuals. When a non-responsive individual takes these medications, they are not only not receiving an analgesic effect, but they are also being exposed to unnecessary risk as a result of the potential side effects of the drug. Our previous data indicate an interplay between opioid and dopamine signaling pathways. Here, we attempted to identify potential biomarkers in a rodent model of chronic pain that can predict opioid responsiveness prior to administration. Eighteen 8-12 week old Long-Evans rats were used in this study. Hargreaves testing was used on both hindlimbs to record thermal pain reflex latencies pre- and post-injury and blood samples (1 ml) were collected from the tail vein and stored for mass spectrometry. Animals then underwent ligation surgery of the left sciatic nerve, resulting in a chronic neuropathic pain condition. Pain reflex latencies were reevaluated on both hindlimbs for up to 10 days post-injury. Following SNL, all animals showed a significant reduction in pain thresholds on the side of injury at all time points post injury (p<0.001). After 10 days, animals were randomly assigned to receive subcutaneous injections of morphine (2 mg/kg) or a saline control 30 minutes prior to reflex testing. When pain thresholds were re-assessed after injection of morphine, we found that a subset of animals consistently behaved as non-responders, while another one behaved as opioid responders. These data indicate that SNL injury model leads to a morphine response profile that is similar to that observed in the clinic. We are currently analyzing the blood samples of the animals to identify metabolomic profiles in opioid responders and opioid non-responders.
Altered Hypothalamic Transcriptome in a Mouse Model of Multiple Sclerosis

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Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that is a leading cause of disability among young adults. In addition to presence of inflammatory white matter lesions and neurological symptoms, MS patients are also more likely to report mood and energy disturbances including anxiety, depression, chronic fatigue, and weight change. The hypothalamus is a critical integration and regulation center of neuroendocrine signaling and plays a central role in regulating mood, stress, and energy balance. Experimental autoimmune encephalomyelitis (EAE) is an animal disease that recapitulates several features of MS and represents the ideal model to explore MS pathogenic mechanisms in vivo. However, few studies have directly examined the impacts of autoimmune disease on hypothalamic function. To fill this gap, here we investigated the impact of the myelin oligodendrocyte glycoprotein 35-55 (MOG35-55)/C57Bl6 EAE paradigm on the hypothalamus transcriptome. RNA-seq technology was employed to capture the gene expression profiles of hypothalamic tissues dissected from EAE-immunized female mice and mock-injected controls at key disease stages, namely the pre-symptomatic phase (10 days post-injection, dpi), disease peak (20 dpi) and the chronic phase (40 dpi). Notably, differential expression analysis identified statistically significant changes already at 10dpi, providing support to the notion that altered CNS functions precede clinical symptoms. Gene ontology (GO) enrichment highlighted persistent inflammatory signatures at all timepoints, even though the hypothalamus is typically spared from lesions. Among the differentially expressed genes, orexigenic neuropeptide Agrp was initially downregulated pre-onset, but then significantly upregulated during the acute phase when EAE mice experience severe weight loss. During the acute phase of the disease, there was also significant reduction in Pomc which encodes a peptide precursor for several relevant hormones including α-Melanocyte-stimulating hormone and adrenocorticotropic hormone. Further, we found upregulation of several genes involved in glucocorticoid response including clinically relevant Fkbp5 which has been linked to depression in human patients. Together, our results show that hypothalamic function is perturbed in response to an encephalitogenic challenge and offer mechanistic clues to the neuroendocrine disruption underlying mood and energy symptoms in the context of autoimmune demyelination.
Neuroprotection by Cannabidiol (CBD) Against Degeneration of Synapses in Area X and RA in Zebra Finch

Yasmine Habal, Cassandra Thomason, Dr. Ken Soderstrom

The non-euphorigenic phytocannabinoid Cannabidiol (CBD) has been used successfully to treat childhood epilepsy, a condition associated with developmental delays that includes vocal communication. Translational to human speech, zebra finch song is a complex behavior learned during a sensitive period of vocal development, and therefore is a promising model to understand mechanisms responsible for potential CBD-related improvement of vocal learning. We found previously that CBD both reduces the magnitude of lesion-related song pattern disruption, and speeds vocal recovery. Preliminary results from our lab indicate that CBD-improved vocal recovery is associated with anti-inflammatory and antioxidant activity. Interestingly, neuroinflammation is a dynamic process that has reparative effects but can be detrimental if left unregulated. The process of synaptic reorganization after injury is regulated by Microglia but chronic activation can lead to cytotoxic effects that go beyond tissue repair. Because this overactivation can damage cellular processes and ultimately lead to cell death, we hypothesized that CBD treatment would decrease neuronal degeneration after lesioning the pre-motor vocal area HVC. Adult songbirds were given once daily injections in a volume of 50 µl IM to pectoralis. Six daily treatments were given prior to surgical procedures, followed by daily postoperative treatments depending on the post lesion time point. Microlesion surgery targeted left HVC for partial ablation. Treatments included vehicle or 10 mg/kg/day CBD (lot of >99% pure CBD provided by GW Research Ltd, Cambridge, UK). The lesioned and perfused brains were sent to the Neuroscience Associates in Tennessee to be stained using a silver copper stain, and sectioned using a Cryostat machine, then sent back to our lab where regions of importance were analyzed. The brain regions Robust nucleus of the archistriatum, or RA (Song control nucleus) and Area X (a striatal regions that receives midbrain dopaminergic input and is necessary for song learning) were of the most important to us, as the degeneration of these neurons will indicate whether CBD will have a greater impact on song learning in the zebra finch. RA and Area X were our chosen regions to analyze as we know they contains projection neurons as well as interneurons directly connected to the HVC area, which for short we can refer to as the sensorimotor learning circuit. The results indicated that there was no statistical difference between the groups analyzed although there was a difference between the hemispheres. Overall, CBD had no effect on protecting neurons of RA and Area X from degenerating. However, no statistical significance does not translate to no biological relevancy. There are many factors to consider when reviewing the results. For example, the number of neurons present from the beginning could vary across groups. There is also the issue of the silver copper stain that was used, as it targets neurons rather than synapses, making it non-specific, which would hinder a study conducted to figure out specifically synaptic degeneration. The sample size (18 birds) was also relatively small, and more time points could have also been added to provide more data. More data would have contributed to a more accurate representation of the population and lowered the uncertainty by identifying outliers.
Neurodegeneration refers to a significant loss of functional neurons, which is present in neurodegenerative diseases such as Alzheimer’s (AD) and Parkinson’s disease (PD). Despite considerable progress in our understanding of neurodegeneration, how to integrate this information to gain fundamental insights into the molecular mechanism is still severely lacking.

