SRHSB Spina Bifida & Hydrocephalus Session

Underline – presenting author

SB1 The national incidence, detection rate and pregnancy outcome of spina bifida in Denmark 2008-2015

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Background: In Denmark (DK) all pregnant women are offered prenatal screening for fetal malformations. Studies have shown that Danish pregnant women don't comply to folic acid guidelines, but still a declining number of new borns with spina bifida (SB) in Western parts of DK has been shown. The aim of this study was to access the incidence, the prenatal detection rate and the pregnancy outcome of SB in DK during 2008-2015 and to compare results to available data from Sweden. **Methods:** Data was retrieved from the Danish Fetal Medicine Database, that holds pre- and postnatal information on all pregnancies that undergo prenatal screening in DK. Data on babies of mothers who had not been scanned prenatally was obtained from the National Patient Register. Cases with SB occulta, lipomyelomeningocele and isolated tethered cord without neurological deficits were excluded after validation of all patient files. Data on livebirths with myelomeningocele (MMC) in Sweden was obtained from a national database. **Results:** In a total of 475,679 pregnancies, there was 234 fetuses with SB in DK (incidence 4.9;10,000). 93% of SB cases were diagnosed prenatally, and 81% resulted in late termination by choice of the parents. Thereby, there was 14 meningocele (1.75/year) and 24 MMC (3/year) born in DK corresponding to an incidence of 0.8:10,000. The incidence of live births with MMC and lipoMMC in Sweden was 1.25:10,000. **Conclusion:** This study covers a total national cohort of registered SB cases in DK. Most cases of SB are diagnosed in utero, and most parents choose a late termination resulting in 3 live births of MMC and 1.75 cases of meningocele per year. The prenatal detection and the termination rate in DK is high, probably because of a well working prenatal screening. Comparisons to Sweden show that the rate of live births are higher in Sweden compared to DK without any clear explanation of this.

SB2 Bring it on: promoting self-management through the use of a mobile application during transition in emerging adults with spina bifida and hydrocephalus

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Evidence suggests that chronically ill children are not adequately prepared to autonomously manage every day aspects of care when they transition from paediatric to adult services. This manifests in poorer disease control, increased hospital presentations and associated care spending, and decreased patient follow-up during adulthood. A comprehensive literature review was conducted to identify structured transition programmes utilised worldwide. The findings suggest that despite global efforts, there are currently no universal, evidence-based standards to promote optimal self-efficacy amongst emerging adults. As such, we are attempting to amalgamate several transition tools to fit the specific needs of our young service users, harnessing their digital skills and familiarity with an online environment.

The Bring IT On Project aims to improve transitional services for those with spina bifida and/or hydrocephalous by creating a person-centred mobile application to improve upon and compliment the existing desktop platforms. It is envisaged that the app will include a multitude of holistic features that cater to complex management, including: health summary data, a digital Hydrocephalus Shunt Alert Card, an interactive zone for providers and service users to connect remotely to share insights and 'stories,' and seamless integration with other technologies, such as fitness trackers.

In the process of creating the app, engaging with service users to elicit their needs will fill current gaps in knowledge about digital platforms and the coproduction of digital data to promote wellness. The Bring IT On project sets to embrace technology already used by most young people and is a natural progression in accomplishing worldwide goals for transition management for a multitude of chronic illnesses. We argue that by engaging users through a digital health channel, young people will be better equipped to play an active role in their own transition journey.

SB3 **Using Emotional Touch Points as an innovative method for collecting research data**

Sharon Levy

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Often, new-born and young children with Spina Bifida have complex care needs that may be perceived as a significant burden on their family as a whole. As they grow up and move from paediatric focused care to being supported by adult services, these youngsters are expected to take more responsibility for their own health and well-being. Yet, the literature reports a mainly negative experiences of young people with the condition, as they progress along a transition pathway. More knowledge is needed to recognise the impact the condition has on young people's well-being, their understanding of and involvement in their own care, and their evolving needs as emerging adults.

There has been a growing international recognition of the importance of listening to and consulting with children regarding their lives. Despite initiatives such as the United Nations Convention on the Rights of the Child, children's experiences of living with Spina bifida and their views on involvement in their own care, are rarely elicited. Rather, parents are often asked to report on their child's health and well-being as a proxy agent in research or

medical focused consultations. Such clinical practice and research focus offer limited insight into childrenâ€™s lived experience and understanding of the condition from a patient's perspective. Obtaining children's own views is critical in efforts to fully understand and improve the experience of transitions.

The presentation will describe a novel method to elicit views of children and carers, where the focus is on emotions and feelings, rather than on describing events and transition milestones. Elaborating on the way the â€˜Emotional Touchpointsâ€™ were used, in a small qualitative study, will demonstrate the potential this technique has in co-production of knowledge. As will be discussed, this new knowledge is not just informing the interaction between the researcher and the subjects, but giving a new insight to parents and their children.

SB4 **Practice Preferences for Neurosurgical Management in Spina Bifida: a survey of the American Society for Pediatric Neurosurgery**

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Background: To better quantify the difference is Neurosurgical practice preferences we developed a survey that widely explored common Neurosurgery issues in Spina Bifida and utilized Survey Monkey to distribute it to 232 members of the American Society of Pediatric Neurosurgery (ASPN). **Materials and Methods:** A broad based survey was developed by a neurosurgical working group that widely surveyed practice preferences for a variety of Neurosurgical problems encountered across the lifespan in patients with SB. The survey was distributed via Survey Monkey. **Results:** There were 32 ASPN members who were not available by e mail or had retired from clinical practice. Of the remaining 200 members there were responses from 80 members (40% response rate). All results are self reported and non-validated. Results: A multi-disciplinary SB clinic (MDSBC) is present at 80% of centers. More than 50% of the MDSBCs had specialists in Neurosurgery, Orthopedics, Urology, Physical Therapy, Social Work, Orthotics, Physical Medicine and Wheel Chair Repair. Between 20-50% of clinics have specialists in Developmental Pediatrics, Gastroenterology, Nutrition, Neurology and OB-GYN while small numbers of clinics have additional medical specialty services (Nephrology, Endocrinology) available in the MDSBC. About 70% of clinics staffed by these Pediatric Neurosurgeons are purely pediatric while 30% serve children and adults. A transition program is in effect in 37% of these clinics and and 37% of surveyed Pediatric Neurosurgeons follow their SB patients through adulthood. **Conclusion:** Transition remains an acute need in coordinated care for SB. About a third of current MDSBCs staffed by this cohort of academic Pediatric Neurosurgeons follow adult patients and just over a third of Neurosurgeons follow their Pediatric patients with SB into adulthood.

