



FLOW

Hydrocephalus Research Symposium

at

HA **CONNECT**²⁶

PROGRAM AND ABSTRACTS



JULY 23 - 25, 2026
Indianapolis, Indiana



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THURSDAY, JULY 23, 2026

4:30-6:15 PM

Opening and Welcome

4:30 PM - 4:38 PM

Monica Chau, PhD and Samantha Lanjewar, PhD
Hydrocephalus Association

Genetics

Keynote: How Chromatin Remodelers Cause Congenital Hydrocephalus

4:38 PM - 4:51 PM

Ryann Fame, PhD
Stanford University

Keynote: A Developmental Genomic Atlas of the Human Cerebrospinal Fluid-Ventricular System

4:51 PM - 5:04 PM

Kristopher Kahle, MD, PhD
Massachusetts General Hospital

Engineering and Device Development

Keynote: Decoding Shunt Obstruction: The Role of the Microenvironment

5:04 PM - 5:17 PM

Carolyn Harris, PhD
Wayne State University

Simulating Hydrocephalus in Cadaveric Models: An MRI-Validated Approach to CSF Flow Dynamics Training

5:17 PM - 5:25 PM

Kayla Gray, MS
St. Joseph's Hospital and Medical Center

Current VP Shunt Valves Fail to Control Gravity- and Pulsation-Driven Overdrainage

5:25 PM - 5:33 PM

Joyce Koueik, MD, MS
University of Wisconsin

Home ICP Monitoring – A New Paradigm for Management of Patients with Hydrocephalus

5:33 PM - 5:41 PM

Sarah-Jane Guild, PhD
University of Auckland

Keynote: Quantitative, Non-Invasive Shunt Flow Measurement for Improved Management of Shunted Hydrocephalus

5:41 PM - 5:54 PM

Peter Chiarelli, MD, PhD
Phoenix Children's Hospital

Computational Analysis of Progressive Clogging in a Ventriculoperitoneal Shunt Under Pulsatile Flow

5:54 PM - 6:02 PM

Alireza Asgharpour Masouleh, MS
Oregon State University

Longitudinal MRI Characterization of Ventricular Expansion in a Porcine Model of IVH

6:02 PM - 6:10 PM

Tarek Bacha, BS
University of California, Davis

Multimodal Modeling for Personalized Prediction of Shunt Valve Pressure in Pediatric Hydrocephalus (virtual)

6:10 PM - 6:15 PM

GuoXuan Liu, Zhejiang University



FRIDAY, JULY 24, 2026

8:30-10:30 AM

Opening and Welcome

Monica Chau, PhD and Samantha Lanjewar, PhD
Hydrocephalus Association

8:30 AM - 8:35 AM

Distinguished Lecture

Distinguished Lecture: Critical Overview of Preclinical Modeling for Therapeutic Development

James 'Pat' McAllister II, PhD
Virginia Commonwealth University

8:35 AM - 8:50 AM

Modeling

Keynote: Developmental Stage-Dependent Transcriptomic Responses to Neonatal Intraventricular Hemorrhage

Brandon Miller, MD, PhD, FAANS
Medical University of South Carolina

8:50 AM - 9:02 AM

Keynote: Feasibility of Short-Term Multimodal Assessment in a Neonatal Piglet Model of Intraventricular Hemorrhage

Alexandra Hochstetler, PhD
Boston Children's Hospital and Harvard Medical School

9:02 AM - 9:14 AM

Altered Functional Connectivity in a Mouse Model of Neonatal Germinal Matrix Hemorrhage-Intraventricular Hemorrhage

Shriya Koneru, BA
Washington University in St. Louis

9:14 AM - 9:22 AM

An In Vivo Method for Quantifying Complex Dysregulated CSF in a Rat Model of Posthemorrhagic Hydrocephalus of Prematurity Shows Tunable CSF Dynamics

Hawley Helmbrecht, PhD
Johns Hopkins University School of Medicine

9:22 AM - 9:30 AM

Mechanisms

Keynote: The Hydrocephalus Research Center, Indiana University, Indianapolis

Bonnie Blazer-Yost, PhD
Hydrocephalus Research Center, Indiana University, Indianapolis

9:30 AM - 9:42 AM

TRPV4-AMPK Signaling Axis as a Therapeutic Target for Hydrocephalus

Gowthami Mahendran, PhD
Indiana University, Indianapolis

9:42 AM - 9:48 AM

Inflammatory Modulation of TRPV4 in Human Choroid Plexus Epithelial Cells

Maryam Torabi, MS
Indiana University, Indianapolis

9:48 AM - 10:54 AM



FRIDAY, JULY 24, 2026 (CONTINUED)

8:30-10:30 AM

Drug Treatment

Keynote: SCEMPI: Insights from Preclinical Studies to Clinical Trial

Lauren Jantzie, PhD

Johns Hopkins University School of Medicine

9:45 AM - 10:06 AM

Ventriculomegaly Disrupts Neurogenesis and Promotes Neuronal Hypertrophy and Inflammation in a Tmem67^{-/-} Rat Model of Congenital Hydrocephalus

David Audu, PhD

Indiana University, Indianapolis

10:06 AM - 10:14 AM

Serum Glucocorticoid-Induced Kinase 1 (SGK1) Inhibition as a Preclinical Therapy for Hydrocephalus

Fatemeh Bidgoli, BSc

Indiana University, Indianapolis

10:14 AM - 10:22 AM

Access to Care

An Integrated Model to Improve Access to Care and Quality of Life for Children with Hydrocephalus in Uganda (virtual)

Ronald Kibirige, PhD

Makerere University, Uganda

10:22 AM - 10:30 AM



SATURDAY, JULY 25, 2026

3:00-4:30 PM

Poster Presenters

Optic Nerve Head Edema Associated with Ventriculomegaly in Aged TMEM67+/- Rats

Hamid Aboutalebkhodaeian, PhD
Indiana University, Indianapolis

Dosing and Treatment Timing Refinement of AAV-Based Choroid Plexus Ablation

Leena Bandaras
University of Cincinnati

Living Beyond the Shunt: Occupational Therapy, Family Voices, and Quality of Life in Pediatric Hydrocephalus

Lauren Bange, BS
Notre Dame of Maryland University

Histopathological Evidence of Ependymal Disruption and Altered IBA1+ Macrophage Organization in a Neonatal Piglet Model of Intraventricular Hemorrhage

Waizo Chen, BS
Massachusetts General Hospital and Harvard Medical School

Cortical Iron Metabolism is Chronically Altered in Posthemorrhagic Hydrocephalus

Lauren Guyer, BA
Johns Hopkins University School of Medicine

Reducing Brain Inflammation After Brain Bleeds by Inhibiting CSF Immune Cells

Audrey Kruse, BS
Indiana University, Indianapolis

Cerebrospinal Fluid Obstruction and Ventriculomegaly in Experimental Hydrocephalus

Angela Lane
Washington University in St. Louis

Under Pressure: Investigating the Role of the Mechanosensitive Channels TRPV4 and Piezo1 in a Human Choroid Plexus Epithelial Cell Model

Verayna Newland, BS
Indiana University, Indianapolis

Characterizing a Genetic Adult Rat Model of Normal Pressure Hydrocephalus

Jane Obiako, MS
Indiana University, Indianapolis

Retinal and Optic Nerve Head Structural Changes in an Adult Post-Hemorrhagic Hydrocephalus Rat Model

Nasim Shafiee Nejad, BS
Indiana University, Indianapolis

Temporal and Regional Mitochondrial Dysfunction Following Neonatal Intraventricular Hemorrhage

Hemendra Vekaria, PhD
Medical University of South Carolina

Circadian Rhythm Disruptions in a Post-Hemorrhagic Hydrocephalus Animal Model

Amber Zack, BS
Indiana University, Indianapolis

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GENETICS



THURSDAY, JULY 23
4:30 - 6:15 PM

How Chromatin Remodelers Cause Congenital Hydrocephalus

Arjun Rajan^{1,2}, Ran Chen³, Luke Liu¹, Ryan Humphries¹, Ryann M. Fame¹

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ABSTRACT

Congenital hydrocephalus (CH) afflicts 1:770 babies every year. Genetic factors account for over 40% of cases of CH, a suite of these genes encode chromatin remodeling complexes that shifts expression in very early brain development. How early chromatin remodeling regulates patient relevant CSF dynamics remains largely unexplored.

Using a new conditional mouse model, we find that heterozygosity for one such chromatin remodeler in neural progenitors causes obstructive hydrocephalus, accompanied by neural progenitor chromatin state shifts, linking chromatin remodeling to CSF homeostasis. **Thus, we propose that inappropriate dosing of chromatin remodelers during early development causes hydrocephalus by dysregulating chromatin remodeling in neural progenitors to alter regional fate specification in a way that blocks CSF outflow.**

Here, we present a new heterozygous mouse model of CH that presents with key patient-relevant phenotypes. First this model is heterozygous for the disease-causing mutation, which is consistent with patients who present with dominant mutations. Second, the CH phenotype is partially penetrant, consistent with patients who inherit these mutations from unaffected parents. Third, this model develops progressive perinatal obstructive hydrocephalus. Fourth, this model does not present with neural tube closure defects, consistent with CH patients who harbor this mutation. Because this model so closely resembles patients, we use it to investigate key questions. We identify **when** chromatin remodeling regulates CSF volume during development; **where** chromatin remodeling changes chromatin accessibility; and **how** target-specific chromatin binding enables function. **Outcomes include uncovering fundamental basic mechanisms of early CSF volume regulation and informing underlying disease mechanisms of congenital obstructive hydrocephalus.**

LAY SUMMARY

Congenital hydrocephalus (CH) afflicts 1:770 babies every year, causing 40,000 annual hospital admissions and lifelong neurological morbidity including dozens of brain surgeries for a single child. Our goal is to improve the screening and diagnosis of hydrocephalus by identifying the causes and processes that lead to hydrocephalus (e.g. genetic influences, inflammation). Building on recent findings that early neural stem cells express genes associated with CH, we are using cutting-edge imaging, genetic, molecular, and genomic techniques to test the hypothesis that neural progenitors in early brain development regulate CSF volume via these hydrocephalus-associated genes. Outcomes of this innovative research program will have implications for how we understand fundamental mechanisms of CH and will inform future efforts to target CSF-modulating tissues to mitigate disorders of CSF accumulation.