The long-term research objectives are to identify key regulators of neurodegeneration using the nematode *C. elegans* as a model organism. Although the *C. elegans* is an invertebrate, they contain a well-studied nervous system. Its nervous system has extensively been characterized and found to be similar, in structure and function, to mammals. Their nervous system has been completely mapped, laying out the various neurons and their interactions within the animal. Specifically, PD is a neurodegenerative disease that is the result of dopaminergic neuron cell death. In addition to this loss of DA neurons, there is an accumulation of Lewy bodies. Lewy bodies are classified as clumps of protein such as aggresomes. Lewy bodies are a common phenotype in neurodegenerative disorders in humans. In PD, $\alpha$-Synuclein ($\alpha$-Syn) has been identified as the primary protein that Lewy bodies are comprised of. $\alpha$-Syn proteins are mainly expressed in the brain at presynaptic terminals, but it is not naturally expressed in the *C. elegans*. Notably, overexpression of alpha-synuclein (a-Syn) in *C. elegans* dopaminergic neurons mimics key symptoms of PD patients, including neurodegeneration and abnormal behaviors. Using this model animal, we have identified PUF-9 RNA-binding protein as a potential regulator of PD. PUF-9 protein is a conserved post-transcriptional regulator, but its role in neurodegeneration has not yet been reported.

Using multiple approaches, we found that *puf-9(ok1136)* mutation significantly delays a-Syn-induced neurodegeneration during aging. Expression analysis using CRISPR/Cas9-*puf-9::gfp* worms reveals that PUF-9 is highly expressed in the intestine and hypodermis, but not highly expressed in dopaminergic neurons. These preliminary findings led us to test the hypothesis that PUF-9 may induce PD phenotype non-cell autonomously. Our ongoing genetic experiments will elucidate the novel function of PUF-9 in a-Syn-induced neurodegeneration. Since PUF-9 is highly conserved in most eukaryotes, a similar mechanism may control neurodegeneration (e.g., PD) in other organisms, including humans.
Observing Mice in Virtual Hunting Experiments to Investigate Their Acoustic Navigation

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Acoustic navigation is the process that allows animals to locate sound cues in space. It is an action that relates to the auditory system and self-awareness. In this study, the hunting behaviors of male adult mice were examined to better understand their methods of acoustic navigation. Prior experiments completed outside of the lab in uncontrolled environments indicate that mice have behavioral flexibility when it comes to movement patterns. However, their methods of utilizing acoustic navigation to adjust their strategies has not been explored. The experiment was completed using a virtual hunting arena and was composed of two parts: habituation training and operant testing. The goal of habituation training was to determine if mice could learn that they would receive a reward by poking their nose into a port. Once habituated, the goal of operant testing was to determine whether mice would associate the reward with a sound cue and navigate towards the correct port. We found that mice could learn to poke their nose in a port to acquire a reward but were unable to learn the operant acoustic navigation task. These results will help us better develop acoustic navigation tasks in the lab and eventually determine how mice alter their navigation strategy as they walk on surfaces that make different noises.
Clinical Poster Abstracts

(listed by presenting author in alphabetical order)
**Intraosseous Capillary Hemangioma in the Skull of a 2-Month-Old Girl: A Rare, Benign Developmental / Benign Neoplastic Lesion**

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A wide range of neoplasms can affect the skull including primary, metastatic, and hematopoietic neoplasms and lesions directly extending from the scalp or the dura / intracranial region. Skull neoplasms in young children are uncommon and the differential diagnosis is much more limited than in an adult. We present the case of a primary skull hemangioma in a young child.

A 2-month-old girl presented with a left skull lesion, firm and rounded, first note at about age 1 week, increased in size over time. Imaging identified a lucent, 1.4 X 0.5 cm left parietal bone lesion, centered in the diploic space, with extension along the outer table without a definite periosteal reaction or a soft tissue component. Her history was otherwise unremarkable with no known systemic disease processes. The radiologic differential diagnosis included Langerhans cell histiocytosis (eosinophilic granuloma), intraosseous hemangioma, or less likely of metastasis from an unknown primary site. An excision of the skull region containing the lesion was carried out. Sectioning of the specimen following decalcification revealed a distinctly spongy appearance with spaces containing dark material consistent with blood. Histologic evaluation of the specimen revealed expansion of inter-trabecular marrow spaces by abundant, thin-walled vascular spaces, most containing red and white blood cells, lined by histologically benign-appearing blood vessel endothelial cells (CD34 and CD31 immunohistochemistry) with no evidence of lymphatic vascular differentiation (D2-40) in the absence of endothelial cell hyperplasia, atypia, mitotic activity, or necrosis. Findings were diagnostic of a capillary hemangioma. There was no evidence of any other disease process including Langerhans cell histiocytosis as evaluated histologically and by immunohistochemistry (S100, CD1a, CD163).