SB5 **Exome analysis in an Estonian multiplex family with neural tube defects - a case report**

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Neural tube defects (NTDs) are a group of common and severe congenital birth defects that occur during early embryonic development due to incomplete closure of the neural tube. The genetic architecture of human NTDs, including spina bifida and hydrocephalus, is highly heterogeneous, with multiple genes/loci and both gene-gene and gene-environment interactions involved. In multiplex NTD families, whole-exome sequencing (WES) provides an alternative approach to investigate the genetic heritability of both rare and common coding variants. To date, there is only one published WES study conducted with sporadic NTD patients of European descent; however, no studies with familial NTD cases have been published. We present a multiple-spouse family with one pedigree lineage where three brothers are affected with NTDs: two lumbar spina bifidas without hydrocephalus and one obstructive hydrocephalus. We sequenced the exomes of three NTD patients and their parents. The analysis revealed a heterozygous c.844ins68 variant in CBS carried by all affected individuals and being inherited maternally. All affected individuals had a variable set of additional variants in genes involved in folate metabolism, sulphur amino acid metabolism, and planar cell polarity (PCP) signaling pathways.The involvement of variants in multiple genes and pathways denotes a scenario describing variable expression of a single shared genetic variant in the presence of sibling-specific sets of multiple modifier variants, each having weak individual effect, in genes that underlie the phenotypic variation. Likewise, we assume that combined additive effects of common and low frequency variants in one-carbon metabolism, sulphur amino acid metabolism, and PCP signaling pathway genes might be sufficient to disrupt the development and closure of the neural tube in our patients.

Hydrocephalus 1: Experimental Hydrocephalus

Underline – presenting author

H1 **Genetic Characterization of a New Mouse Model of Pediatric Hydrocephalus**

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Objectives: To discover the causative mutation on mouse chromosome 3 in the "progressive hydrocephaly (prh)" mouse mutant isolated in N-ethyl-N-nitrosourea (ENU)-mutagenesis screen. **Materials and Methods:** A whole genome sequencing the Illumina HiSeq2500 platform was performed in a phenotypic prh mouse mutant. The homozygous and unique nucleotide changes were investigated using publicly available mouse genome databases. The T>A mutation in a conserved splice donor site within Coiled-coil domain containing 39 (Ccdc39) gene was exploited in RT-PCR and western blotting. Involvement of other genetic changes in the hydrocephalus development derived from original mutagenesis experiment were tested in genetic complementation assay with an independently established $Ccdc39^{tm1a(KOMP)Wtsi}$ allele. **Results**: Bioinformatics filtering applied to the whole genome sequencing data revealed 34 unique homozygous changes within the 0.4 Mb interval to the prh mouse mutant compared to 21 deposited mouse strain genome databases. The TaqMan probe-based genotyping in hydrocephalus mice (n=51) showed that the homozygous mutation in Ccdc39 was thoroughly associated with the hydrocephalus phenotype. The mutation was

found on a highly conserved thymidine resides within mRNA splicing donor site sequence (AGgu*ragu) essential for the correct joining of exons. Sanger sequencing of the brain cDNA library showed that the mRNA splicing between exons 7 and 8 of the Ccdc39 gene was disrupted by the prh mutation. Western blotting showed that there is no Ccdc39 protein detectable in the mutant brain lysate. The genetic complementation of the prh allele with $Ccdc39^{tm1a(KOMP)Wtsi}$ allele resulted in recapitulation of the hydrocephalus phenotype, which indicated that the splice site mutation in Ccdc39 is solely responsible for the hydrocephalus phenotype in the prh mouse mutant. **Conclusion**: We identified a novel mutation in the Ccdc39 gene that is responsible for early postnatal hydrocephalus phenotype in the prh mutant mice.

H2 **Defective Ependymal Motile Cilia Causes Hydrocephalus in a New Model of Neonatal Hydrocephalus, the prh mouse mutant**

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Background: To investigate the contribution of the Coild-coil domain containing protein 39 (Ccdc39) gene in the ependymal cilia functions and to the development of the neonatal hydrocephalus phenotype in the "progressive hydrocephaly (prh)" mouse mutant. **Materials and Methods:** Temporal and subcellular localization of Ccdc39 protein was analyzed using immunohistochemistry with confocal microscopy. Morphology and ultrastructural of the nascent ependymal cilia were investigated using scanning and transmission electron microscopies. High speed video-microscopy used for direct visualization of the beating pattern of the ependymal cilia and the cerebrospinal fluid (CSF) flow through tracking of the fluorescent micro-beads introduced ex vivo brain slice. The in vivo CSF flow was traced after injection of the Evans blue dye using stereotactic instrument into the left lateral ventricle. **Results:** Immunohistochemical analysis revealed that Ccdc39 protein is expressed in the cilia of the forebrain ventromedial wall ependymal cells and choroid plexus cells at embryonic day 18, which was absent/undetectable in the prh mutants. The prh mutant ependymal cilia failed to have the molecular markers of the inner dynein arm proteins, Dnali1 and Gas8, within the cilia axoneme, and those proteins were abnormally accumulated in the cytoplasm of the mutant cells. The electron microcopy analysis shows that the mutant ependymal cilia appeared shorter and smaller in diameter and lack the inner dynein arm, and proper formation of nexin-dynein regulatory complex. All are structures needed for the back-and-forth motion of motile cilia beat, a highly conserved motion essential for generating local CSF flow. Video-microscopy confirmed the mutant cilia beat at statistically significant low frequency compared to the wild-type cilia (n=10). The local CSF flow rate was significantly reduced in the prh mutant (11±0.07μm/sec) to the wildtype (68±0.7μm/sec, n=6), p = 1.3993E-247). Marked reduction of the Evans blue dye was observed in the fourth ventricle in the prh mutant brains (5/8) compared to the wildtype (n=5). **Conclusions:** The Ccdc39 protein is necessary for proper ciliogenesis of the motile ependymal cilia essential for CSF flow and circulation. We believe that this finding contributes to the development of hydrocephalus in this novel model.