A Developmental Genomic Atlas of the Human Cerebrospinal Fluid-Ventricular System

Garrett Allington^{1,2#}, Evan Dennis^{1#}, Qiang Li^{1#}, Stephen McGee³, Neel H. Mehta¹, Kedous Y. Mekbib^{1,2}, Phan Q. Duy¹, Baojian Fan¹, Kristopher T. Kahle^{1,4,5}

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ABSTRACT

The cerebrospinal fluid (CSF)-ventricular system plays a central role in brain development, yet the genetic mechanisms that coordinate its formation with cerebral cortical development remain incompletely understood. To define the developmental genetic architecture of the human CSF-ventricular system, we performed an integrated genomic and multi-omic analysis of approximately 2,700 parent-offspring trios affected by congenital cerebral ventriculomegaly (CCV), a common developmental brain phenotype characterized by enlargement of the cerebral ventricles. We identified a substantial contribution of rare damaging de novo variants in mutation-intolerant genes, implicating dozens of significant and high-confidence risk genes. These genes converged on biological pathways regulating chromatin remodeling, epigenetic control of gene expression, and phosphoinositide 3-kinase signaling. Developmental transcriptomic analyses revealed that implicated genes are preferentially expressed in fetal neural progenitor populations and periventricular neurogenic regions during critical periods of corticogenesis. Functional studies in mouse models demonstrated that disruption of representative risk genes alters both ventricular morphogenesis and cortical development through dysregulation of neural progenitor proliferation, differentiation, and maturation. Despite diverse genetic etiologies, pathogenic variants converged on shared developmental mechanisms linking CSF dynamics with the growth and organization of the cerebral cortex. These findings support a model in which coordinated genetic programs govern the coupled development of the ventricular system and brain parenchyma, and that disruption of these programs contributes to a spectrum of neurodevelopmental phenotypes. More broadly, this work establishes the CSF-ventricular system as an integral component of human brain development and provides a framework for understanding how early developmental perturbations influence lifelong neurological outcomes.

LAY SUMMARY

Congenital enlargement of the brain's fluid-filled ventricles (ventriculomegaly) is a common developmental brain abnormality that is often associated with hydrocephalus, autism, and other neurodevelopmental disorders. By studying nearly 2,700 affected children and their

parents, we identified genetic changes that disrupt key pathways controlling early brain and cerebrospinal fluid system development. Our findings show that many cases result from altered regulation of neural stem cells, which are essential for normal brain growth. This work helps explain why some children continue to experience developmental challenges despite successful treatment of hydrocephalus. In the future, combining genetic testing with brain imaging may improve diagnosis, guide clinical care, support earlier intervention, and provide families with more accurate information about prognosis and long-term outcomes.



ENGINEERING AND DEVICE DEVELOPMENT



THURSDAY, JULY 23
4:30 - 6:15 PM

Decoding Shunt Obstruction: The Role of the Microenvironment

Carolyn Harris, PhD^{1,2}, Christopher Roberts¹, Madelynn Thomas², Prashant Hariharan, PhD^{2,3}, Kenae Thompson², Sebastian Pernal⁴, Anastasia Smith, PhD⁵, Regan Gaskin⁵, and Brandon Rocque, MD⁵

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ABSTRACT

Ventricular catheter shunt obstruction is a major problem in the treatment of hydrocephalus, with current treatments relying on a nearly one-size-fits-all approach to ventricular catheter design that craves optimization. With a heterogenous population, we look to large data aggregates from our multi-center biobank with specific descriptive snapshots during accrual for the last two years. Here, we present a cohort of these results with specific attention to how and why shunt catheters are obstructing. We examined how varying shunt placement, modifications to catheter architecture, and ventricular morphology shifted obstruction outcomes. Specifically, we categorized data into that which was analyzed in the operating room via endoscope (overall in the lumen and in each catheter hole), that which was analyzed on pre- and post-revision imaging, symptomatology, and that which was analyzed on and in the catheter at the time of failure. We compared these data to computational fluid dynamic simulation models of flow distribution through the shunt catheter as a function of ventricular morphology, insertion approach, and shunt catheter architecture. These data indicate that, surprisingly, shunt obstruction does not always follow a linear trend with flow distribution or overall resistance as was previously postulated. The impact of shear and pressure gradient on and in the catheter holes and on neighboring tissues should be considered for shifts in the microenvironment around the catheter that can instigate cellular reactivity and tissue contact or pull-in. Some of these variances are currently under investigation and discussed in brief. Generally, these data suggest that shunt obstruction is likely driven by the dynamic microenvironment surrounding the ventricular catheter, influenced by not only flow distribution, but by effects of tissue contact or proximity.

Simulating Hydrocephalus in Cadaveric Models: An MRI-Validated Approach to CSF Flow Dynamics Training

Kayla E. Gray^{1,2}, Jenna Meyer^{3,4}, Lucas Conner⁴, Michael Foster², James Mankin², Peter Chiarelli⁴

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ABSTRACT

Background: Despite hydrocephalus' prevalence, models that represent the condition have been primarily limited to benchtop shunt configurations, absent the realistic human anatomy of ventricular and cisternal architecture. Existing platforms are limited in their ability to study physiological properties of ventricular dilation or CSF dynamics, in relation to interactions generated between the CNS space and mechanical shunt hardware.

Purpose: This pilot study describes the development and preliminary validation of an anatomically relevant cadaveric model created through the Knowledge Donor Program (KDP). We utilized novel tissue fixative methods and realistic shunt design that allow for simulation of the in vivo shunted condition. We aim to establish feasibility of inducing/confirming radiographic hydrocephalus in a cadaveric specimen using real-time knowledge and direct manipulation of fluid inflow, intraventricular pressure, and intra-abdominal pressure, along with the combined use of both invasive and non-invasive methods for shunt system assessment/visualization

Methods: Whole-body cadaveric specimens were prepared through KDP, and baseline cranial MRI was obtained to characterize ventricular anatomy. External ventricular drain placement and controlled isotonic saline injection were used to influence ventricular pressure and simulate CSF production, in a manner consistent with elevated pressures in hydrocephalus. Post-injection MRI was performed to observe ventricular response to graded pressure and fluid inflow conditions.

Results: Preliminary findings show feasibility of this approach. The model was able to successfully replicate gross morphological changes associated with increased intraventricular CSF volume.

Conclusion: This pilot work aims to establish proof of concept for a cadaveric hydrocephalus model that is well-integrated with typical neuroimaging modalities (e.g. structural CT/MRI, advanced flow-imaging MRI, neuro-vascular mapping techniques) that may be used to better study shunted hydrocephalus and fluid dynamics in shunted patients. The KDP platform offers a reproducible simulation platform that may yield insight into CSF physiology, allowing a facile means for device development, unique training, and CSF flow research.

LAY SUMMARY

A whole-body-donor-based model of hydrocephalus has been designed to replicate basic anatomy relevant to hydrocephalus, allowing direct investigation of factors such as ventricular enlargement as well as flow patterns within the brain and shunt itself. Images can be performed that are the same as those performed for living patients, with the model allowing us to better understand and interpret the meaning of interactions between the human central nervous system and a shunt. This early-stage work shows that it is possible to create a tool to study human physiology that contains realistic human anatomy, providing surgeons, trainees, and researchers a safe and realistic way to practice procedures and study how fluid moves through the brain.

Current VP Shunt Valves Fail to Control Gravity- and Pulsation-Driven Overdrainage

Joyce Koueik MD, MS¹, Roy Chebel MD¹, Anas Abou Merhi MD¹, Alex Pinto MA, Joshua Medow MD, PhD¹, Christopher Luzzio MD², Murielle Hsu, PhD², David Hsu MD, PhD^{2*}, Bermans Iskandar MD^{1*}

¹Department of Neurological Surgery, University of Wisconsin, Madison, Wisconsin

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ABSTRACT

Background: The Pseudo-Ventricle (PV) platform was developed at the University of Wisconsin–Madison to evaluate ventriculoperitoneal (VP) shunt valve performance under physiologic conditions known to influence drainage, including patient position (gravity), pulsations (cardiac or Valsalva-like forces), and ventricular/brain compliance.

Objective: This study aimed to compare the performance of commercially available shunt valves, focusing on the consistency of cerebrospinal fluid (CSF) drainage and the occurrence of over- and under-drainage.

Methods: The PV platform consists of a rigid pseudo-ventricle, compliance chamber, pulsation generator, position control unit, and integrated pressure sensors. The system quantified flow rates across different shunt valves over 10-minute intervals under controlled simulated physiologic conditions, including orientation (horizontal vs. vertical), compliance (low, medium, high), and pulsation force (none, low, medium, high). Valves tested included low-, medium-, and high-pressure Chhabra®; non-programmable low-, medium-, and high-pressure PS Medical®; Delta 2.0®; OSV®; Codman Certas® Plus (4.0); and the Strata® valve (1.0). Statistical analysis was performed using three-way ANOVA, with significance defined as $p < 0.05$.

Results: Compared with the horizontal position, the vertical position resulted in increased drainage across all valves. Pulsation similarly increased drainage across valve types. The magnitude of gravity- and pulsation-driven drainage was strongly influenced by system compliance, regardless of valve type. Importantly, no statistically significant differences in drainage magnitude were observed among the valves tested.

Conclusion: VP shunt valves appear inherently susceptible to chronic overdrainage, particularly in the vertical position. No currently available valve, whether low-cost devices commonly used in low- and middle-income countries or advanced programmable valves used in high-income settings, is specifically designed to mitigate the combined effects of gravitational and pulsatile forces. As long as shunt valves remain exposed to these physiologic pressures, which generate repetitive bursts of high CSF outflow, overdrainage is likely to persist.

LAY SUMMARY

We tested a lab model that mimics the brain and spinal fluid system to see how different ventriculoperitoneal (VP) shunt valves drain fluid under everyday forces like body position (standing vs lying down), the pulsing of the heart or any straining force. Across many commonly used valves — from basic, low-cost non-programmable valves to advanced

programmable ones — we found that standing up and heartbeat-like pulses both increase drainage. The stiffness of the brain/ventricle system also changed how much extra drainage occurred. Importantly, no valve in our tests reliably prevented this extra drainage. That means all current shunt valve designs can be prone to overdraining in real life, especially when the person is upright.

Home ICP Monitoring – A New Paradigm for Management of Patients with Hydrocephalus

Sarah-Jane Guild^{1,2}, Sang Ho Kim², Peter Heppner³, John Windsor¹, P Alan Barber^{1,3}, Doug Campbell³, Davina McAllister³, Simon Malpas^{1,2}

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ABSTRACT

INTRODUCTION: Intracranial pressure (ICP) is usually measured in controlled hospital environments. However, shunt failure in hydrocephalus remains unpredictable, and the ability to monitor ICP remotely over long periods is a major unmet clinical need. A novel telemetric ICP system (Kitea Health) has recently been approved for first-in-human studies in New Zealand. This study reports early safety outcomes and initial evidence of efficacy.

METHODS: Adults and children undergoing cerebrospinal fluid (CSF) shunt insertion or revision at Auckland City Hospital were eligible. The Kitea sensor was implanted intraparenchymally, parallel to the ventricular catheter, during surgery. Participants were followed for three months under standard clinical care, with continued optional use thereafter.

RESULTS: Twenty-one participants (11 adults, 10 paediatric) with normal pressure hydrocephalus, idiopathic intracranial hypertension, or acquired hydrocephalus were recruited. No sensor-related adverse events occurred. All devices remained functional throughout the study, and ICP readings were stable over time. Many participants continued ICP monitoring beyond three months, with the longest follow-up extending to 24 months without complication. Patients reported decreased anxiety due to the ability to measure ICP at home. Several participants presented with symptoms concerning for shunt failure; in all cases, mean ICP and ICP waveform amplitude were elevated, demonstrating a strong correlation between symptoms and raised ICP.