Primary skull hemangiomas are uncommon benign lesions, comprising fewer than 1% of bone neoplasms, with cavernous, capillary, and mixed variants. Most intraosseous hemangiomas occur in vertebral bones with only a small number reported in the skull, most commonly in middle-aged adults. Only a few case reports have described this lesion in early childhood. This report adds another case of intraosseous hemangioma to the literature and emphasizes the essential role of histologic and immunohistochemical evaluation in the definitive diagnosis of lesions identified on imaging studies.
Desmoplastic Infantile Ganglioglioma/Astrocytoma Presenting as Large Cystic and Solid Mass of a Child

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Desmoplastic infantile gangliogliomas/astrocytomas are rare primary central nervous system neoplasms which present as large cerebral hemisphere lesions with solid and cystic components. They represent 1.25% of intracranial neoplasms in childhood. They typically present prior to 24 months of age and there is a slight male:female ratio, 1.8:1.

A 17-month-old boy presented with left-sided weakness, with progressive loss of the use of his left arm and leg during the previous 7 months. Magnetic resonance imaging (MRI) of his brain identified a right cerebral hemisphere lesion, cystic and solid, 8.5 X 9.2 X 8.0 cm with the solid component 1.8 X 3.6 X 4.5 cm, and a 1.5 cm right-to-left shift across midline. A subtotal resection was undertaken. Histologic and immunohistochemical evaluation revealed a primary central nervous system neoplasm with (1) glial elements, predominantly astrocytic phenotypically and (2) neuronal elements, somewhat subtle histologically, but clearly discernable by synaptophysin, neurofilament, and chromogranin A. In addition, (3) a small cell component was also present with prominent glial fibrillary acidic protein and, to a lesser extent, neuronal antigen expression and a mildly increased Ki67 proliferation index. Combined histologic and immunohistochemical evaluation were consistent with diagnosis of desmoplastic infantile ganglioglioma/astrocytoma, World Health Organization grade 1. Molecular evaluation identified multiple losses of parts of or complete chromosomes along with a gain of chromosome 12p. A mutation in the ARID2 gene was detected but was a variant of uncertain significance. No specific, pathogenic genetic alterations were identified. Subsequent MRI scans identified postoperative changes with subtle residual contrast enhancement in the right temporal and posterior frontal lobes consistent with residual tumor and unexplained dural thickening on the right side. The patient is being followed closely.

This case report illustrates the presentation, histopathology, and molecular features of a rare primary central nervous system neoplasm.
Transsphenoidal Diagnosis, Pathological Analysis, and Management of a CNS WHO Grade 4 Astrocytoma Isolated to the Optic Chiasm: A Rare Presentation with Long-Term Follow-Up

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CNS WHO grade 4 astrocytoma, with integrated histologic and immunohistochemical data, glioblastoma (GBM), of the optic chiasm is a rare pathology typically leading to rapid blindness and death despite evolving treatment modalities.

Glioblastoma, IDH-wildtype, is a diffuse astrocytic neoplasm comprising approximately 45-50% of primary malignant CNS tumors. These entities can affect all cerebral lobes with predilection of the subcortical white matter often with extension into adjacent grey matter. Less often reported, present in the spinal cord and brainstem. Herein, we report a rare presentation of a diffuse astrocytic neoplasm originating in the optic chiasm. The patient is a 79-year-old man presenting with 30-40 days of vision loss and diplopia. MR imaging of the brain identified a mass in the optic chiasm extending to the left optic nerve and tract and left mesial temporal lobe with heterogenous enhancement.

Following biopsy of the lesion, histological analysis revealed an infiltrative glial neoplastic process with histologic features of the neoplastic cells consistent with an astrocytoma phenotype. Diffuse immunoreactivity of OLIG2 expression in nuclei of aforementioned cells confirmed the glial nature of the neoplasm. Occasional mitotic figures were identified, along with patchy necrosis, and microvascular proliferation. The neoplasm was immunonegative for IDH1 R132H, ATRX, BRAF V600E, H3 K27M, and H3 K27ME. Based on combined histologic and immunohistochemical data, findings are diagnostic of a high-grade glial neoplasm and consistent with designation as a glioblastoma, IDH-wildtype, CNS WHO grade 4 originating from the optic chiasm. The patient was treated with the Stupp regimen consisting of concurrent and adjuvant temozolomide with a standard fractionated course of external beam radiation therapy (EBRT) which was completed to a total of 54 Gy in 30 fractions. The patient passed approximately one year following diagnosis without overt signs of clinical progression.

Approximately 38 cases of GBM involving the optic chiasm have been reported in the literature, this being the eighth case to solely originate in the optic chiasm. With the Stupp regimen, our patient saw extended time to blindness (7 months) with no signs of glioblastoma progression. Despite relatively quick diagnosis and initiation of treatment, our patient saw minimal extension of survival.
Deep Sea Diving Death due to Ruptured Arteriovenous Malformation: Role of Medical Examiner System

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The presentation of neurological symptoms or death in a diver, post-dive, elicits a broad differential diagnosis including the possibility of decompression illness as well as the manifestation of underlying disease processes. We report the first known autopsy case of a ruptured cerebral arteriovenous malformation in the setting of a dive.

A 40-year-old, experienced male diver became unresponsive on ascension from a dive. Resuscitation efforts were unsuccessful. An unrestricted, forensic autopsy revealed (1) acute, diffuse cerebral swelling, greater in the right cerebral hemispheres, and (2) on sectioning the brain an acute intracerebral hematoma, 1.8 cm in greatest dimension, in the right frontal lobe white matter at the level of the nucleus accumbens with (3) multiple distended blood vessels identified in intact neuropil at the periphery of the hematoma. Microscopic evaluation of sections demonstrated variably sized arteries and arterialized and partially sclerotic veins admixed in neuropil in a background of acute hemorrhage. In addition, (1) subacute changes adjacent to the abnormal blood vessels, consisting of plump, active-appearing macrophages with small to moderately coarse hemosiderin aggregates within lysosomes, (2) more chronic changes including macrophages with older to chronic accumulation of hemosiderin along with gliosis, consistent with recent (days to weeks old) leakage or focal hemorrhage from the malformation, along with (3) gliosis, subacute and chronic. Findings were diagnostic of a vascular malformation and consistent with the diagnosis of arteriovenous malformation with evidence of previous subacute and chronic leakage. A literature review identified no publications describing ruptured vascular malformations.