H3 **Gene expression profiling analysis of the choroid plexus in a novel mouse model of pediatric hydrocephalus**

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Background: Hydrocephalus is the most common brain malformation found at birth. Although the surgical intervention can greatly ameliorate outcomes, currently there is no medical cure for this condition. In addition, about 30% of these cases have unknown etiology. In order to identify molecular mechanisms involved in congenital hydrocephalus development, we investigated the molecular characteristics of the choroid plexus in the progressive hydrocephaly (prh) mouse mutant, in which we recently identified a homozygous mutation in Ccdc39 (coiled-coil domain containing protein 39) gene. **Methods**: We performed a next generation RNA sequencing using choroid plexus tissue isolated from the prh mutant mouse (n=3) and wild-type littermate (n=3). Significant genes were reviewed for potential role in hydrocephalus based on previous works citing possible cilia function, previous correlation with congenital hydrocephalus, or role in the embryonic development of choroid plexus. Selected genes then underwent ΔΔCt qPCR validation testing to confirm significance. **Results**: The RNA sequencing data revealed 130 statistically significant genes of a total 15,019 genes sequenced. Of the 130 statistically significant genes, we identified 16 genes thought to be important in cilia formation, choroid plexus formation, or development of congenital hydrocephalus. Of those, seven genes were validated with ΔΔCt qPCR. Four of the validated genes are downregulated in mutant mice and all play a role in cilia formation. The other three genes each play a role in formation of choroid plexus. **Conclusion**: Together, these data indicate that mutations of these genes may disrupt the motility of choroid plexus cilia in the developing brain and suggest the possible involvement of choroid plexus cilia in the development of congenital hydrocephalus.

H4 **Valsartan treatment effects on the choroid plexus in spontaneously hypertensive rats**

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Background: Hypertension is one of the most important modifiable risk factors for cardiovascular disease. Its effects on hemodynamic variables and cerebral vascular remodeling have been extensively studied. However, its harmful effects on the highly vascular structure and function of the choroid plexus need to be studied. On the other hand, there is evidence that spontaneously hypertensive rats present a progressive ventricular dilatation and CSF accumulation. Moreover, whether these effects can be prevented by drug treatment still remains unknown. Therefore, the aim of this study is to analyze cerebrovascular disorders produced by chronic hypertension in the choroid plexus to determine whether early treatment with an anti-hypertensive treatment (Valsartan) can prevent the effects of the disease. **Materials and Methods:** We used anti-hypertensive drug

(Valsartan) with an SHR model of hypertension (spontaneously hypertensive rat) and control WKY rats from the eighth week after birth up to 26 weeks of age. We studied the functionality and structure of both choroid plexus and cerebral blood vessels with immunohistochemical techniques using antibodies against: aquaporin 1 (AQP1), collagen IV, Na-K ATPase and transthyretin. **Results:** One of the effects of hypertension was an increased level of collagen IV in both the choroid plexus and cerebral vessels. An elevation of the aquaporin-1 and a decrease of transthyretin expression were noted in the Valsartan treated group. Variations in Na-K ATPase and AQP1 localization were also observed in the hypertensive and treated groups. **Conclusions:** Early treatment of hypertension prevents the pathological accumulation of collagen IV in the choroid plexus and the blood vessels studied. It can also prevent the negative effects associated with hypertension on choroid plexus function and ventricular dilatation.

H5 **Blood-derived lysophosphatidic acid signaling alters mitotic spindle orientation and subsequent cell fates of neuroprogenitor cells in post-hemorrhagic hydrocephalus**

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Background: Mitotic spindle orientation influences symmetric vs asymmetric cell division during ventricular zone (VZ) development and corticogenesis. We tested the hypothesis that blood factors, such as lysophosphatidic acid (LPA), found in cerebrospinal fluid of post-hemorrhagic hydrocephalus (PHH) infants, can alter mitotic spindle and neuroprogenitor fate during ventriculomegaly and PHH using an ex vivo cortical culture and in vivo mouse model of fetal-onset hydrocephalus. **Methods:** Mouse fetal brains at embryonic day E13.5 were cultured in or injected with serum or LPA and harvested and fixed at select time points. Dividing cells were assessed for cleavage plane angle, as well as markers for cell proliferation, adhesion and polarity. Lineage relationships of dividing to post-mitotic cells were established. **Results:** LPA exposure shifted dividing NPCs from vertical to non-vertical apico-basal cleavage angles, consistent with bias towards asymmetric division. In addition, LPA induced altered apical adherens junctions, cell polarity, and subsequent altered neural fates compared with controls. Exposure to either plasma or serum - known significant sources of LPA - also produced similar changes. Genetic removal of both LPA1 and LPA2 receptors abrogated these changes, yet also resulted in unstimulated cleavage plane orientation alterations comparable to wild-type controls, indicating normal influences on cleavage plane through endogenous LPA actions on its receptors. These changes can also be blocked using LPA receptor antagonists. **Conclusion:** These data identify LPA as a soluble, extracellular signal acting through at least two cognate LPA receptors to influence neuroprogenitor cell fate under basal development and neuropathological conditions that elevate LPA. These pathological stimuli alter brain development towards hydrocephalus and may likely be blocked by pharmacological compounds.