CONCLUSIONS: This first-in-human study demonstrates that the Kitea telemetric ICP sensor is a safe and reliable tool for long-term ICP monitoring in patients with hydrocephalus requiring CSF shunting. These early findings support its potential integration into routine care to enable remote, home-based ICP surveillance.

LAY SUMMARY

People with hydrocephalus often rely on a shunt to drain excess fluid from the brain. Shunts can stop working without warning, and doctors currently have no way to monitor brain pressure at home. This study tested a new wireless pressure sensor from Kitea Health that can be implanted during shunt surgery to continuously measure brain pressure.

Twenty-one patients received the device, including children and adults. No safety problems occurred, and the sensor continued to work reliably for up to two years. The pressure readings helped identify when symptoms were caused by rising brain pressure. This technology may help patients and clinicians make decisions and reduce stress by allowing pressure checks at home.

Quantitative, Non-Invasive Shunt Flow Measurement for Improved Management of Shunted Hydrocephalus

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ABSTRACT

Disorders of abnormal cerebrospinal fluid (CSF) flow are common conditions treated by neurosurgeons, yet many questions still exist pertaining to clinical management and operative decision-making that lack tools to guide therapy. Hydrocephalus is a serious condition of inappropriate imbalance between CSF production and reabsorption, and ventricular shunts are used for life-saving cerebrospinal fluid diversion. Existing methods for shunt evaluation provide correlative/qualitative information, leading to commonplace clinical diagnostic challenges. Our group has focused on non-invasive MRI-based sequence development and direct clinical investigation to address answers to neurosurgical questions with an active clinical need. Both phase-contrast MRI methods and spin-labeled inversion-recovery methods were used to provide measurement of CSF flow within ventricular shunts during the study period. We were able to investigate shunt flow rate/physiology in human patients, including a first-of kind assessment for mean cerebrospinal fluid flow rate, along with differences in flow rate among certain hydrocephalus etiologies and shunt types. New application of scanning has focused on the flow dynamics within catheter tubing, with the aim to decipher patterns of flow that are reflective of shunt malfunction and could also provide information that guide improved shunt technology development. There are a wide landscape and a research need for the development of non-invasive biomarker strategies that can be specifically designed to address common questions within standard surgical workflow. The mission of our multi-institutional CSF Flow Dynamics Group (CFDG) is to bridge MRI physics with patient care and address real problems among conditions pertaining to CSF flow in the human brain, for the benefit of kids and their families.

Computational Analysis of Progressive Clogging in a Ventriculoperitoneal Shunt Under Pulsatile Flow

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ABSTRACT

Ventriculoperitoneal (VP) shunt obstruction is a leading cause of shunt failure, yet the fluid and structural effects of progressive clogging are not fully understood. In this study, a computational model evaluated a VP shunt within a surrounding fluid domain under pulsatile flow across four conditions: unclogged, 50% clogged, 66% clogged, and 75% clogged. The simulations evaluated changes in velocity, pressure, shear-related flow behavior, and structural deformation as occlusion severity increased. The results demonstrated that progressive clogging significantly changed the internal and local flow environment of the catheter. In the unclogged case, flow exchange through the inlet-hole region was more spatially distributed, leading to smoother velocity and stress distribution. As clogging intensified, flow was increasingly redirected through the remaining open portals, producing localized jet-like flows, steeper velocity gradients, and more focused fluid-mechanical loads near the functional holes. Although the pressure response remained pulsatile in all cases, higher levels of clogging led to greater spatial variability in the pressure distribution. Structural analysis showed deformation primarily resulted from an axial displacement gradient along the catheter, with local stress and deformation becoming more focused near the open inlet holes as obstruction worsened. The 75% clogged case exhibited the most notable flow channelization and local concentration effects. These findings suggest that progressive shunt clogging does more than diminish flow area; it also redistributes hydraulic and mechanical loads, which may contribute to ongoing dysfunction and failure. This computational framework could aid in designing VP shunts with better resistance to obstruction and more stable flow under physiological pulsatile conditions.

LAY SUMMARY

VP shunts are medical tubes used to drain excess cerebrospinal fluid from the brain, but they often fail because their tiny inlets become blocked over time. In this study, we used computer simulations to examine how different levels of blockage affect fluid flow and mechanical behavior in a shunt under pulsating conditions that mimic the body. We compared an unclogged shunt with shunts that were 50%, 66%, and 75% clogged.

The simulations showed that as more holes became blocked, the fluid was forced to pass through fewer open pathways. This made the flow more concentrated and uneven, resulting

in stronger local fluid velocities and sharper changes in pressure and stress around the remaining open holes. The shunt also exhibited changes in deformation patterns, with more localized mechanical effects becoming apparent as clogging worsened. The most heavily clogged case exhibited the highest flow and loading concentrations.

These results suggest that shunt clogging is not only a matter of reduced flow but also a change in how forces and pressure are distributed within the device. Understanding these effects can help researchers and engineers design shunts that are more reliable and less likely to fail.

Longitudinal MRI Characterization of Ventricular Expansion in a Porcine Model of IVH

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ABSTRACT

Hydrocephalus affecting infants, in the earliest and most vulnerable phase of brain development, warrants deeper investigation with representative large animal models. Intraventricular hemorrhage (IVH) remains a major complication of prematurity, with severe cases frequently progressing to post-hemorrhagic hydrocephalus and long-term neurodevelopmental impairment. Piglet models of hydrocephalus have rarely been reported, and normal developmental trajectories of brain and segmented ventricular volumes are not available. Here, we developed a machine learning (ML) pipeline to quantify fluid compartment volumes across the first month of development in piglets, establishing normative growth trajectories. Building on this approach, we next characterized volumetric changes in a piglet model of IVH. IVH was induced in 1–2-week-old pigs by intracerebroventricular injection of 2cc autologous blood (n=4) with uninjected littermates as controls (n=4). Magnetic resonance imaging (MRI) was performed 2 days prior to surgery, and at 2, 7, 14, and 21 days post-injection. In controls, ML-based volumetric analysis revealed coordinated growth of brain parenchyma (1.55-fold) and CSF compartments (1.4-fold) over postnatal days 1–35, with stable intracranial volumes (parenchyma ~75%, CSF ~25% of skull volume). Ventricular CSF remained ~10% of total CSF throughout development. In this piglet IVH model, the lower volume of blood injection (2cc) effectively replicated Papile grade 2 IVH with variable progression to grade 3. Three animals showed moderate ventriculomegaly (2–3-fold increase in ventricular CSF), while one animal (25%) developed symptomatic hydrocephalus (10-fold increase). This variability mirrors clinical heterogeneity observed in humans and the methods establish a replicable protocol for assessing hydrocephalus in piglets.

LAY SUMMARY

The development of improved animal models may accelerate the development of novel therapies for infants with post-hemorrhagic hydrocephalus (PHH). PHH develops when preterm infants suffer from spontaneous brain bleeding into the brain's fluid-filled spaces, disrupting normal fluid absorption and causing the accumulation of excess brain fluid and pressure. Currently, patients are implanted with shunt catheters to divert excess fluid to other regions of the body. Surgical failures are common, and patients often require multiple surgeries throughout their lifetime. Our lab is studying piglet models of this condition to support the development a one-time gene therapy to reduce fluid production and prevent dangerous buildup. This approach has shown success in mice and should be tested in the piglet model to support a future clinical trial.

Multimodal Modeling for Personalized Prediction of Shunt Valve Pressure in Pediatric Hydrocephalus

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ABSTRACT

Hydrocephalus is the leading cause of pediatric neurosurgery, and ventriculoperitoneal shunting is the primary treatment. However, the setting of shunt valve pressure heavily relies on physicians' experience and iterative clinical tests, which may lead to complications such as underdrainage or overdrainage. This study proposes a multimodal deep learning model which enables personalized prediction of shunt valve pressure based on neuroimages and clinical reports via foundation models. In the proposed method, a large language model (Qwen3-Max) was employed to extract etiological semantics from clinical reports and a prompt-free fine-tuned Segment Anything Model (SAM1) was developed for the lateral ventricular segmentation utilizing multi-axis slice inputs. By integrating etiology, MRI morphological features (ventricular volume and ventricular-to-brain ratio [VBR]), and clinical symptoms (Glasgow Coma Scale [GCS] and sunset sign), a logistic regression model was developed to predict shunt valve pressure. The proposed model achieved a mean AUC of 0.863 (± 0.101) on a cohort of 200 cases using 5-fold cross-validation and an AUC of 0.849 on an internal validation set of 50 cases. Notably, the model maintained a 93.1% recall for the high-pressure setting group, prioritizing high sensitivity to minimize overdrainage-related complications. Furthermore, feature importance analysis revealed that tumor-related etiology was the strongest predictor of a high-pressure setting, whereas a high VBR and infectious etiology were the primary indicators for a low-pressure setting.

LAY SUMMARY

Pediatric hydrocephalus often requires the surgical implantation of a shunt system to drain excess cerebrospinal fluid. However, the shunt valve pressure is mainly decided based on clinical experience. Improper shunt pressure settings may lead to additional clinical visits and further adjustments. In this work, we developed an AI model that analyzes the patient's etiology, brain MRI, and clinical symptoms to recommend the most appropriate shunt valve pressure to physicians. This approach could enable personalized pressure settings for each patient with improved accuracy, which may reduce the likelihood of repeated pressure adjustments and assist physicians in evaluating surgical benefits preoperatively.



DISTINGUISHED LECTURE



FRIDAY, JULY 24
8:30 - 10:30 AM



Critical Overview of Preclinical Modeling for Therapeutic Development

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ABSTRACT

The development of effective therapies for hydrocephalus depends on the availability of preclinical models that accurately replicate the biological, physiological, and clinical features of the disease. Additional considerations should also be given to FDA guidelines for biocompatibility/safety and funding agency requirements for efficacy. Over the past several decades, experimental hydrocephalus research has expanded substantially, incorporating congenital, acquired, and genetic models across multiple species, as well as *in vitro* approaches which are often an important prerequisite for *in vivo* testing. These models have provided important insights into disease pathogenesis, neuroinflammation, white matter injury, cerebrospinal fluid (CSF) dynamics, and treatment response. However, no single model fully captures the multifactorial complexity and heterogeneity of hydrocephalus observed in patients.

This presentation will provide a broad critical overview of the strengths, limitations, and translational relevance of commonly used preclinical hydrocephalus models. Particular emphasis will be placed on selecting models that are appropriate for specific research questions, including studies of disease mechanisms, biomarker discovery, device development, and pharmacological interventions. The presentation will also discuss lessons learned from large-animal and rodent models, the importance of incorporating clinically relevant outcome measures, and considerations for improving reproducibility and therapeutic translation. Recent advances in experimental modeling, neuroimaging, and longitudinal assessment have created new opportunities to evaluate potential therapies beyond traditional surgical approaches.