This report highlights the critical role that forensic pathology plays in the investigation of unexpected deaths, establishing both (1) the cause of death, in this case acute intracerebral hemorrhage in the context of an arteriovenous malformation, and (2) the manner of death (e.g. natural, accidental, suicide, homicide, undetermined), in this case a natural manner as rupture of a vascular malformation is a known and expected complication of this developmental abnormality. This case report emphasizes the role of an autopsy in determining the cause of death of a diver and establishes a ruptured arteriovenous malformation as a potential cause of death in a diver.
Pineal Melanocytic Neoplasm with Diffuse Leptomeningeal Dissemination: A Rare Primary Melanocytic Disease Process

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Metastatic melanoma commonly metastasizes to the brain and represents the most common melanocytic disease process affecting the central nervous system (CNS). The origin of metastatic melanoma can be occult, and metastasis from the eye must be ruled out. However, as melanocytes are present within the arachnoid, primary melanocytic lesions also occur and can be confused with metastatic disease processes. The 2021 World Health Organization Classification of Tumors of the Central Nervous System classifies primary CNS melanocytic lesions as melanocytoma, intermediate grade melanocytic lesion, and malignant melanoma based on the absence or presence of brain invasion (excluding Virchow-Robin space spread) along with mitotic acidity and Ki67 proliferation index. We present a case of a patient with a primary melanocytic disease process.

A 50-year-old woman presented with confusion and speech alterations. Magnetic resonance imaging identified a 2.0 pineal region mass with extension along the thalami, tectal plate, and superior vermis of the cerebellum and involvement of the leptomeninges of the anterior temporal and medial occipital lobes. The differential diagnosis included a melanocytic neoplasm (based on T1-hyperintensity), pineal parenchymal tumor (e.g. pineoblastoma), germ cell tumor, and metastatic disease. Biopsy of the right temporal lobe identified a melanocytic lesion involving subarachnoid space and neuroparenchyma with invasion of Virchow-Robin spaces favored but brain invasion not ruled out, consistent with leptomeningeal dissemination from a primary pineal lesion. Immunohistochemistry for BRAF V600E was negative and molecular evaluation revealed an alteration in the BAP1 gene but no alteration in BRAF, KIT, or NRAS (for which therapeutic interventions exist). These findings argue against metastatic melanoma which typically manifests multiple genetic alterations. Findings straddle classification as melanocytoma with dissemination and intermediate grade melanocytic lesion.

As the presumed pineal primary lesion cannot be easily biopsied or resected and as imaging and biopsy have demonstrated a melanocytic lesion with aggressive biologic activity, the patient is undergoing chemotherapy to treat her disseminated disease.

While the vast majority of melanocytic neoplasms affecting the CNS represent metastatic melanomas, primary melanocytic neoplasms can rarely be identified. Clinicians, radiologists, and pathologists must be aware of this disease entity to avoid confusion with a metastatic disease process.
A Case of Classic Pyridoxamine 5'-Phosphate Oxidase (PNPO) Deficiency in a Newborn Presenting with Status Epilepticus

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Introduction
Pyridoxamine 5'-phosphate oxidase (PNPO) deficiency is a rare genetic disorder that leads to severe epileptic encephalopathy in neonates. It results from pathogenic variants in the PNPO gene, which encodes for an enzyme that catalyzes the last step in the conversion of pyridoxine and pyridoxamine to pyridoxal-5'-phosphate (PLP). PLP is an essential cofactor for more than 100 different enzymes and biochemical reactions and is involved in the metabolism of neurotransmitters. Neonates with PNPO deficiency cannot synthesize intracellular PLP, leading to severe seizures resistant to common antiepileptic medications and pyridoxine supplementation. A literature review revealed that less than 20 cases had been reported.

Case Presentation
A preterm neonate born at 35 weeks, estimated gestational age to consanguineous parents of Yemeni origin, who developed generalized and focal seizures at 1 hour of life. He was treated with phenobarbital, pyridoxine, levetiracetam, and benzodiazepines, with frequent breakthrough seizures requiring additional medications. An extensive laboratory evaluation revealed anemia, lactic acidosis, and elevated creatine kinase, with urine organic acid analysis showing elevated vanillactic and vanilipyrvic acid levels. A gene epilepsy panel and whole exome sequencing exposed a homozygous pathogenic variant c.263 G>C p.(R88T) in the PNPO gene. PLP was administered with cessation of seizures; all other antiepileptic agents were tapered down before hospital discharge.

Discussion
The current standard of care for refractory neonatal seizures includes the administration of pyridoxine, which will not treat PLP-dependent seizures. Studies are currently advocating early initiation of PLP for preterm neonates with neonatal encephalopathy and refractory seizures, as PLP administration will treat both pyridoxine-dependent and PLP-dependent seizures. In addition, the developmental outcomes in reported patients are likely to depend on prematurity, the timing of seizure-onset, and the time of appropriate therapy initiation. Therefore, early treatment with PLP may improve neurodevelopmental outcomes and the survival of this patient population.

Conclusion
Vitamin B6-dependent epilepsy due to PNPO defect is an important differential diagnosis in neonates with drug-resistant seizures, and gene testing can facilitate the correct diagnosis. Prompt diagnosis and treatment led to excellent seizure control in most patients.
Endodermal (Neurenteric, Enterogenous) Cysts of the Central Nervous System: A Clinical and Histopathological Review of Five Cases

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Endodermal (neuroenteric, enterogenous) cysts are rare, developmental, non-neoplastic cysts representing congenital remnants of neuroectoderm. These mature, epithelial-lined lesions represent no more than 0.01% of annual CNS diagnoses, most commonly identified in the pediatric population. These lesions occur most commonly in association with the spinal column and spinal cord but can also be identified in supratentorial and posterior fossa regions. Herein, we report five cases of endodermal cysts highlighting each of these locations. The patient population had ages ranging from 2 to 73 years with cystic lesions arising in supratentorial, midline posterior fossa (mesencephalon, pons, cerebellum), and spinal column locations. Clinical presentation depends on location, and included nausea, headaches, choking, facial droop, gait instability, ataxia and lower extremity weakness. MRI imaging identified cystic lesions without associated enhancement. In two of the posterior fossa lesions, there was associated obstructive hydrocephalus. Following surgical fenestration with biopsy and cyst drainage, clinical improvement was observed without post-operative complications.