H6 **Ventricular zone disruption in a new gyrencephalic model of post-hemorrhagic hydrocephalus**

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Background: Ventricular zone (VZ) disruption has been observed in lissencephalic animals and humans with congenital or post-hemorrhagic hydrocephalus (PHH), but systematic studies of this pathophysiology are lacking in young animals with a gyrencephalic cortex. To test the hypothesis that VZ disruption occurs following intraventricular hemorrhage (IVH), we have analyzed tissue from our recently developed infant ferret model of IVH. **Methods**: Two-week old ferrets received unilateral intraventricular injections of the thrombin component lysophosphatidic acid (LPA) or autologous blood to induce ventriculomegaly. Sham controls received similar injections of sterile saline. Neuroimaging experiments (T2-weighted MRI, magnetic resonance elastography and diffusion tensor imaging) were performed biweekly until approximately 150 days following induction. Fixed tissue from frontal and parietal regions was analyzed using immunohistochemistry for neuroepithelial/ependymal cells (glial fibrillary acidic protein, GFAP; S-100□, aquaporin-4), neural progenitors (□□□□□ tubulin), multiciliated ependymal cells (□-IV tubulin), astrocytes (GFAP), and cell-adhesion molecules (N-cadherin, L1-cell adhesion molecule). **Results**: Mild-moderate ventriculomegaly developed after about two weeks, confined to the lateral ventricles and more severe in the body and occipital horns. The surrounding cortical mantle was compressed and the periventricular white matter developed edema, although no post-induction neurological deficits were detected. Controls had an intact VZ with multiciliated ependymal cells, but PHH animals all exhibited patches of denuded ependyma, VZ cells lacking cilia and radial processes, and eruptions of VZ regions into the ventricle. These alterations were more prevalent along the lateral ventricular wall. In addition, GFAP+ reactive astrocytes appeared in regions of VZ disruption. **Conclusion**: These findings suggest that VZ disruption is a consistent consequence of IVH.

H7 **Ventricular zone disruption in a novel in vitro model of posthemorrhagic hydrocephalus: the role of cell junctions**

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Background: Despite advances in neonatal and neurosurgical care, the neurological outcomes of preterm infants with posthemorrhagic hydrocephalus (PHH) remain among the worst in newborn medicine, being the most common etiology of pediatric hydrocephalus in North America and a leading culprit in neurosurgical revision surgery, accounting for over $605 million in healthcare spending each year. In order to improve significantly the care and

outcome of these most vulnerable patients, we must first define the mechanisms that drive the development of PHH and mediate its devastating neurological effects. Most types of foetal-onset hydrocephalus present with ventricular zone (VZ) disruption with cell junction pathology as a fundamental event of pathogenesis. We have developed a VZ in vitro model of PHH to examine the mechanisms underlying this disease. **Materials and Methods:** Newborn brains from the same litter were dissected and the ependymal progenitor cells from the ventricular wall were dissociated and plated onto coverslips where they start to differentiate as a monolayer of ependymal cells (EC). Five days later 25µL of sibling blood was added to the cultures for 24 hours. Controls received 25µL of PBS. The cells cultures were analyzed by immunocytochemistry against βIV tubulin, S100, N-cadherin, Connexin 43, and GFAP. **Results:** EC cells grown without blood exposure mature normally and develop N-cadherin positioned at the cell membrane. In contrast, the cells exposed to blood exhibit a highly abnormal, diffuse cytoplasmic expression of N-cadherin, lower numbers of mature ependymal cells and a remarkable glial reactivity. **Conclusions:** Our results confirm that blood causes a cell junction pathology which promotes VZ disruption and glial activation. Furthermore, this work employs a reproducible and reliable model of PHH as a new tool for understanding the physiopathology of this disease.

H8 **Role of Ventricular Zone Junctional Biology in Posthemorrhagic Hydrocephalus.**

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Background: Post-hemorrhagic hydrocephalus (PHH) develops in approximately 20% of infants with severe intraventricular hemorrhage (IVH), indicating that critical selective mechanistic triggers downstream of the hemorrhage are required for development of this disorder. However, despite the fact that IVH is the most common neurological complication of preterm infants, the specific effect of blood on the ventricular zone (VZ) that forms the wall of the ventricles is unknown. Most types of fetal-onset hydrocephalus present with cell junction pathologies in the VZ, such as a loss of adherens junctions formed by N-cadherin which leads to the disconnection of the cells lining the cerebral ventricles. The disintegrin Metalloproteinase 10 (ADAM10) is a widely expressed zinc metalloprotease that principally regulates cellular adhesion and migration. In the brain ADAM10-mediated proteolysis of the extracellular domain of N-cadherin disrupts cadherin-dependent homotypic intercellular interactions. We hypothesize that the hyperactivity of ADAM10 can be one of the underlying mechanisms causing the disruption of the VZ in PHH. **Materials and Methods:** Newborn mouse brains were dissected and the ependymal progenitor cells from the ventricular wall were dissociated and plated onto coverslips where they start to differentiate as a monolayer of ependymal cells (EC). Five days later, 3 treatments were applied: (1) 25µL of blood, (2) 20 hemolytic units of α-hemolysin (activator of ADAM10), (3) GI254023X (inhibitor of ADAM 10); these treatments were continued for 2 hours. **Results:** Preliminary data show an overexpression of ADAM10 and decreased transepithelial resistance with blood treatments, suggesting a defect in adherens junctions. Ongoing results with and without modulation by ADAM10 inhibitors and activators will be presented. **Conclusions:** Overexpression of ADAM10 that may implicate the sheddase ADAM10-mediated cleavage of N-cadherin in VZ disruption.