MODELS



FRIDAY, JULY 24
8:30 - 10:30 AM

Developmental Stage-Dependent Transcriptomic Responses to Neonatal Intraventricular Hemorrhage

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ABSTRACT

Neonatal intraventricular hemorrhage (IVH) is a major complication of preterm birth, yet how developmental stage influences the brain's response to injury remains unclear. Our prior work showed that injection of blood products and postnatal day 5, but not postnatal day 2, leads to ventricular enlargement and white matter loss. To follow up on these results, we planned to analyze all brain cell populations in this model to understand how developmental stage affects the brain's response to IVH.

We performed single-nucleus RNA sequencing on rat brains 24 hours after IVH at postnatal day 2 (PND2) or day 5 (PND5) to define transcriptional responses across cell types. We identified 42 distinct cell populations and found that PND5 brains exhibited a markedly stronger immune and inflammatory response to IVH, with a threefold increase in differentially expressed genes compared to PND2. Microglia were the most perturbed cell type at both stages, showing increased oxidative stress and polarization toward both pro- and anti-inflammatory phenotypes at PND5. Ligand-receptor and regulon analysis revealed a shift from reparative IGF2 and TGF- β signaling at PND2 to proinflammatory Wnt signaling and activation of Runx1 and Stat5 at PND5. These findings highlight the importance of developmental timing in shaping the neuroimmune response to IVH and identify potential stage-specific therapeutic targets.

LAY SUMMARY

Our work uses a model of neonatal intraventricular hemorrhage to understand how hydrocephalus may develop in premature neonates. We have found that small differences in brain development affect how inflammation and hydrocephalus develop after intraventricular hemorrhage.

Feasibility of Short-Term Multimodal Assessment in a Neonatal Piglet Model of Intraventricular Hemorrhage

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ABSTRACT

Intraventricular hemorrhage (IVH) is a major cause of neonatal hydrocephalus and long-term neurological disability, yet translational progress has been limited by the lack of large-animal models amenable to multimodal assessment during the neonatal period. Here, we evaluate the feasibility of short-term multimodal assessment in a neonatal piglet model of spontaneous IVH. IVH was induced in postnatal day 4–7 piglets using intraperitoneal glycerol, and animals were assessed over a one-week period using neurological scoring, magnetic resonance imaging (MRI), histopathology, and cerebrospinal fluid (CSF) proteomics. Glycerol-treated piglets developed spontaneous hemorrhage within the lateral ventricles with imaging and histological features comparable to Papile grade II/III IVH observed clinically. Subarachnoid hemorrhage was frequently observed, whereas subdural hemorrhage was absent; thus, the precise vascular origin of bleeding could not be definitively resolved within this paradigm. Due to the intensive nature of neonatal large-animal experimentation, this feasibility study employed small sample sizes with sham littermate controls and emphasized effect size estimation over hypothesis testing. Acutely, IVH piglets exhibited ventriculomegaly, alterations in periventricular white matter microstructure, and impairments in motor performance. Histological analyses demonstrated changes in intraventricular macrophage populations, disruption of ependymal integrity, and altered expression of a choroid plexus water transporter. CSF proteomic profiling was feasible during this acute window and revealed three IVH-associated biomarkers. Together, these findings demonstrate the feasibility of short-term, multimodal assessment of neonatal IVH in a gyrencephalic large-animal model. This platform enables integrated neuroimaging, histological, and CSF-based analyses during early post-hemorrhagic stages and provides a foundation for future longitudinal and interventional studies, including application to preterm piglet models.

LAY SUMMARY

Bleeding into the brain of a newborn, known as intraventricular hemorrhage (IVH), is a leading cause of hydrocephalus and lifelong neurological disability. Despite its seriousness, treatment options remain limited, in part because researchers lack models that accurately

reflect the developing human brain. In this study, we show that newborn piglets can be used to closely model IVH seen in human infants and to track early brain injury using the same tools used in hospitals, including MRI, neurological assessments, and brain fluid analysis. This approach allows researchers to study how IVH damages the brain during the critical early period when intervention may be most effective. By providing a realistic platform to test new therapies and identify early biomarkers of injury, this research has the potential to accelerate the development of treatments that protect the brain and improve long-term outcomes for affected infants and their families.

Altered Functional Connectivity in a Mouse Model of Neonatal Germinal Matrix Hemorrhage-Intraventricular Hemorrhage

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ABSTRACT

Introduction:

Germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) is the most common cause of brain injury in very preterm infants, often leading to post-hemorrhagic hydrocephalus. However, it remains unclear how GMH-IVH impacts network formation and whether impairments to functional connectivity (FC) underlie neurocognitive deficits.

Methods:

GMH-IVH was induced via bilateral intraventricular hemoglobin injection in P4 *Thy1*-GCaMP6f mice, which contain the genetically encoded calcium indicator GCaMP in excitatory *Thy1* neurons. *Post-hoc*, we classified injected mice as having moderate or severe GMH-IVH using ventricular volumes. One cohort underwent wide-field optical imaging and behavioral analysis, while a second cohort was sacrificed for histology.

Results:

GMH-IVH mice exhibited weaker whisker stimulus-evoked calcium responses vs controls. Moderate GMH-IVH mice also had reduced spontaneous calcium activity in low-frequency bands. Resting state functional connectivity (RSFC) matrices revealed reduced anti-correlations between multiple regions in both moderate and severe GMH-IVH mice vs controls, indicating a loss of discrete network borders. GMH-IVH mice performed worse on learning and memory tasks, which correlated with decreased bilateral calcium-based FC. Cresyl violet stains revealed cortical thinning, neuronal loss, and abnormal organization after GMH-IVH. Severe GMH-IVH mice had fewer inhibitory parvalbumin interneurons, while moderate GMH-IVH mice had fewer *Thy1* neurons marked by GFP.

Conclusions:

GMH-IVH leads to disruptions in brain architecture, including reduced stimulus-evoked and spontaneous calcium activities and a loss of network anti-correlations. We show a loss of parvalbumin and *Thy1* neurons, which may underlie the aberrant resting state networks observed after GMH-IVH.

LAY SUMMARY

Our data shows that resting state-fMRI may both serve as an early prognostic measure for infants with GMH-IVH to highlight aberrant resting state networks early in life, offering opportunity for earlier intervention, and act as a means to evaluate improvements in neuronal network connectivity as new treatments are developed.

While grade I and II GMH-IVH (GMH without ventricular dilation or PVH) in patients has traditionally been thought of as relatively benign, our data recognizes that this injury pattern is in fact associated with abnormal resting state networks and neurocognitive deficits.

Finally, we provide evidence of an imbalance between excitatory and inhibitory cortical neurons after GMH-IVH, which may underlie the high rates of seizure-like activity in patients, thus offering a window for potential therapeutic intervention.

An *In Vivo* Method for Quantifying Complex Dysregulated CSF in a Rat Model of Posthemorrhagic Hydrocephalus of Prematurity Shows Tunable CSF Dynamics

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ABSTRACT

Introduction: Posthemorrhagic hydrocephalus of prematurity (PHHP) commonly occurs within the first few days of life after an intraventricular hemorrhage. Characterized by enlarged ventricles, increased intracranial pressure, and macrocephaly, PHHP causes lifelong physical and cognitive deficits. We aimed to develop a preclinical tool for *in vivo* imaging of complex CSF dynamics for PHHP to test future treatments for hydrocephalus.

Methods: PHHP Rat Model: At embryonic day 18, pregnant rats underwent laparotomies with 60-minute transient uterine artery occlusions followed by lipopolysaccharide injections into the amniotic sac (40 µg, 0111:B4). At postnatal day 1 (P1), rats were injected with 20 µL of lysed red blood cells into each lateral ventricle. Some rats were treated with an immunomodulatory cocktail from P21-P30. Imaging: At P60, rats were anesthetized with dexmedetomidine and underwent a T1 FLASH-3D weighted image followed by a 10µL injection of gadolinium into the cisterna magna and 3 more hours of imaging. Statistics were performed in GraphPad Prism with an n=3 per group with a one-way ANOVA.

Results: PHHP rats have enlarged ventricles that persists lifelong (p<0.05). After gadolinium injection, PHHP rats displayed T1 hyperintensity throughout all ventricles compared to the controls and immunomodulated rats which show gradual uptake (p<0.05). In the parenchyma, PHHP causes decreased gadolinium uptake (p<0.05).

Conclusion: PHHP is a lifelong injury that causes a major burden on patients and their families due to cognitive and motor deficits. Immunomodulation of the tissue parenchyma improves different aspects of dysregulated CSF and may serve as future therapeutic and interventional targets.

LAY SUMMARY

Introduction: Posthemorrhagic hydrocephalus of prematurity (PHHP) typically develops after a brain bleed within the first few days of life. PHHP is caused by dysregulated cerebrospinal fluid (CSF). We used magnetic resonance imaging (MRI) in rats to image CSF movement.

Methods: As newborns, rat pups were given PHHP. We injected an MRI contrast into the CSF of adult PHHP and imaged CSF movement.

Results: The CSF of PHHP rats accumulates quickly with very little movement into the surrounding brain compared to controls. When PHHP rats were given a therapeutic, their CSF moved more similarly to the controls.

Conclusions: PHHP causes complicated CSF issues that can be partially restored with therapeutics. Our method provides a tool for testing therapeutics to improve CSF movement in PHHP.



MECHANISM



FRIDAY, JULY 24
8:30 - 10:30 AM

The Hydrocephalus Research Center, Indiana University, Indianapolis

Bonnie Blazer-Yost¹, Teri Belecky-Adams¹, Alexandra Hochstetler¹, Christine Hehnly¹

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ABSTRACT

The Hydrocephalus Research Center was established in 2023 with funding provided by a Congressionally Directed Medical Research Program grant which also funds collaborative studies between Indiana University (Bonnie Blazer-Yost and Teri Belecky-Adams) and Johns Hopkins University (Lauren Jantzie and Shenandoah Robinson). With generous support from Indiana University, the Center has grown in size and scope and has expanded collaborations to include national and international researchers. The ultimate goal of all of the research in the Center is the development of potential pharmaceuticals to treat hydrocephalus. The research teams in Indianapolis are broadly divided into those investigators studying animal models and those using cultured cells. Within that context, the members of the Animal Team are developing new and more physiologically relevant animal models including mice, rats and pigs. They are testing how well the models mirror the sequelae of hydrocephalus like disturbances in brain development, circadian rhythm, visual acuity, gait and behavior. Our models are also being used to determine the effect of potential drug treatments, particularly in how they can stop or reverse ventriculomegaly and neuroinflammation. The Cell Culture Group is using a human choroid plexus cell line to unravel the complex pathways that control the amount and composition of the CSF. These studies are important for identifying new drug targets. This group also does first line testing for compounds that have the potential to decrease CSF production in clinically meaningful ways. There are daily interactions between the two teams and a spirit of collaboration to achieve our ultimate goal.

LAY SUMMARY

The Hydrocephalus Research Center at Indiana University Indianapolis is focused addressing one of the major priorities of the hydrocephalus community – the development of non-surgical treatments. We are a committed and interactive group of faculty, post-docs and students who are passionate about our mission of drug development.