Histologic examination revealed well-differentiated cuboidal to columnar and pseudo-columnar epithelium showing unequivocal cilia formation with in one case goblet cell formation. Inflammatory infiltrates including xanthogranulomatous change was noted in some cases. In two cases, squamous metaplastic change was noted. Immunohistochemistry confirmed the diagnoses with diffuse immunoreactivity for cytokeratin 7 (CK7), cytokeratin 8/18 (CK8/18), and epithelial membrane antigen (EMA). In both cases exhibiting squamous metaplasia, immunoprofiling identified expression of cytokeratin 5/6 (CK5/6).

This case series provides a comprehensive review of the range of benign, developmental cystic entities that can occur in association with midline structures. It emphasizes the need for a broad differential diagnosis particularly in the setting of progressive neurological symptoms and obstructive hydrocephalus prior to histological evaluation. It is important to note histological variance within these lesions, particularly those of which that are long-standing as to prevent misdiagnosis or misinterpretation. Microscopic changes include xanthogranulomatous change, aforementioned squamous metaplasia, and hemorrhage, as exhibited in one of our reported cases. This histological sequela can be accounted for by the accumulation of cyst contents gradually; wherein neurological features present upon expansion or due to reactive change.
Placement of a radiation source within a neoplasm, brachytherapy, has been used effectively to treat a variety of neoplasms. This localized delivery of radiation therapy has been shown to be effective and avoids external beam radiation and associated morbidities. The Food and Drug Administration recently cleared the use of an implanted device consisting of cesium-131 seeds embedded in a collagen carrier tile, GammaTiles (GT Medical Technologies, Tempe, AZ), for use after resection in newly diagnosed malignant and all recurrent intracranial neoplasms. This study reports findings from a multi-institution consortium of centers deploying GammaTiles as part of treatment of CNS neoplasms. A phase 4 observational study opened on 11/14/2020 (NCT04427384) to prospectively enroll 600 subjects at 50 sites capturing demographics, pathology, survival, local control, adverse events (AE), and quality of life. The objective of the study was to evaluate the patterns of clinical application and evaluate the safety profile through characterization of morbidity, mortality, and readmission within 30 days across institutions and tumor types. Through 06/01/2022, 65 patients from 12 enrolling institutions were consented with 46 completing the 30-day postoperative evaluation. Data was abstracted from the study registry on patients with possible, probable, or definitively attributable surgical- or radiation-related grade $\geq 3$ AE. Of 46 treated tumors in 46 patients, 18 were glioblastoma, 14 metastatic neoplasm, 7 meningioma, and 7 miscellaneous tumors; 40/46 were recurrent after prior therapy. Six attributed Grade $\geq 3$ AE occurred in five patients (11%): one patient had both cerebral edema (day 2) and urinary tract infection (day 30); one patient each manifested with intracranial hemorrhage (day 5), left hemiparesis (day 0), transient expressive aphasia (day 0), or new onset seizure disorder (day 25) (2%). GammaTile therapy is emerging as an important treatment option for CNS neoplasms. The 30-day morbidity and readmission rates appear similar to those previously reported for patients undergoing conventional craniotomy for resection of a neoplasm and support a highly-favorable safety profile for this therapeutic approach. Follow-up and accrual are ongoing and future reports will help benchmark clinical outcomes of this treatment, allow for comparison to existing treatments, and facilitate future clinical trials.
Acute Presentation of Glioblastoma in the Context of Macroscopic Hemorrhage: A Diagnostic Challenge

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Background: Glioblastoma is a high-grade glial neoplasm, the most aggressive primary tumor of the central nervous system in adults with diffuse invasion of neuroparenchyma precluding resection. Glioblastomas are characterized histologically by microvascular proliferation and / or necrosis. The presentation of this high-grade neoplasm often includes new-onset seizures or / and progressive neurologic symptoms, variable by the location of the lesion, including weakness, aphasia, and visual deficits. Acute onset of symptoms due to macroscopic hemorrhage and associated vasogenic edema is seen in a small proportion of cases. When hemorrhage is substantial, the presence of an associated neoplasm is difficult to detect on a screening computed tomography (CT) scan. We present two cases of individuals with acute-onset neurologic symptoms due to a large hemorrhage associated with a GBM.

Case Descriptions: Case A: A 48-year-old man presented with acute-onset right-sided weakness with a history of on-and-off right lower extremity weakness of 2-weeks duration. CT and CT-angiography (CT-A) studies identified a left frontoparietal hemorrhage and associated edema. Magnetic resonance imaging distinguished a mass lesion with underlying hemorrhage. Case B: A 59-year-old man with no significant past medical history was found down with left hemiparesis and neglect. CT and CT-A studies identified a right cerebral hemisphere hematoma with nodular peripheral enhancement, possibly an associated mass, and associated edema. In both cases, CT scans of chest, abdomen, and pelvis were negative for a primary or metastatic neoplastic processes. Resections were undertaken and histologic and immunohistochemical evaluation revealed findings diagnostic of a high-grade astrocytoma and consistent with glioblastoma, World Health Organization grade 4.