H9 **Developing new therapies to treat brain ventricular wall damage during hydrocephalus**

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NO ABSTRACT PUBLICATION REQUESTED BY AUTHORS

H10 **NG2 cells in an animal model of congenital hydrocephalus**

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NO ABSTRACT PUBLICATION REQUESTED BY AUTHORS

H11 **Hydrocephalus Association Network for Discovery Science**

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The mission of the Hydrocephalus Association (HA) is to promote a cure for hydrocephalus and improve the lives of those affected by the condition. We aim to accomplish this mission by collaborating with patients, caregivers, researchers and industry, raising awareness, and funding innovative, high-impact research to prevent, treat and ultimately cure hydrocephalus.

As part of this effort, HA created the HA Network for Discovery Science (HANDS) in 2015. HANDS is a platform for communication and collaboration among hydrocephalus basic, translational, and clinical researchers with a focus on mentorship, innovation, and shared infrastructure to support high quality, high impact research. The goal of HANDS is to become a central resource and point of contact for hydrocephalus researchers, to actively support the needs of hydrocephalus researchers, and to accelerate progress in hydrocephalus research. Through HANDS (hands.hydroassoc.org), members currently have access to a CSF biobank supported by Washington University School of Medicine, databases for research models, genetics and prevalence, and research grants. HANDS members play an active role in the development of new infrastructure, and we are currently in the process of expanding available resources.

To date, three grant cycles have been run through HANDS, and, in 2016, HANDS held the Posthemorrhagic Hydrocephalus Workshop at the NIH Neuroscience Center. The workshop brought together a diverse group of researchers including pediatric neurosurgeons, neurologists, and neuropsychologists with scientists in the fields of brain injury and development, CSF dynamics, and fluid barriers in the brain. The workshop spurred many new collaborations and brought new researchers into the fold.

SRHSB Guthkelch Award Finalist Presentations

Underline – presenting author

G1 **The incidence and effect of tethered cord release for tethered cord syndrome in myelomeningocele patients - population based study**

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Aim: To establish an incidence and assess the effect of tethered cord release for tethered cord syndrome in patients with myelomeningocele. **Method**: The Western Denmark Myelomeningocele Database contains all patients born with myelomeningocele in western Denmark since 1970. All patients born between 1970 and 2015 were extracted from this database and cross-referenced in 2015 with a database for surgical procedures. This latter database contains all surgical procedures performed in the central Denmark region since 1996. Therefore, only patients alive at some point between 1996 and 2015 were included. Incidence were calculated and presented for year of age and chronological year. File reviews were conducted for all patients who underwent the procedure. Follow-up was divided into short term and long term follow-up. **Results**: Of the extracted population, 166 patients were alive in various lengths of time between 1996 and 2015. Of these, 45 patients underwent the procedure. Seven were re-operated. Mean age for the procedure was 13 years. Incidence was bimodal with high incidence in children and adolescents (maximum = 15 years of age). Incidence for chronological year was high between 2002 and 2012 (maximum = 2005). The most common indications were progressive spine deformity (40%), deteriorating ambulation (38%) and deteriorating neurogenic bladder and/or bowel dysfunction (32%). Mean short time follow-up was 4.7 months and mean long term follow-up was 72.6 months. Postoperative, the majority had improved (27%) or stabilized (29%) at short term follow-up. At long term follow-up, most patients were stable (26%) or had deteriorated (26%). At both follow-ups there was a loss of approximately one third of all patients. Complications occurred in 17% of the procedures. **Conclusion**: Tethered cord release has the highest incidence in childhood and adolescents. In chronological year, the highest incidence was in the year of 2005. The beneficial effect of the procedure seems to be short termed. Due to the uncertainty of a long term effect of the procedure in patients with myelomeningocele and the registered complications, surgeons should have a solid indication before performing the procedure.

G2 **Bacterial colonization of urinary catheters: how does this affect symptom presentation?**

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Background: Catheter-associated urinary tract infections (CAUTI) are a significant clinical and financial burden to patient populations that rely on urinary catheterisation to manage their bladder. The current criteria for diagnosing CAUTI is a combination of symptom presentation and microbiological characterisation of urine culture. There is little understanding of the bacteria attached to the balloons (representative of the bladder environment) and catheter lumens. Therefore, this study aims to identify and quantify microorganisms attached to the lumens and balloons of urinary catheters and relate this to patient-specific information.

Materials and Methods: Indwelling urethral urinary catheters were collected when removed from patients at Nottingham University Hospitals NHS Trust, Nottingham, UK. The balloon was separated and placed in sterile phosphate buffered saline(PBS) and the lumen was filled (ports discarded) with PBS, and its ends clamped. The lumen and balloon were sonicated and microorganisms in the sonicate were enumerated, identified, and tested for antibiotic susceptibilities. Antibiotic use and symptoms were recorded. **Results**: Sixty-one catheters were analysed. Escherichia coli and Enterococcus faecalis were the most commonly isolated organisms. 19.7% of patients received antibiotics while catheterised and 25% of those had a multi-drug resistant (MDR) organism. All lumens were colonised irrespective of antibiotic use. Conversely, 2.04% of catheters from patients not known to be receiving antibiotics had a MDR organism present. Symptom presentation did not correlate with numbers of colonising organisms. **Conclusions**: Lumens and balloons of urinary catheters were colonised irrespective of presence of antibiotics. If diagnosis was solely reliant on meeting microbiological criteria 2/8 patients would have been missed, and 29 (54.7%) of asymptomatic patients meeting the microbiological diagnosis criteria might have been over-treated.