TRPV4–AMPK Signaling Axis as a Therapeutic Target for Hydrocephalus

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ABSTRACT

Disruption of cerebrospinal fluid (CSF) production or flow is a leading cause of hydrocephalus. CSF production and balance are regulated by ion and water channels in the choroid plexus, the tissue responsible for producing most of the CSF. Among these channels, transient receptor potential vanilloid 4 (TRPV4) may play a critical role under pathological stress conditions such as hydrocephalus. Although previous animal studies have shown that TRPV4 inhibition reduces hydrocephalus severity, the mechanisms by which TRPV4 regulates fluid balance remain unclear. To address this gap, we used a human choroid plexus epithelial cell model (HIBCPP cells) to investigate TRPV4 regulation and downstream signaling pathways. Using a phosphoproteomic approach, pharmacological activation (GSK1016790A) and inhibition (RN1734) of TRPV4 were investigated to identify downstream phosphorylation changes. Our findings showed significant alterations in phosphorylation of key proteins involved in barrier integrity and cellular metabolism, including Zonula Occludens-1 (ZO-1), AMP-activated protein kinase (AMPK), and Claudin-7 (CLDN7). Notably, TRPV4 activation increased the inhibitory phosphorylation of AMPK at Ser496 residue. Furthermore, inhibition of protein kinase A (PKA), an upstream regulator of AMPK, followed by TRPV4 activation resulted in significant changes in electrogenic ion flux and epithelial barrier permeability. Sequential inhibition of PKA and AMPK prior to TRPV4 activation significantly reduced barrier permeability. Together, these findings reveal functional coupling between AMPK signaling and TRPV4-mediated ion transport, highlighting the AMPK–TRPV4 axis as a potential therapeutic target for hydrocephalus.

This study was supported by DoD Congressionally Directed Medical Research Program Grants #HT94252310296 and #HT94252310401 (BBY).

LAY SUMMARY

Cerebrospinal fluid (CSF) production is controlled by specialized cells in the choroid plexus that regulate the movement of electrolytes and water. TRPV4 is a stress-sensing channel that may influence fluid balance. Although blocking TRPV4 improves outcomes in animal models, how it works at the cellular level is not well understood. Using human choroid plexus cells, we turned TRPV4 on and off and examined changes in cell signaling. We found that TRPV4 alters the activity of key proteins involved in energy regulation and barrier stability, including a protein called AMPK. These changes affected electrolyte movement and the permeability of the cell barrier in the brain. Our findings show that TRPV4 works closely with AMPK to regulate barrier function, identifying TRPV4-AMPK pathway as a potential therapeutic target.

Inflammatory Modulation of TRPV4 in Human Choroid Plexus Epithelial Cells

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ABSTRACT

Recent evidence indicates that inflammation contributes to cerebrospinal fluid (CSF) imbalance in hydrocephalus via an effect on the choroid plexus epithelium (CPE). Although studies in a genetic rat model show that inhibition of transient receptor potential vanilloid 4 (TRPV4), an osmo-, shear-, temperature-, pressure-, and inflammation-sensitive non-selective cation channel expressed in CPE can ameliorate ventriculomegaly, it remains unclear whether inflammatory mediators directly modulate TRPV4 activity in CPE. To address this gap, we employed the human choroid plexus papilloma cell line (HIBCPP) to investigate the effects of lipopolysaccharide (LPS) and hemoglobin, key inflammatory drivers in post-infectious and post-hemorrhagic hydrocephalus, respectively. Cells were treated with physiologically relevant concentrations of LPS (10 ng/mL) or bovine hemoglobin (1.4 mg/mL) to model inflammatory conditions. Using Ussing-style electrophysiology, we measured transepithelial ion flux and transepithelial conductance (a measure of transepithelial permeability) before and after TRPV4 activation with the selective agonist GSK1016790A. LPS altered ion transport across the epithelium following both short-term (10 min) and long-term (24 h) exposure, with the strongest effects observed after addition to the blood side of the polarized cells. 24-hour LPS exposure significantly affected the baseline TRPV4-mediated ion flux and increased transepithelial conductance. In contrast, short-term hemoglobin exposure did not significantly affect ion transport or conductance. These findings suggest that selective inflammatory mediators may modulate TRPV4 activity and epithelial barrier function, potentially contributing to CSF dysregulation in hydrocephalus and add further evidence for considering TRPV4 as a potential therapeutic target.

LAY SUMMARY

Hydrocephalus is the condition in which too much cerebrospinal fluid (CSF) accumulates inside the brain. This occurs mostly caused by infection or bleeding. The fluid build-up can lead to high pressure, which can cause serious neurological problems. Our research has focused specifically on one protein channel called TRPV4, which is found in choroid plexus, a tissue responsible to produce cerebrospinal fluid. We have found that inflammation can affect the function of this channel, which can lead to problems with the regulation of CSF inside the brain. This is the link between inflammation and hydrocephalus. Our research aims to target this protein channel to help reduce fluid buildup in the brain and potentially decrease the need for surgical intervention.



DRUG TREATMENT



FRIDAY, JULY 24
8:30 - 10:30 AM

SCEMPI: Insights From Preclinical Studies to Clinical Trial

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ABSTRACT

SCEMPI (Safety of Combination of Erythropoietin and Melatonin for Preterm Infants with Intraventricular Hemorrhage NCT05617833) is NICHD-funded investigator-initiated trial to study the safety of high dose enteral melatonin plus erythropoietin (EPO) in very preterm neonates with intraventricular hemorrhage (IVH), and now moderate to severe white matter injury. Preterm babies are deficient in melatonin, yet protective EPO signaling requires melatonin-dependent downstream signaling transduction. SCEMPI is a single institution, multi-site 2-step trial to test the safety of high dose enteral melatonin and EPO in very preterm neonates with IVH and moderate to severe white matter injury from enrollment up to 34 weeks PMA. The primary outcome is serious adverse events related to study drugs. The initial open-label step enrolled 10 neonates. Overall, treatment was well-tolerated. Here, we discuss the preclinical work that preceded the trial to support the rationale, design and its execution, and the challenges, solutions and initial results. Additionally, we review our insights from the design, implementation and execution phases of the trial, and lessons learned along the way. Best practices on adaptive trial design, unanticipated barriers to enrollment, biomarker development and our progress to date will be shared. Unanticipated challenges that impacted enrollment were related to physical, social and emotional tolls from an unexpected preterm delivery. Serum melatonin levels varied and were unrelated to melatonin doses. At term, serum EPO levels trended higher in those who had melatonin. Serum levels of GFAP, neurofilament-light and Tau, lipocalin-2, and malondialdehyde at term did not differ. By contrast, serum Neural-plex biomarkers (mitochondrial health marker GDF-15, lysosomal marker GPNMB, and neurorepair marker Amphiregulin (Areg)) indicated differences based on treatment. Neurodevelopment and neuroimaging will be correlated with serum biomarkers. SCEMPI was designed by a multidisciplinary team and was built on the foundation of 7 years of preclinical experimentation in our labs. Our goal is to provide non-surgical therapeutic options for people with hydrocephalus.

LAY SUMMARY

SCEMPI (Safety of Combination of Erythropoietin and Melatonin for Preterm Infants with Intraventricular Hemorrhage) is an NIH-funded investigator-initiated trial to study the safety of high dose enteral melatonin plus erythropoietin (EPO) in very preterm neonates with intraventricular hemorrhage (IVH) and now moderate to severe white matter injury. SCEMPI was designed by a multidisciplinary team and was built on the foundation of 7 years of preclinical experimentation in our labs. Here, we discuss the preclinical experimentation that preceded the trial to support the rationale, design and execution. The initial results, challenges and our solutions will also be presented. Our goal is to provide non-surgical therapeutic options for people with hydrocephalus and associated neurological injury.

Ventriculomegaly Disrupts Neurogenesis and Promotes Neuronal Hypertrophy and Inflammation in a *Tmem67*^{-/-} Rat Model of Congenital Hydrocephalus

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ABSTRACT

The global prevalence of congenital hydrocephalus (CH) has been estimated at approximately 176 per 100,000 births, and genetic disorders are a major contributor. Hydrocephalus is associated with accumulation of cerebrospinal fluid (CSF) leading to enlarged ventricles that can damage the subventricular zone (SVZ), a critical site for neurogenesis. Treatment intervention relies hugely on surgical CSF shunting, which is often complicated by mechanical failure or infections, highlighting the need to better define the underlying pathological mechanisms and develop pharmacological therapies.

Previous studies using *Tmem67*^{-/-} rat model of CH have demonstrated ventriculomegaly before postnatal day 7 (P7). In this study, we hypothesize that early ventricle enlargement could disrupt neurogenesis in SVZ. Brain tissues from P15 *Tmem67*^{+/+} (wild-type, control) and *Tmem67*^{-/-} (hydrocephalic) rats were studied using immunohistochemistry to evaluate the expression of nestin (a neural progenitor marker) and NeuN (mature neuronal marker). We observed increased nestin expression within SVZ of hydrocephalic rat brains. In addition, NeuN staining revealed disrupted neuronal migration toward the cortex, neuronal hypertrophy (swelling), significant reduction in cortical neuronal density ($p < 0.05$) compared with the controls. In addition, there was a hydrocephalus-associated inflammatory response as indicated by a highly significant ($p < 0.001$) increase in cortical neuronal NLRP3 inflammasome.

In conclusion, this study reveals that early ventriculomegaly in CH is associated with impaired neuronal migration, swelling and inflammation within the SVZ and cortex. These findings suggest that preservation of neuronal integrity and regulation of inflammatory pathways may represent therapeutic targets to mitigate neurodevelopmental injury in CH.

LAY SUMMARY

Congenital hydrocephalus is a condition present at birth with fluid accumulation in the brain, causing the brain's ventricles to enlarge. It is usually treated with surgical shunts; however, these devices often fail due to infection or mechanical problems and may require repeated surgeries. In this research we used a genetic rat model of congenital hydrocephalus to understand how early enlargement of the ventricles affects both developing and mature brain cells (neurons). The results show that ventricle enlargement disrupts normal neuron movement in the brain, causes neuron swelling, and increases inflammation of these brain cells. These early changes could contribute to long-term developmental challenges in affected children and understanding these effects may help researchers develop new medications to protect neurons and reduce need for repeated surgeries.

Serum Glucocorticoid-Induced Kinase 1 (SGK1) Inhibition as a Preclinical Therapy for Hydrocephalus

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ABSTRACT

Hydrocephalus is a serious clinical condition caused by accumulation of cerebrospinal fluid (CSF) and currently has no treatment other than invasive, repetitive surgeries. Serum and glucocorticoid-regulated kinase-1 (SGK1) is a serine/threonine kinase belonging to the AGC (protein kinase A, G, and C) family. Our laboratory previously demonstrated that the SGK1 inhibitor SI113 reduced ventriculomegaly in the *Tmem67* rat model of hydrocephalus (Hochstetler et al., 2023). In that study, dimethyl sulfoxide (DMSO) was used to solubilize SI113; however, DMSO is not clinically suitable.