Results: Literature review found that presentation of glioblastoma due to macroscopic hemorrhage is uncommon, seen in between 0.54% and 6.4% of cases. The etiology of hemorrhage in the setting of a glioblastoma is unknown, possibly associated with rupture of neovascular blood vessels within areas of necrosis or large vessel invasion by neoplasm, exacerbated in some cases by a coagulopathy

Conclusions: While uncommon, glioblastomas can be associated with macroscopic hemorrhage and present with acute neurologic dysfunction. As the hemorrhage may obscure an underlying vascular malformation or neoplasm, CT-A and MRI studies are warranted.
Thiamine Deficiency-Associated Peripheral Neuropathy (Dry Beriberi) Resulting from a 20-Day “Water Fast”

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Thiamine (vitamin B1) is a water-soluble vitamin that is needed for a variety of bodily functions. Thiamine deficiency is rarely seen in developed countries and is often associated with malnutrition as in alcohol dependence, post-bariatric surgeries, or severe restriction of oral intake. It can present with a range of clinical manifestations including cognitive impairment as in Wernicke's encephalopathy or cardiovascular manifestations (wet beriberi). Peripheral neuropathy can be a manifestation of profound thiamine deficiency, so-called dry beriberi, a very rare disease process in the United States. We present a case of a 35-year-old woman whose clinical workup is consistent with dry beriberi. The patient presented initially with a complaint of weakness, affecting the lower extremities, associated with bilateral lower extremity pain exacerbated by cold temperature. Physical examination shows +1 bilateral pitting edema. The clinical picture was initially suggestive of Guillain-Barré syndrome (GBS), a rare autoimmune disorder wherein demyelination of the peripheral nerves occurs. Her lumbar puncture, however, revealed a normal protein content. The patient reported a “water fast” for almost 20 days with no food and a weight loss of approximately 65 pounds. This severe nutritional restriction raised the possibility of vitamin deficiency. Subsequently, EMG was performed and was significant for severe acute BLE sensorimotor axonopathy involving all nerves and muscles tested. At the time, there was little evidence of reinnervation (no polyphasic) but some more innervations remain (interference pattern). MR imaging showed no evidence of transverse myelitis or compressive lesions in the spine. Infectious, toxicological, and other autoimmune etiologies were investigated as well. Her workup was negative for West Nile Virus, with a normal ANA screen, ceruloplasmin, hepatitis panel, serum electrophoresis, and serum vitamin E. Her vitamin B1 level was low (27 nmol/L, the normal range is 70-180 nmol/L). This constellation of findings including the clinical picture, abnormal lab value for vitamin B1, and negative workup for other etiologies, was strongly suggestive of dry beriberi as the cause of her symptoms. Following a month of vitamin supplementation, a balanced diet, and physical therapy sessions, her vitamin B1 level is restored to normal (151 nmol/L). The patient reported improvement in mobility and less dependence on walking aids. We report this case to emphasize the importance of vitamin supplementation in hospitalized patients with a similar condition, especially after rapid significant weight loss.
Postnatal Myelomeningocele Repair of a 26 Weeks Estimated Gestational Age Neonate with Favorable Outcome

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Myelomeningocele (MMC) is a common neural tube defect that leads to lifelong physical and neurological disabilities. Fetal surgery for MMC repair was first introduced in the Management of Myelomeningocele Study (MOMS) trial. This showed improved neurologic outcomes with prenatal repair performed between estimated gestational age (EGA) of 19 0/7 to 25 6/7 weeks. Limited data exists on postnatal MMC repairs at less than 30 weeks EGA and extremely low birth weight due to high mortality rates in this age group.

Our case describes an MMC repair performed postnataally on a 26 6/7 weeks EGA neonate with weight of 650 grams on day of life 3. Due to significant hemodynamic instability requiring vasoactive medications and high-frequency oscillator ventilator (HFOV) support, the repair was performed at bedside in the Neonatal Intensive Care Unit (NICU). No literature exists regarding MMC repair in the NICU and the risks associated with bedside surgical repair. Following the MMC repair, the neonate did well with no infectious concerns. The patient achieved full enteral feeds by mouth and was weaned off all respiratory support prior to discharge. No cerebrospinal fluid (CSF) diversion was needed during the hospitalization or at last follow up at 3 months corrected EGA. An MRI of the brain was performed prior to discharge that showed stable ventriculomegaly with minimal hindbrain herniation.

This case report shows that postnatal MMC repair can be successfully performed on an extremely premature, extremely low birth weight neonate who weighed 650 grams at the bedside on HFOV and inotropic medications. Per the MOMS trial, fetal MMC repair is associated with a 50% reduction in CSF diversion procedures, such as ventriculoperitoneal shunts (VPS). VPS are associated with life-long risk of malfunction and these complications have a negative impact on neurologic outcomes. This case illustrates that early postnatal repair in extremely preterm neonates may also be associated with decreased risk of CSF diversion. Furthermore, fetal surgical repair could be considered past the 25 6/7 weeks EGA cutoff established by the MOMS trial. Long-term follow-up is needed to determine the impact of postnatal repair in premature neonates on their neurodevelopmental outcomes.
Concurrent Diagnosis of Hodgkin Lymphoma and Meningioma in a 17-Year-Old Girl

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Lymphoma is the second most common cancer in adolescents with Hodgkin lymphoma (HL) comprising approximately 3% of cancer diagnoses in children 14 years and younger and approximately 11% of adolescents aged 15-19 years. Meningiomas are uncommon in children aged 0-18, comprising approximately 0.4-4.6% of primary central nervous system (CNS) neoplasms in this age range. We present a case report of concurrent diagnoses of Hodgkin’s lymphoma and meningioma and a comprehensive review of the pediatric literature.

A 17-year-old girl presented with bulky cervical lymphadenopathy along with transient right foot and ankle paresthesia and weakness. Evaluation included an excisional lymph node biopsy and the diagnosis of classical Hodgkin lymphoma, nodular sclerosing subtype, Stage IIIA, intermediate risk was made. During staging of this malignancy, a large intracranial, extraaxial lesion was identified incidentally. The patient’s Hodgkin lymphoma was treated with 4 cycles of chemotherapy, Children’s Oncology Group study AHOD0031, which resulted in complete remission. Resection of her brain lesion was then undertaken and the diagnosis of meningioma, World Health Organization grade 1, was rendered. Interval head imaging studies are ongoing.