G3 **Effect of bone marrow-derived mesenchymal stem cells on congenital hydrocephalus in the hyh mouse**

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NO ABSTRACT PUBLICATION REQUESTED BY AUTHORS

G4 **Micro-fabricated arachnoid granulations for treating hydrocephalus**

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Hydrocephalus is often treated by permanently shunting fluid out of the cerebral ventricles, but this can cause severe neurological deficit because the outflow is not physiologically regulated. Treatment has remained virtually stagnant since inception of the shunt in 1952, despite shunting being the only treatment device, and shunting having the highest failure rate in all neurosurgical procedures; 40% failure after 1 year, and 98% failure rate after 10 years.
With our long-term goal in mind of developing successful physiologically-driven treatment, we propose to test and manipulate a micro-fabricated arachnoid granulation (MAG) device. The novel MAG device will allow CSF to be physiologically absorbed from the sub arachnoid space (SAS) to the superior sagittal sinus (SSS). We circumvent the absorption problems caused by hydrocephalus by mimicking the role of native arachnoid granulations. We treat the patient without standard shunting, and in doing so eliminate shunt-related complications accounting for a majority of the $2-billion yearly cost and patient suffering associated with hydrocephalus. The MAG will provide a long-term solution for hydrocephalic patients, without tens if not hundreds of surgical revisions caused by shunt failure.
The MAG consists of an array of microneedles which control the outflow rate of the CSF, regardless of the patient CSF production rate. The needles overlay one way hydrogel valves. The valves are pressure regulated allowing for outflow through the needles at physiological pressures while completely resisting backflow similar to native arachnoid granulations. To meet our end-goal of clinical translation of the MAG device, the project aims for clinical-trial

readiness through implantation in hydrocephalic animal models, followed by clinical trials. By directly addressing the pathology of hydrocephalus and utilization of micro-fabrication techniques, we are providing a novel, simple and effective treatment for hydrocephalus.

Hydrocephalus 2: Clinical Hydrocephalus & Biomedical Engineering

Underline – presenting author

H12 **Novel optical diagnostic for infant hydrocephalus in both the developed and developing world**

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Background: Infant hydrocephalus is a severe burden across the world, with eighty percent of cases occurring in developing countries. Current assessments of disease progression and its treatment are crude, with little power for predicting neurodevelopmental impairment (NDI). Thus, the developed and developing world both urgently need new approaches to quantitatively assess hydrocephalus and guide interventions to greater success. **Methods**: Cerebral blood flow (CBF) is a promising biomarker for evaluating hydrocephalus and its effects on brain physiology. We have developed a new optical technology, frequency-domain near-infrared spectroscopy (FDNIRS) with diffuse correlation spectroscopy (DCS) to measure non-invasively oxygen saturation (SO_2), cerebral indexes of microvascular blood flow (CBF_i) and oxygen metabolism ($CMRO_{2i}$) in an infant's brain, right at their bedside. We aim to test whether CBF_i and $CMRO_{2i}$ can be new indicators of cerebral health to guide hydrocephalus treatment and NDI prognosis. **Results**: We are investigating post-hemorrhagic hydrocephalus and spinal bifida at Boston Children's Hospital (BCH), and post-infectious hydrocephalus infants at CURE Children's Hospital Uganda (CCHU). In the BCH cohort, we found successful hydrocephalus treatment increases CBF_i and restores normal cerebral metabolism, whereas cerebral SO_2 shows no change. Primary infectious injuries in PIH caused more severe damage to brain structure than in PHH. Measurements of the distortion of light propagation through a subject's skull accurately detected brain structure abnormalities. Decreases in brain optical scattering immediately post-surgery had high predictive value for treatment failure within 6 months. Most importantly, brain regions with higher $CMRO_2$ had better recovery of brain structure after 6 months by CT scan. NDI testing at 24 months is planned. **Conclusions**: We have demonstrated our method is sensitive to the state of hydrocephalus in both high and low resource settings.

H13 **Cerebrospinal fluid parameters alone do not inform infection management in posthemorrhagic hydrocephalus**

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Background: Preterm posthemorrhagic hydrocephalus (PHH) is often managed with ventricular reservoir or shunt placement, which carry infection rates as high as 10%, necessitating long-term antibiotics. In patients who undergo a septic workup, cerebrospinal fluid (CSF) samples may show pleocytosis, precipitating antibiotic treatment despite the lack of positive cultures. In this study, we analyze the CSF and complete blood count (CBC) profile from the same day in subjects with culture positive (CP) meningitis compared to culture-negative CSF across 8 groups, including patients with PHH. **Materials and Methods:** A retrospective analysis was performed on 200 subjects – 30 controls, 9 central line associated blood stream infection (CLABSI), 38 intraventricular hemorrhage (IVH) grade I or II, 9 IVH grade III or IV, 36 culture negative PHH, 43 CP viral meningitis (VM), 25 CP bacterial meningitis (BM), and 10 CP/BM with PHH. Subjects on antibiotics or ≤ 7 days post antibiotics were separated into another group. CSF samples were obtained by lumbar puncture, reservoir tap, or operating room procurement. Statistical significance was based on one-way analysis of variance (ANOVA) among all groups and Tukey's multiple comparison test between groups ($p < 0.05$). **Results**: Significant results were: CSF total protein was higher in PHH compared to other groups, including VM. Macrophages in IVH III/IV were higher compared to other groups. White blood cells (WBC) were higher in CLABSI than other groups. VM WBC was lower than PHH. Hemoglobin was lower in PHH than VM and IVH I/II. Hemoglobin in PHH with BM was lower than controls. Hematocrit in PHH was lower compared to other groups. Platelets in CLABSI were lower compared to VM. **Conclusions**: CSF profile alone should not be used to dictate antibiotic initiation. CSF and blood culture results in combination with CSF and CBC profiles may be a better guide for infection management.