We hypothesized that replacing DMSO with 1-methyl-2-pyrrolidinone (NMP), a solvent used in clinical applications, could provide a viable alternative. To test this, we administered SI113 dissolved in NMP to *Tmem67* rats with congenital hydrocephalus. T2-weighted MRI was used to compare ventriculomegaly between treated and untreated *Tmem67*^{-/-} (hydrocephalic) and *Tmem67*^{+/+} (wild-type) rats. Ventricular enlargement was reduced in NMP solubilized SI113 treated hydrocephalic animals with no effect on body weight.

CSF and plasma samples were collected from animals treated with SI113 at 30 minutes and 24 hours to evaluate drug concentration and barrier penetration. Plasma concentrations were significantly lower at 24 hours compared to 30 minutes, and CSF levels were higher at 30 minutes. Samples collected at 2 hours are currently being analyzed to compare all groups and determine optimal dosing. Future studies will examine the mechanism of SGK1 inhibition in hydrocephalus, particularly within the choroid plexus as a potential pharmacological target.

LAY SUMMARY

Hydrocephalus is a condition in which excess fluid builds up in the brain, often requiring repeated surgeries to manage. There are currently no effective drug treatments. Our research investigates whether blocking a protein called SGK1 can reduce brain swelling in hydrocephalus. We tested a drug called SI113 in a rat model and found that it reduced brain ventricle enlargement without affecting body weight. Importantly, we used a clinically acceptable solvent to make the drug more translatable for future human use. We also measured how much of the drug enters the bloodstream and brain fluid over time to better understand dosing. This work brings us closer to developing a safe, non-surgical treatment option for patients with hydrocephalus.

References: Hochstetler AE, et al. (2023) Fluid Barriers CNS 20:61

This research was conducted with the support of DoD congressional Directed Medical Research Program Grants #HT94252310296 and #HT94252310401 (BBY).



ACCESS TO CARE



FRIDAY, JULY 24
8:30 - 10:30 AM



An Integrated Model to Improve Access to Care and Quality of Life for Children with Hydrocephalus in Uganda

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ABSTRACT

Introduction: Globally, 88 per 100,000 children are living with hydrocephalus, the most common childhood brain disorder treated by neurosurgeons, particularly for developing countries due to high prevalence of CNS infections. There is a substantial demand for hydrocephalus care among children, however the limited access to healthcare has affected their quality of life. Hydrocephalus remains a significantly under-addressed neurological condition in Uganda, where delayed diagnosis, limited neurological services, high treatment costs, stigma, and fragmented rehabilitation services contribute to poor outcomes.

This study will focus on understanding access to comprehensive care, while advancing strategies to improve quality of life among children with hydrocephalus in Uganda. The study seeks to generate evidence to strengthen care systems across the lifespan from early identification to community reintegration.

Methods: First, we will examine access to care. Using mixed-methods approaches, to investigate delays in diagnosis, financial and geographic barriers to neurosurgical services, caregiver knowledge and beliefs, and health system readiness. We shall collaborate with neurosurgical units, rehabilitation providers, community health workers, and families to map patient journeys and identify access to care gaps. Applying implementation science frameworks, we will develop and test feasible interventions such as referral pathway strengthening, caregiver education models, and community-based follow-up strategies.

Second, we will focus on quality of life and functional outcomes. Beyond survival, individuals with hydrocephalus often experience challenges in mobility, communication, learning, participation in daily activities, and mental health challenges. We will assess long-term functional outcomes using culturally appropriate measures and explore factors associated with better participation in the community.

LAY SUMMARY

The study will generate context-specific evidence to strengthen hydrocephalus care systems across the lifespan from early identification and referral to surgery, rehabilitation, and community reintegration. This will result into the following:

First, the study will generate a framework that provides evidence to inform policy and service planning to reduce disparities among children with Hydrocephalus in Uganda.



POSTER PRESENTERS



SATURDAY, JULY 25
3:00 - 4:30 PM

Optic Nerve Head Edema Associated with Ventriculomegaly in Aged TMEM67+/- Rats

Hamid Aboutalebkhodaeian¹, Jane Uchechi Obiako¹, Nasim Shafie Nejad¹, Nour Ghoneim¹,
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ABSTRACT

Hydrocephalus and impaired cerebrospinal fluid (CSF) dynamics can produce neuro-ophthalmic complications including optic nerve head (ONH) edema, known as papilledema. TMEM67, a cilia-associated gene implicated in ciliopathies, has been linked to abnormalities in ventricular development and CSF regulation, but the associated visual pathway manifestations remain poorly defined.

In this study, we tested whether TMEM67+/- related ventriculomegaly in aged rats is associated with structural evidence of papilledema. Ventricular morphology, intraocular pressure (IOP), and ONH characteristics in aged (>1 year) TMEM67+/- rats compared with wild-type (WT) controls were assessed. Magnetic resonance imaging (MRI) revealed significant enlargement of the lateral ventricles in TMEM67+/- rats compared with WT (Mann–Whitney test, $p = 0.0017$), confirming ventriculomegaly consistent with chronic hydrocephalus.

IOP values demonstrated small but statistically significant differences, although all measurements remained within a physiological range, suggesting that ONH changes were unlikely to be glaucoma-driven. To quantify papilledema-related changes, ONH edema intensity histograms were analyzed across nasal, superior, temporal, and inferior quadrants. While the left eye showed no significant differences between groups, the right eye demonstrated significantly increased edema intensities in TMEM67+/- rats compared with WT. These changes are consistent with increased ONH damage and edema characteristic of papilledema.

These findings indicate that aged TMEM67+/- rats develop ventriculomegaly accompanied by ONH changes consistent with papilledema and provide a potentially useful translational model for investigating the mechanisms, visual consequences and therapeutic treatment of hydrocephalus-associated ONH swelling.

LAY SUMMARY

The increased cranial pressure associated with hydrocephalus can damage the optic nerve, which carries visual information from the eye to the brain. The increased cranial pressure compresses the optic nerve and causes swelling at the back of the eye, leading to a disease called papilledema. In this study, we used a rat model with a change in a gene called TMEM67, which affects tiny cellular structures known as cilia and is linked to fluid problems in the brain. Older TMEM67+/- rats developed enlarged brain ventricles, like chronic hydrocephalus in people. We examined the eyes and found changes at the optic nerve head consistent with swelling, as well as slightly higher intraocular pressure. These results suggest this model may help researchers understand how hydrocephalus leads to papilledema and vision problems, and support testing new treatments.

Dosing and Treatment Timing Refinement of AAV-Based Choroid Plexus Ablation

Leena Bandaras¹, Gwendolyn Sebring^{1,2}, Paloma Merchan-Sala², Stephanie Stephens², Crystal Shula², Soner Duru², Francesco Mangano^{2,3}, June Goto^{1,2,3}

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ABSTRACT

Adeno-associated viruses (AAVs) are widely used in gene therapy due to their ability to deliver genetic material to cells without triggering an immune response (Naso et al., 2017). However, the application of AAV-based therapies targeting choroid plexus (ChP) epithelial cells remain insufficiently investigated. This study investigates optimal dosing and treatment timing for AAV-mediated choroid plexus ablation and its impact on cerebrospinal fluid (CSF) regulation. Neonatal C57BL/6 mice received bilateral intracerebroventricular injections of choroid plexus-targeting AAV delivering a suicide gene system at either high dose or low dose at postnatal day (P) 0. Rapamycin was administered intraperitoneally at different developmental time points, at P2, P5, P14, or P30, to activate the ChP ablation. Ventricular volume was measured using T2-fluid sensitive 3D MRI and quantified with the IMARIS software using scans at P30, P42, and P90. Both high and low-dose AAV treatments significantly reduced ventricular volume compared to untreated controls, indicating effective ChP ablation. Earlier rapamycin administration produced stronger and more sustained effects, with P5 treatment maintaining the largest and most statistically significant reduction in ventricular volume up to three months. Treatments at P14 were additionally significant but less effective, while P30 treatment showed no significant change in ventricular volume. Control groups receiving AAV-Chp alone or rapamycin alone showed no significant change in ventricular volume. These findings suggest that early postnatal activation of AAV-mediated choroid plexus ablation, particularly at P5, is most effective in reducing ventricular volume. Future studies will evaluate long-term effects, including six-month treatment outcomes and potential impacts on overall brain development and behavior.

Reference:

Naso, M. F., Tomkowicz, B., Perry, W. L., 3rd, & Strohl, W. R. (2017). Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. *BioDrugs: clinical immunotherapeutics, biopharmaceuticals and gene therapy*, 31(4), 317–334. <https://doi.org/10.1007/s40259-017-0234-5>

LAY SUMMARY

The choroid plexus is a network of cells, tissue, and blood vessels that produce cerebrospinal fluid (CSF) within the brain's ventricles. Hydrocephalus can develop when the choroid plexus produces an excess of CSF or if the fluid is not properly drained, which then enlarges the ventricles. Current treatments for hydrocephalus involve highly invasive brain surgery to place shunts that drain excess fluid. However, these shunts may fail and often require replacement surgeries over time. This study tested an adeno-associated virus (AAV) gene therapy approach

to selectively reduce the CSF-producing activity of the choroid plexus. Our findings indicated that treatment early in life resulted in the greatest reduction in the ventricular size. These findings may inspire treatments for the management of pediatric hydrocephalus that are safer and less invasive than the current treatments offered, improving the quality of life for patients.

Living Beyond the Shunt: Occupational Therapy, Family Voices, and Quality of Life in Pediatric Hydrocephalus

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ABSTRACT

Children with hydrocephalus experience persistent uncertainty related to shunt failure, medical crises, and participation in school and home activities, which can disrupt family routines and overall well-being. While occupational therapy (OT) has the potential to enhance independence, participation, and adaptation in daily life, its specific contributions throughout the hydrocephalus care continuum remain insufficiently defined. This qualitative study investigates caregivers' experiences with OT compared with standard neurosurgical and medical care without consistent OT involvement. Semi-structured interviews will be conducted with two groups of caregivers: those whose children receive ongoing pediatric OT (in outpatient, school, or hospital settings) and those whose children have not received regular OT. Using a phenomenological approach and principles of brain-based learning, the interviews will examine how caregivers address shunt-related uncertainty, facilitate their child's participation at home and school, coordinate fragmented services, and interpret quality of life. Thematic analysis will elucidate the influence of OT involvement on perceived support, caregiver burden, and hope, and will highlight areas where families without OT report feelings of isolation or overwhelm. Recommendations derived from caregivers will inform systematic integration of OT into hydrocephalus care pathways and support the development of family-centered practice guidelines, interdisciplinary collaboration, and advocacy to enhance participation and quality of life for children with hydrocephalus and their families.

LAY SUMMARY

Hydrocephalus is a lifelong condition in which children often rely on a shunt to drain extra fluid from the brain, and a shunt problem can quickly become life-threatening. Families must constantly watch for subtle warning signs, coordinate many medical visits, and help their child participate in everyday life at home and school. Occupational therapists are trained to support children's independence, routines, and school participation, yet many hydrocephalus care plans do not routinely include OT. This project will listen to parents whose children do and do not receive OT to learn what has helped, what is missing, and what changes they recommend. Their insights can shape future care so that more families feel supported, less alone, and better able to help their children live full lives.