A PubMed.gov literature search was performed using the following keywords: Hodgkin’s lymphoma (AND) meningioma, Hodgkin’s lymphoma (AND) brain tumor published between 1964-2022. Articles were filtered for human, and English Language. Since 1964, there have been fewer than 10 published articles regarding Hodgkin’s lymphoma with CNS involvement and 2 articles regarding a concurrent diagnosis of Hodgkin’s lymphoma and CNS tumors, both in adults.

This study describes a patient with concurrent HL and a meningioma and highlights the rarity of concurrent diagnoses of two distinct malignancies, CNS and non-CNS, in the pediatric population. To our knowledge this is the first description of the concurrent presentation of these two neoplasms. Given the rarity of CNS involvement, current staging guidelines for Hodgkin lymphoma do not involve screening of the head in pediatric patients. Given this case, future consideration should be made for baseline CT imaging of the head, especially in cases with minor neurological deficits.
Intraventricular Lesions in Adults: Meningioma and Solitary Fibrous Tumor Are in the Differential Diagnosis

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Background: Intraventricular meningiomas are uncommon but well-described lesions which presumably arise from arachnoidal cells. Solitary fibrous tumors are rare neoplasms of the dura presumably arising from mesenchymal cells incorporated during the formation of the choroid plexus. Herein, we describe two cases of intraventricular lesions indistinguishable by neuroimaging, a meningioma, and a solitary fibrous tumor.

Case Histories:

Patient A:
The patient is a 26-year-old woman, who has a history of seizures and a previously excised left frontal lobe meningioma, WHO grade 2. Her surveillance imaging identified multiple extra-axial, dura-based lesions, the largest along the lateral left frontal lobe, 4.9 x 3.3 x 3.9 cm. Resection of the right intraventricular lesion identified a predominantly fibrous meningioma with extensive collagen deposition. The lesion met criteria for WHO grade 2 based on the identification of focal brain invasion.

Patient B:
The patient is a 39-year-old woman with who presented with several months of worsening headaches. Imaging of her brain revealed a lesion within the atrium of the lateral ventricle, 5.2 x 4.9 x 4.0 cm, with avid contrast enhancement. The lesion was resected, and histologic evaluation revealed haphazardly arranged, and mostly “patternless” cells focally forming fascicular structures with hyalinized staghorn-shaped vasculature. Immunoreactivity for STAT6 was present in nuclei of over 95% of neoplastic cells. Taken together, findings were consistent with solitary fibrous tumor, WHO grade 2.

Literature Review: Meningiomas constitute only 9.8 to 14% of all intraventricular tumors (2). Solitary fibrous tumors are rare intracranial neoplasms that constitute less than one percent of central nervous system tumors (4). To our knowledge, approximately 29 cases of intraventricular SFTs have been described in the current literature. Within the ventricular system, approximately 91% of SFTs were located in the lateral ventricles. Likely similar to the propensity of intraventricular meningiomas to originate in the lateral ventricles, the choroid plexus associated with the lateral ventricles is denser compared to the third and fourth ventricles (1,3).

Conclusions: The differential diagnosis of an intraventricular lesion in an adult typically includes meningioma. While rare, the differential should also include solitary fibrous tumor. Histologic evaluation is necessary to make the diagnosis.
Cystic Meningothelial Lesion of the Skull of an Adult: A Unique Cystic Meningioma vs. Pacchionian Granule-Associated Cyst

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Meningiomas are thought to arise from arachnoid rests, most often in association with the dura, and they may involve the skull. Primary, skull-based, intraosseous (intradiploic, calvarial) meningiomas lacking an associated extraosseous component, often with an associated scalp mass, are occasionally noted, perhaps arising from arachnoid cells associated with a pacchionian granule. This primary intraosseous lesion is distinct from meningioma invasion of the skull from en plaque or dura based, extracranial meningiomas. We describe a unique, cystic skull lesion associated with meningothelial proliferations.

A 39-year-old man underwent a head CT scan after being struck on the left side of his head by a 2 X 4 at work. Imaging identified a right parietal region lytic skull lesion, 3 cm in greatest dimension, with inner and outer tables thinned and a focal dehiscent defect in the inner table; the underlying dura and brain was unremarkable. This lesion was considered to be incidental to the head trauma. The skull containing the lesion was resected and macroscopic and microscopic evaluation of the specimen revealed a benign, lytic / cavitary lesion within the specimen with associated, scant clusters of meningothelial cells with expression of epithelial membrane antigen and E-cadherin. There was no histologic or immunochemical evidence of a blood vessel lesion (e.g. hemangioma) or of an hematopoietic or metastatic neoplasm. Combined findings are consistent with either a meningioma or, less likely, pacchionian granule(s) with associated cystic dilation of the skull. Intracranial meningiomas can manifest with associated cysts, seen in up to 2-4% of cases and are classified as variably typed 1-4. However, no reports in the literature describe a skull-based meningioma with cystic features. Only one somewhat similar case was identified in the literature, with a predominantly skull-based, solid meningioma producing a lytic lesion; this lesion was associated with an intradural rather than intraosseous cyst. Alternatively, arachnoid granulations can produce osteolytic changes but histologic evaluation reveals arachnoid rest-like structures within the bone and minimal cystic change. This report summarizes a unique case of a large, single cystic lesion with associated arachnoid nests.
Choriocarcinoma of the testis is a rare, aggressive germ cell tumor that frequently metastasizes prior to diagnosis with a high incidence of brain metastasis. We present a case of a patient with undiagnosed testicular choriocarcinoma presenting after metastasis to the brain. An 18-year-old man with no significant past medical history presented with headache, nausea, and vomiting. Approximately two weeks prior to presentation he began to experience bitemporal headaches along with visual changes in which he felt his eyes would cross, he felt as if his right eye was bigger and heavier than the left eye, and had a period where his right eye "blacked out," and experienced vomiting 1-2 times per day after the onset of headaches. He felt generally fatigued but with no specific localizing lesions on neurologic evaluation. A computerized tomography (CT) scan of his head revealed a large right inferior frontal intraparenchymal hemorrhagic mass with severe associated edema, right-to-left shift across midline, and brainstem compression. He was admitted to the neuroscience intensive care unit for close observation and surgery was scheduled for the next day. However, he developed a blown right pupil and was taken for urgent resection of the mass. During preoperative urinary bladder catheterization, enlarged right testicle was noted. A right frontal craniectomy was performed for tumor resection. Histologic and immunohistochemical evaluation revealed metastatic germ cell neoplasm with choriocarcinoma differentiation with a majority of neoplastic cells expressing cytokeratin and beta-hCG. No expression of OCT 3/4 was identified, ruling out seminoma and embryonal carcinoma differentiation. CT scan of the chest, abdomen and pelvis documented marked enlargement of the right testis along with multiple bilateral lung lesions. Testicular ultrasound showed an enlarged, heterogeneous, and hypervascular right testis with lobularity and nodularity highly suspicious for neoplasm. Serum beta-hCG was 90,289 IU/L (reference range <1.4 IU/L). Right radical inguinal orchiectomy was performed. Examination identified choriocarcinoma with no histologic or immunohistochemical evidence of other forms of germ cell differentiation. Chemotherapy was initiated. This report documents an unusual presentation of a testicular germ cell neoplasm to the brain and underscores the importance of regular testicular examinations in young men.
Thiamine Deficiency-Associated Peripheral Neuropathy (Dry Beriberi) Resulting from a 20-Day “Water Fast”