H14 **Multicentre randomised trial of drainage, irrigation and fibrinolytic therapy (DRIFT) for premature infants with posthaemorrhagic ventricular dilatation; neurodisability at school-age**

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Background: Intraventricular haemorrhage (IVH) with post-haemorrhagic ventricular dilatation (PHVD) is a serious neurological complication seen in preterm infants, with significant neurodisability in survivors. No medical intervention has been proven to reduce long-term neurodisability after PHVD. Drainage, irrigation and fibrinolytic therapy (DRIFT) was developed as a novel method of irrigating the ventricles to clear the effects of haemorrhage. The DRIFT trial, conducted in 2003-6 randomised preterm infants to either DRIFT or standard therapy (cerebrospinal fluid tapping to control PHVD). At 2-years there was a reduction in severe cognitive disability in the DRIFT group (Pediatrics. 2010

Apr;125(4):e852-8). However, as cognitive assessment at 2-years has limited validity, our aim was to perform definitive assessment at 10-years, to reach a valid conclusion about the sustained efficacy of DRIFT. **Materials and Methods**: Long-term follow-up of a randomised controlled trial. Primary Outcome: Cognitive Quotient; alive without severe disability. Secondary outcomes: Visual function, sensorimotor disability, emotional/behavioural difficulties. **Results:** 52 children were assessed at 10-years. Trial recruitment, randomisation, 2 and 10-year follow-up are summarised in figure 1 and primary/secondary outcomes in Table 1. Results are in parallel with those at 2-years, with crude estimates giving weak evidence that the DRIFT intervention increases CQ at 10-years (p=0.096). The DRIFT group had a 23.47 point CQ advantage after adjustment for gender, birthweight and grade of IVH (p=0.009) and was almost 4 times more likely to be alive without severe disability at 10-years (OR 3.82, 95% C.I. 1.19, 12.23, p=0.024 and OR 10.69, 95% C.I. 2.12, 53.86), p=0.004 after adjustment). There were no differences in secondary outcomes. **Conclusions**: DRIFT is the first intervention to reduce long-term disability after PHVD. This life changing intervention should now be developed as standard care for preterm infants with PHVD.

H15 **Early or precocious puberty in children with shunted pre/perinatal hydrocephalus with and without myelomeningocele**

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Background: Girls and boys with myelomeningocele (MMC) and hydrocephalus run an increased risk of early or precocious puberty (E/PP). Increased intracranial pressure perinatally has been reported to be a strong predictor. However, there is only limited information available on pubertal development in children with shunted hydrocephalus without MMC. The aim of the present study was to investigate the occurrence of and risk factors behind E/PP in children with shunted pre/perinatal hydrocephalus with and without MMC. **Materials and Methods:** Medical data on all children with pre/perinatal hydrocephalus, born 1980 - 2002, treated with shunt and living in the counties of Uppsala and Västmanland (n=84) was obtained from hospital records. Data was sufficient to evaluate in 74 (37 girls) patients, of which 39 children had MMC (23 girls). Early puberty was defined as pubertal signs before 10 years and two months for boys and 9 years and two months for girls. Precocious puberty was defined as the appearance of pubertal signs before 9 years in boys and before 8 years of age in girls. **Results**: Early or precocious puberty was found in 30 of the girls (81 %) and in 10 of the boys (27 %). Median ages for start of puberty was 11.1 years for boys both with and without MMC, 8.5 years for girls with MMC and 8.7 years for girls without MMC, i.e. significantly lower than reference values. There was a strong negative correlation between age at start of puberty and head circumference at birth for girls with MMC. **Conclusions**: Children with shunted pre/perinatal hydrocephalus, both those with and without MMC, are at risk of developing E/PP. The risk is most marked for girls, especially those with MMC and high intracranial pressure at birth. Growth and pubertal development should be monitored for all children with shunted pre/perinatal hydrocephalus in order to diagnose early development of puberty.

H16 **Heat shrink tubing for secure connection of valve and shunt**

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Shunt disconnections are classified as either complete separation of the valve and catheter, tearing of the catheter, or calcification of the catheter tubing leading to breakage. Approximately twenty percent of shunt revision surgeries are due to shunt disconnection, a purely mechanical, and preventable failure which inevitably leads to hundreds of thousands of shunt revision surgeries each year, and significantly impacts the lives of hydrocephalic patients. A simple, FDA approved, market available solution has been proposed to minimize shunt disconnection failures. Medical grade heat shrink tubing, is already employed to increase mechanical integrity and to protect endoscope wires. Heat shrink tubing may be placed over the connection between the valve and catheter, a heating element may then be used to shrink the tubing in place. The addition of a heat shrink tubing works to standardize the connection point, hold the suture in place, increase the mechanical integrity of the catheter tubing, and protect the catheter from degradation in the in-vivo environment. In addition, our findings have shown that catheter tubing is inevitably damaged by clamping instruments used during the operation, placement of heat shrink tubing compensates for the micro-tears and damage of the catheter. Preliminary experiments testing the tearing of the catheter due to cyclic stress and strain have shown that the shrink tubing reduces failure due to breakage or tearing of the catheter by adding mechanical reinforcement and rigidity to the catheter tubing. The proposed solution is relatively inexpensive, and requires under ten minutes of additional operating time. Most significantly, the shrink tubing is not specific to any company, or valve allowing for easy adoption. A clamped resistive heating element is being designed to allow for uniform heating of the shrink tubing in the operating room. This simple solution may lead to reduction of emergency and life threatening scenarios that arise due to shunt disconnection.