Histopathological Evidence of Ependymal Disruption and Altered IBA1⁺ Macrophage Organization in a Neonatal Piglet Model of Intraventricular Hemorrhage

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ABSTRACT

Intraventricular hemorrhage (IVH) is a major cause of neonatal neurological disability and post-hemorrhagic hydrocephalus, yet early pathological changes at the ventricular–cerebrospinal fluid (CSF) interface remain incompletely understood. Inflammatory responses involving IBA1⁺ macrophages/microglia, ependymal injury, and choroid plexus dysfunction may contribute to disease progression. We evaluated histopathological changes in a neonatal piglet model of spontaneous IVH with emphasis on IBA1-associated cellular responses and CSF-interface pathology. IVH was induced in postnatal day 4–7 Yorkshire piglets by intraperitoneal injection of 50% glycerol (6.5 g/kg). The study included littermate sham controls and IVH groups. Piglets underwent neurological assessment and magnetic resonance imaging (MRI), and brains were analyzed using hematoxylin and eosin staining and chromogenic immunohistochemistry to evaluate intraventricular hemorrhage, ependymal integrity, choroid plexus architecture, and IBA1⁺ cell distribution. Glycerol administration produced spontaneous intraventricular hemorrhage within 1–24 hours, often accompanied by subarachnoid hemorrhage. Intraventricular hematomas occurred in 6/7 IVH piglets and none of the shams. Ependymal disruption was present in all IVH animals (7/7) and was characterized by loss of β IV-tubulin staining, ciliary disruption, and abnormal subependymal cellular organization. In the choroid plexus, IBA1 immunolabeling revealed altered macrophage organization with a reduced epiplexus-to-stromal macrophage ratio (Hedges 'g = -2.23). In contrast, cortical and periventricular parenchyma showed preserved architecture and no significant increase in IBA1⁺ cell density. Spontaneous IVH in neonatal piglets produces ventricular-zone pathology including intraventricular hematomas, ependymal disruption, and altered IBA1⁺ macrophage organization in the choroid plexus. This gyrencephalic model provides a translational platform for investigating early inflammatory and CSF-interface mechanisms underlying post-hemorrhagic hydrocephalus.

LAY SUMMARY

Intraventricular hemorrhage (IVH), a leading cause of hydrocephalus, is a type of brain bleeding that occurs in premature infants that can lead to serious and lifelong neurological challenges. However, scientists do not fully understand how this injury develops or how to prevent its long-term effects. In this study, we developed a neonatal piglet model that closely resembles the human infant brain to study IVH. We found that bleeding in the brain disrupts the cells lining the brain's fluid spaces and alters immune cells that help regulate brain fluid. It is by understanding these early changes that may help researchers identify new treatment targets and improve therapies aimed at preventing brain injury and hydrocephalus in newborns.

Cortical Iron Metabolism is Chronically Altered in Posthemorrhagic Hydrocephalus

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ABSTRACT

Posthemorrhagic hydrocephalus (PHH) is an acquired form of hydrocephalus that may occur after intraventricular hemorrhage (IVH) and subarachnoid hemorrhage (SAH). Blood products activate inflammatory responses, limiting recovery of cerebrospinal fluid (CSF) dynamics and leading to chronic brain injury. The only treatment is surgical to divert CSF, therefore identifying potential pharmacological targets by characterizing disrupted metabolic pathways is of great interest. We hypothesized that PHH upregulates expression of toxic iron metabolites, thereby contributing to the chronic self-propagation of CNS damage.

To model PHH in rats, we initiated inflammation by injecting lipopolysaccharide at postnatal day 21 (P21) and P23, followed by IVH with littermate lysed red blood cells into both lateral ventricles at P25. We performed qPCR on P45 cortex and striatum, focused on expression of ferroportin (*Fpn1*), transferrin receptor (*TfR1*), and divalent metal transporter 1 (*DMT1*).

Cortex from PHH animals demonstrated elevated levels of all three iron metabolism markers ($p < 0.05$) ($n=11$). In contrast, the striatum revealed no significant expression differences ($n=8$).

These results suggest that cortex from PHH animals exhibits disrupted iron metabolism several weeks after hemorrhage. The increased expression of these markers reflects the lasting upregulation of toxic iron metabolites secondary to IVH. The striatum remains protected potentially due to regional glial differences in toxic metabolite clearance. Characterizing regional differences in vulnerability will improve understanding of PHH pathophysiology. Future studies will characterize expression of these genes and others across other specific regions and at later timepoints to identify chronic effects of PHH.

LAY SUMMARY

Posthemorrhagic hydrocephalus (PHH) can occur after a brain bleed. Blood products, including iron, cause inflammation, limiting spinal fluid clearance and leading to chronic brain injury. Using a lab model of PHH, weeks after the bleed we looked at three markers of iron metabolism in the cortex and the striatum, brain regions at risk for long term injury in PHH. The cortex controls complex activities like thinking and movement, while the striatum fine tunes these functions. We found that all three markers of iron were significantly increased in the cortex of PHH animals, but not in the deeper striatum. This helps us understand the impact of PHH on various parts of the brain. These results will inform the development of novel drug treatments for PHH.

Reducing Brain Inflammation After Brain Bleeds by Inhibiting CSF Immune Cells

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ABSTRACT

The cerebrospinal fluid (CSF) system contains populations of immune cells that respond to inflammation, such as that caused by infection or bleeding in the brain. These CSF immune cells play an important role in the development and resolution of inflammation in the brain. One molecule, called TRPV4, has been shown to play a role in the activation of cells similar to the CSF immune cells. Inhibiting TRPV4 has shown promise as a treatment for hydrocephalus in different animal models of the disease. Historically, it was hypothesized that inhibition of TRPV4 slows the production of CSF, but an additional hypothesis is that inhibition of TRPV4 also reduces the activation of CSF immune cells, thus decreasing inflammation in the brain associated with acquired hydrocephalus. To test this hypothesis, blood will be injected into the lateral ventricle of adolescent rats to cause inflammation of the CSF system. Animals will then be treated with the TRPV4 antagonist drug that has been shown to be effective in treating hydrocephalus. Brain tissue, CSF and blood samples will be collected and tested for different markers of inflammation and CSF immune cell activation. Providing evidence to support this hypothesis would suggest that inhibiting CSF immune cells might be a valuable target in the treatment of hydrocephalus and could open doors to a whole new field of research which could lead to further drug treatment options for individuals with hydrocephalus.

LAY SUMMARY

I am testing an experimental drug because, though it has shown promise in treating hydrocephalus in different animal models of the disease, its mechanism of action is not fully understood. I believe that the drug reduces inflammation in the brain by inactivating immune cells which are found in the cerebrospinal fluid system. If my results support my hypothesis, then the scientific search for drug treatments for hydrocephalus might shift to an additional focus on reducing inflammation in the brain by regulating the activity of immune cells in the CSF system. This would add another dimension to hydrocephalus treatment research, which might lead to further drug treatment options for individuals with hydrocephalus.

Cerebrospinal Fluid Obstruction and Ventriculomegaly in Experimental Hydrocephalus

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ABSTRACT

Hydrocephalus is a frequent neurological condition in which excess cerebrospinal fluid (CSF) expands the cerebral ventricles (ventriculomegaly). It is treated primarily by surgical diversion of ventricular CSF to extracranial absorption sites. However, post-operative failures occur at a rate of 90% within 10 years. Experimental injections of kaolin into the subarachnoid space are frequently used to induce ventriculomegaly by producing meningeal inflammation and obstruction that impairs CSF outflow. Distinguishing between the inflammation caused by ventriculomegaly and that related to a kaolin injection is essential in experimental studies of hydrocephalus. Although our kaolin-induced porcine model of hydrocephalus usually produces ventriculomegaly, occasionally the ventricles do not enlarge even though kaolin deposits occur in the subarachnoid basal cisterns; we term these cases “non-hydrocephalic.” To correlate the extent of kaolin blockage and ventriculomegaly, we quantified the kaolin deposits in the basal cisterns and the cerebral ventricular volumes in sham control (n=5), hydrocephalic (ventriculomegaly >2 standard deviations from sham, n=6), and non-hydrocephalic (ventriculomegaly <2 standard deviations from sham, n=5) juvenile pigs on standard T2-weighted MRIs. After establishing an intensity threshold for CSF obstructions using open-source ITK-Snap software, we calculated the percent blockage in each case. Mean kaolin blockage was 0.00%, 95.15%, and 84.19% for the sham, hydrocephalic, and non-hydrocephalic groups, respectively ($p=0.0139$ between hydrocephalic and non-hydrocephalic), demonstrating that near-complete blockage by kaolin correlates with ventriculomegaly. Our results also indicate that the periventricular white matter inflammation in our model may not be due to kaolin injections, as some injections result in no ventriculomegaly.

LAY SUMMARY

Given the risks associated with current management, it is important to understand the pathophysiology of hydrocephalus to optimize treatment. A common feature of hydrocephalus is cellular inflammation lining the ventricles related to ventricular expansion (ventriculomegaly, VM). In young pigs, kaolin clay brain injections cause VM and impaired cerebrospinal fluid (CSF) outflow. Kaolin itself may induce inflammation, which must be distinguished from VM-related inflammation. With MRI scans, we compare kaolin blockages in pigs with large vs. small ventricles. Small ventricle cases were less blocked than large, confirming associations between CSF obstruction and VM. It is implied that inflammation in our model may be reduced in smaller kaolin blockages. Understanding the relations between CSF obstruction, VM, and inflammation will help the development of anti-inflammatory treatments for hydrocephalus.

Under Pressure: Investigating the Role of the Mechanosensitive Channels TRPV4 and Piezo1 in a Human Choroid Plexus Epithelial Cell Model

Verayna Newland¹, Stacy David¹, Bonnie Blazer-Yost¹

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ABSTRACT

A symptom of hydrocephalus is increased intracranial pressure caused by an overproduction of cerebrospinal fluid (CSF). CSF production is regulated by a specialized epithelial layer on the choroid plexus called the choroid plexus epithelium (CPE) that carefully controls electrolyte movement with numerous ion channels, transporters, and pumps. Some of these proteins, such as transient receptor potential vanilloid 4 (TRPV4) and piezo-type mechanosensitive ion channel component 1 (Piezo1) are mechanosensitive channels. TRPV4 has been implicated in CSF production; when it is inhibited in a genetic rat model of hydrocephalus, ventriculomegaly is ameliorated¹. Piezo1 has not been studied in the CPE, however, Piezo1 overexpression in the brain lymphatics of mice with induced hydrocephalus led to increased CSF clearing and reduced ventriculomegaly². In this study, we characterized Piezo1 on the human choroid plexus papilloma cell line (HIBCPP) with RT-PCR and immunocytochemistry. Additionally, we studied the intracellular signaling between Piezo1 and TRPV4 via Ussing-style electrophysiology by measuring the net transepithelial ion flux (short-circuit current) and transepithelial cellular permeability (conductance). The immunocytochemistry showed that Piezo1 is primarily located on the apical side of the HIBCPP membrane. For the electrophysiology experiments, we used GSK1016790A and YODA1 as the TRPV4 and the Piezo1 agonists. Stimulation of Piezo1 caused a change in ion transport that is similar to TRPV4. Activating the channels in sequence (Piezo1 followed by TRPV4 and vice versa) seemed to suggest that TRPV4 has an inhibitory effect on Piezo1. This data can help us better understand how these channels interact and contribute to CSF production.