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Thiamine (vitamin B₁) is a water-soluble vitamin that is needed for a variety of bodily functions. Thiamine deficiency is rarely seen in developed countries and is often associated with malnutrition in the setting of severe restriction of oral intake and following bariatric and gastric bypass surgeries. Deficiency of thiamine can present with a range of clinical manifestations including cognitive impairment with Wernicke's encephalopathy or cardiovascular manifestations (wet beriberi). Peripheral neuropathy can also be a manifestation of profound thiamine deficiency, so-called dry beriberi, a very rare disease process in the United States. We present a case of a patient whose clinical workup is consistent with dry beriberi.

A 35-year-old woman presented with weakness affecting the lower extremities associated with bilateral lower extremity pain exacerbated by cold temperature. Physical examination identified +1 bilateral pitting edema. The patient reported a “water fast” for approximately 20 days with no food and a weight loss of approximately 65 pounds. While the clinical picture was initially suggestive of Guillain-Barré syndrome, lumbar puncture revealed a normal cerebrospinal fluid protein concentration. Electromyography was significant for severe acute bilateral lower extremity sensorimotor axonopathy. Magnetic resonance imaging of the spinal column showed no evidence of transverse myelitis or compressive lesions. The patient’s severe nutritional restriction raised the possibility of vitamin deficiency and her vitamin B₁ level was 27 nmol/L (reference range: 70-180 nmol/L). Her workup was negative for evidence of an infectious disease and antinuclear antibody screen, ceruloplasmin, hepatitis panel, serum electrophoresis, and other tests were within normal limits.

The constellation of clinical and laboratory findings including reduced thiamine and an otherwise negative workup for other etiologies was strongly suggestive of dry beriberi. Following a month of vitamin supplementation, a balanced diet, and physical therapy sessions, her vitamin B₁ level was restored to the normal range (151 nmol/L) and the patient showed improvement in mobility and less dependence on walking aids. We report this case to emphasize the danger of severe nutritional deficiency.
Extramedullary Spinal Presentation of Intracranial Mesenchymal Tumor with FET-CREB Fusion: Case Report with Literature Review

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Intracranial mesenchymal tumors are a recently recognized entity representing a group of neoplasms with FET-CREB fusions. These tumors typically present in children and young adults where a spectrum of clinical behavior has been described, variably with slow growth to quick recurrence and metastasis. As the name suggests, majority of these neoplasms occur within the cranium with close association to the dura, particularly supratentorial. Herein, we report a case of a spinal intracranial mesenchymal tumor; only one other spinal lesion is reported in the literature to date.

A 53-year-old woman presented with recent development of pain radiating to the left inguinal area with associated left leg paresthesia. Magnetic resonance imaging of her spine revealed a contrast-enhancing right-sided T11 mass, 1.8 x 1.3 x 1.9 cm, which extended through the right T11-T12 foramen with displacement of the spinal cord. The radiological differential diagnosis included schwannoma and meningioma. The patient underwent laminectomy with microsurgical resection.

Histologic evaluation of the lesion revealed a predominantly spindle cell neoplasm with ovoid to rounded nuclei. The cells are separated by moderate amounts of extracellular matrix material, containing glycosaminoglycans with admixed collagen banding. Immunoprofiling revealed focal expression of epithelial membrane antigen and S-100 with diffuse expression of desmin, E-cadherin, CD99, and somatostatin receptor 2 (SSTR2). Fluorescence in situ hybridization revealed an Ewing sarcoma (EWSR1) gene rearrangement. Chromosomal microarray and fusion / transcript analysis identified a EWSR1::CREB1 fusion.

Given these combined findings were consistent with diagnosis as intracranial mesenchymal tumor, FET:CREB fusion-positive. EWSR1 is the most frequent FET family gene showing rearrangement. Cases diagnosed to date have a broad range of histologic and immunohistochemical findings, with histology and antigen profile variable with the fusion partners. Molecular evaluation is essential for the diagnosis. These neoplasms typically arise in extra-axial intracranial locations, but rarely are seen in the spine, as in this case, in an extra-medullary location.

The differential diagnosis of an extra-medullary spinal column lesion in an adult includes schwannoma, solitary fibrous tumor, and meningioma. While rare, the differential should also include intracranial mesenchymal tumor. Biopsy or resection with histologic, immunohistochemical, and molecular characterization is necessary for definitive diagnosis.