References:

1. Hochstetler, A. E., et al. (2020). TRPV4 antagonists ameliorate ventriculomegaly in a rat model of hydrocephalus. *Jci Insight*, 5(18), e137646.
2. Choi, D., et al. (2024). Piezo1 regulates meningeal lymphatic vessel drainage and alleviates excess CSF accumulation. *Nat Neurosci*, 27(5), 913-926.

LAY SUMMARY

My research focuses on how cerebrospinal fluid is produced. Overproduction of fluid leads to increased pressure in the ventricles. There are proteins on the choroid plexus that can sense increases in pressure. One of these proteins is called TRPV4. Our laboratory has previously discovered that this pressure-sensitive channel is important for fluid production, however, we believe this channel is not working alone. There is another pressure-sensitive channel called Piezo1 that is important for fluid movement in other parts of the body though this channel has not been thoroughly investigated in the brain. My goal is to study TRPV4 and Piezo1 channels together and see if they are important for fluid production in the brain. This research can help identify drug targets for hydrocephalus therapies.

Characterizing a Genetic Adult Rat Model of Normal Pressure Hydrocephalus

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ABSTRACT

The pathophysiology of Normal Pressure Hydrocephalus (NPH) remains poorly understood, leading to significant rates of misdiagnosis. To understand NPH pathophysiology and develop non-surgical therapies to treat it, development of a reliable experimental model is essential. In a genetic model of hydrocephalus, the *TMEM67*^{-/-} rats have been shown to develop severe hydrocephalus with a survival timeline of 21 days after birth. However, the *TMEM67*^{+/-} litter mates, although present with ventriculomegaly, appear healthy and generally survive past a year. Thus, our hypothesis is that the *TMEM67*^{+/-} rats may display a form of adult communicating hydrocephalus that develops over time, leading to a type of progressive hydrocephalus like NPH. To investigate this and characterize the similarity to human patients, the experimental rats were grouped into wildtype (WT) controls and *TMEM67*^{+/-} rats and T2 weighted-MRI scans were taken to assess ventricular volumes. Our results show that the adult lateral ventricular volumes of the hydrocephalus rats were significantly higher than the WT, suggesting a form of adult hydrocephalus. To further investigate the model's alignment with the NPH phenotype, we investigated gait and motor functions using the CatWalk automated gait analysis system and the rotarod test. Our findings show that the hydrocephalus rats show a significantly dysregulated motor function compared to WT.

Further studies will investigate cognitive dysfunction, urinary incontinence, and measure the intracranial pressure to fully characterize this model.

LAY SUMMARY

Normal Pressure Hydrocephalus (NPH) is often called a "reversible" cause of dementia, yet it remains one of the most frequently misdiagnosed neurological conditions. Because we don't fully understand NPH, doctors often struggle to distinguish it from other conditions like Parkinson's or Alzheimer's. To find better ways to diagnose and treat NPH, we need a reliable laboratory model that accurately mimics what patients experience. Our lab is studying a specific genetic model in older rats to see if they develop the symptoms seen in humans—the "classic triad" of walking difficulties, memory loss, and bladder control. Our early results look promising, the ventricles are significantly increased in the hydrocephalus rats, and they have bad balance and coordination. Our ongoing experiments will more fully characterize this model.

Retinal and Optic Nerve Head Structural Changes in an Adult Post-Hemorrhagic Hydrocephalus Rat Model

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ABSTRACT

Papilledema, optic disc swelling caused by raised intracranial pressure, is a common but under-recognized consequence of hydrocephalus that can lead to irreversible visual loss. Experimental models that recapitulate ventricular enlargement, increased intracranial pressure and papilledema are needed to study mechanisms and test interventions. In this study, a rat model of post hemorrhagic hydrocephalus (PHH) was evaluated to determine whether intraventricular hemorrhage (IVH) reliably produces papilledema and optic nerve head pathology consistent with clinical findings in hydrocephalus. PHH was induced in Sprague Dawley rats at postnatal day 25 (P25) by intraventricular injection of lysed blood cells after intraperitoneal injections of lipopolysaccharide at P21 and P23. Magnetic resonance imaging (MRI), optical coherence tomography (OCT) and H & E-labeled sections at P45, P60, and P100 were used to assess structure of the optic nerve and nerve head (ONH); retinal cryosections were examined for ganglion cell (RGC) loss and vascular pathology.

MRI demonstrated increased cerebrospinal fluid surrounding the optic nerve and ONH protrusion, while OCT revealed ONH enlargement at P60 (mean difference $40.76 \pm 23.95 \mu\text{m}$, $p < 0.01$) and P100 ($27.61 \pm 7.68 \mu\text{m}$, $p < 0.01$) compared with naïve rats. RGC density was markedly reduced across all examined retinal regions at P45 but was restricted to selected regions at P100. Retinal vasculature exhibited increased superficial peripapillary vessel density with compression of the deep capillary plexus. These changes, consistent with human papilledema, support the PHH rat model as a platform to study papilledema mechanisms and potential treatments.

LAY SUMMARY

Consistently elevated intracranial pressure can damage the retina and optic nerve head, ultimately leading to progressive vision loss. Papilledema, or swelling of the optic nerve head, is a key warning sign of increased intracranial pressure. This study investigated optic nerve head and retinal structural changes in a post-hemorrhagic hydrocephalus (PHH) rat model to examine prolonged pressure and excess cerebrospinal fluid around the optic nerve head alter eye structure. Using brain imaging, eye imaging, and tissue analysis, we observed optic nerve head swelling, loss of retinal ganglion cells, and changes in the blood vessels around the optic nerve, all findings that closely resemble papilledema in patients with hydrocephalus. This model provides a controlled way to study how hydrocephalus affects vision and to test new pharmaceutical therapies aimed at protecting the optic nerve and preventing vision loss from papilledema.

Temporal and Regional Mitochondrial Dysfunction Following Neonatal Intraventricular Hemorrhage

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ABSTRACT

Neonatal intraventricular hemorrhage (IVH) is a major cause of long-term neurodevelopmental impairment in preterm infants. The neonatal brain undergoes rapid changes in immune regulation and energy metabolism, leading to stage-specific responses to injury. However, the mechanisms linking early hemorrhagic injury to chronic cognitive deficits remain unclear. We hypothesize that hemoglobin (Hgb) and other blood-derived products trigger an early inflammatory response that spreads through white matter and cerebrospinal fluid (CSF) to different brain regions in a sequential manner. In our model, IVH was induced by intraventricular injection of lysed blood in rats at postnatal day (PND) 2 and PND5. Our published RNA-seq results showed a stronger inflammatory response and greater ventricular enlargement following IVH at PND5 compared with PND2. To determine whether inflammation influences bioenergetic outcomes, mitochondrial function was assessed in cortical, hippocampal, and cerebellar regions at 24 hours, 10 days, and 30 days after IVH induction at PND5. Neuronal development was evaluated using synaptophysin expression, and cognitive function was assessed with the Novel Object Placement Recognition (NOPR) test. Cortical State III respiration decreased 10 days after IVH. At 30 days post-IVH, persistent mitochondrial dysfunction (State III, State V-I, and State V-CII) was observed specifically in the hippocampus. These deficits were accompanied by reduced synaptophysin expression and impaired NOPR performance. Together, these findings suggest that early inflammation and delayed hippocampal bioenergetic dysfunction contribute to long-term cognitive impairment after IVH, highlighting potential biomarkers and therapeutic targets.

LAY SUMMARY

Neonatal intraventricular hemorrhage (IVH) is a type of brain injury that can lead to long-term learning and developmental problems in premature infants. We investigated how this early injury causes lasting brain damage. Using a rat model, we found that blood breakdown products trigger a strong inflammatory response that spreads through the brain leading to enlarged brain ventricles. Importantly, this early inflammation disrupts how brain cells produce energy, particularly in the hippocampus, a region critical for memory. These energy deficits were linked to reduced brain connectivity and poor memory performance over time. Clinically, our findings suggest that targeting early inflammation and mitochondrial dysfunction could help prevent long-term cognitive impairments and identify therapies for early diagnosis and intervention in infants with IVH.

Circadian Rhythm Disruptions in a Post-Hemorrhagic Hydrocephalus Animal Model

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ABSTRACT

Papilledema is a serious, vision-threatening disease that results when pressure inside the skull rises, as it does in hydrocephalus. This edema can compromise not only vision, but also circadian timing by damaging intrinsically photosensitive retinal ganglion cells (ipRGCs) that relay light information to the brain's master clock.

Hydrocephalus arises from excess cerebrospinal fluid (CSF) and elevated intracranial pressure (ICP), which can extend into the optic nerve subarachnoid space and produce papilledema. This optic nerve swelling disrupts orthograde axoplasmic transport, venous outflow, glymphatic clearance, and retinal vasculature, contributing to loss of retinal ganglion cells (RGCs), including the ipRGC subset. Because ipRGCs synchronize circadian rhythms and sleep–wake cycles, their injury provides a mechanistic link between papilledema and the disordered sleep frequently reported in hydrocephalus. In addition to mechanical stress at the optic disc, inflammatory mediators in brain, blood, and CSF may exacerbate RGC and ipRGC loss, further impairing photic entrainment and glymphatic clearance that depend on consolidated sleep.

Using a post-hemorrhagic hydrocephalus animal model, we will define how papilledema severity correlates with ipRGC integrity, circadian behavior, and sleep architecture, and assess inflammatory and vascular changes within the optic nerve head and retina. We will also test whether manipulating circadian cues (light–dark cycles, sleep disruption) or targeting inflammation and CSF dynamics modifies papilledema progression and neuroinflammatory load. This work will establish an experimental platform to dissect bidirectional interactions between hydrocephalus, papilledema, and circadian rhythms, and may reveal novel therapeutic windows that protect both vision and daily physiological rhythms in patients with hydrocephalus.

LAY SUMMARY

Papilledema is swelling of the optic nerve caused by pressure from excess fluid around the brain in hydrocephalus. This swelling can damage retinal ganglion cells, including a special group called intrinsically photosensitive retinal ganglion cells (ipRGCs) that send “light signals” from the eye to the brain's internal clock. When these cells are injured, patients may not only lose vision but also experience disrupted sleep and daily (circadian) rhythms. Many people with hydrocephalus report poor sleep, fatigue, and difficulty maintaining regular routines, but the role of papilledema and ipRGC damage in these problems is not understood. Our work uses an animal model of post-hemorrhagic hydrocephalus to study how optic nerve swelling, inflammation, and retinal changes relate to sleep and circadian disruption. Understanding this link may lead to new treatments that protect both vision and sleep–wake health in people living with hydrocephalus.