SRHSB Poster Presentations

P1 **Masking Shunts with Monolayers of Ciliated Epithelial Cells to Impede the Foreign Body Response in the Treatment of Hydrocephalus**

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Background: Examination and manipulation of the foreign body response (FBR), and inflammation provoked by biomaterials, have been conducted since the first kidney transplants in the 1950s. In the treatment of hydrocephalus, similar problems still plague shunts. A staggering 40% of shunt systems fail after two years, 85% after 10 years; approximately 50% of failures are due to shunt's ventricular catheter becoming occluded. Surface modification techniques such as coating the material with films of natural or synthetic polymers to alter surface chemistry, topology, and roughness, manipulation of catheter architecture, and impregnating surfaces with anti-inflammatory drugs are just some of the many approaches to fighting the FBR and catheter encapsulation. To break from these techniques and instead take a translational approach to this problem, we asked if we could modify the current, commonly used shunt catheter to be bioactive with the objective of evading FBR. We asked if it would be possible to grow a self-sustaining, uniform, monolayer of Ciliated Epithelial Cells on standard ventricular catheters. **Materials and Methods**. Intact endothelial cell sheets were harvested from thermoresponsive cell culture surfaces for preliminary data collection. Subsequently, we cultured choroid plexus epithelial cells (CPECs) and multi-ciliated ependymal cells on traditional poly(dimethylsiloxane) (PDMS, silicone) ventricular catheters to get a 'masked catheter'. We use a custom-made cell culture system that allows for the growth of CPECs on the surface of the catheter. Fluorescently

transduced cells paired with confocal microscopy will be implemented for a deeper understanding of the cell monolayers. **Results**. Preliminary results indicate successful growth of a monolayer of endothelial cells mounted on seven layers of astrocyte monolayers. With our CPECs and multi-ciliated ependymal cell wall, we hope to achieve a similar monolayer. We hope to see the monolayer maintain itself without excessive death or overgrowth. Qualitative analysis on the monolayers and ciliated morphology will reveal interesting trends indicative of cell viability. **Conclusion**. Our initial findings indicate cell viability and lack of cell denudation. We propose the use of CPECs and mutli-ciliated ependymal cells to inhibit the FBR. In future work, samples will be inserted into 3D cell culture systems with fluorescently transduced astrocytes and microglia to compare & study their response to the masked catheter versus a standard PDMS catheter control. Also in future work we test the effect of the monolayer mask on the flow through the catheter.

P2 **Elevated Intracranial Pressure: Modeling Pressure-Induced Cellular Injury ex vivo**

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Objectives: Characterizing the biomarkers associated with elevated intracranial pressure ICP will advance our understanding of the pathologic cascade leading to brain injury, while providing potential therapeutic targets for the treatment of hydrocephalus and other pressure-related brain pathologies. Increasing pressures in both incremental pulses versus sustained increases allows for characterization of possible variable sensitivity of CNS cells, mimicking sudden pressure increase from acute hydrocephalus, progressive hydrocephalus, and other pressure induced neurological diseases. **Methods**: To simulate pressure induced brain injury, we developed an ex vivo model of hydrocephalus, which combines 3D neural cell cultures and a newly developed Pressure Controlled Cell Culture Incubator (PC3I). Cells are maintained in a 3D peptide-conjugated alginate hydrogels and subjected to different pressures to mimic both physiologic and pathologic conditions, and then analyzed for injury/inflammatory biomarkers. **Results:** Inflammatory biomarkers were measurable following both sustained and pulsatile pressure exposures. We demonstrated the ability to maintain greater than 50% cellular viability in 3D alginate hydrogels for up to 4 weeks. ATP-release assays revealed that a time-dependent statistically significant increase in neurons, but not astrocytes, while multiplex assay suggest cytokines IL-6 & IL-8 elevation following sustained pressure exposures compared with controls. **Conclusions**: Using a novel ex vivo model of neonatal hydrocephalus, these data indicate extracellular release of ATP is an important signal associated with elevated pressure, and may be a key in the early secondary injury response to elevated ICP in the developing neonatal brain. The trend towards elevated inflammatory cytokines are also possible key injury mechanisms with roles in cell injury. Further experiments using this model system will determine other cellular biomarkers associated with pathological ICP.

P3 **Ventricular zone disruption in human neonates with intraventricular hemorrhage**

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Background: Dysplastic changes in the ventricular (VZ) zone have been reported in animals and humans with congenital hydrocephalus but not on patients with intraventricular hemorrhage (IVH). Since this mechanism could play a major role in the pathophysiology of post-hemorrhagic hydrocephalus, we sought to determine if VZ alterations are associated with IVH in human infants. **Materials and Methods:** Brain specimens from IVH cases (n=13) were compared to those from controls (n=3) with no hemorrhage or ventriculomegaly who expired from nonneurological causes. Postmortem tissue from frontal cortical and subcortical regions was processed by routine histology and immunohistochemistry for neural stem cells, neural progenitors, multiciliated ependymal cells, astrocytes, and cell adhesion molecules. **Results:** Patient birth and expiration estimated gestational ages were 23.0-39.1 and 23.7-44.1 weeks for IVH cases and controls, respectively; survival was 0-42 days for all cases (median 2.0 days). Controls exhibited monociliated neural stem cells and multiciliated ependymal cells lining the ventricles, abundant neural progenitors occupying the subventricular zone (SVZ), and medial vs lateral wall differences in a complex and dynamic mosaic organization. In IVH, normal VZ/SVZ areas were mixed with multiple sites of neural stem cell and ependymal cell loss, eruption of cells into the ventricle, cytoplasmic transposition of N-cadherin, subependymal rosettes, and periventricular heterotopia. Mature astrocytes populated areas believed to be sites of former VZ disruption. In IVH cases, the cytopathology and extension of the VZ disruption correlated with the developmental age but not with the grade or location of the brain hemorrhage. **Conclusions:** These results corroborate similar findings in congenital hydrocephalus and increase understanding of the pathophysiology-pathogenesis of IVH by showing that VZ disruption occurs consistently in premature neonates with this disorder.

P4 **CRISPR/Cas9-Based Development of Novel Transgenic Rat Model of X-Linked Hydrocephalus**

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Objective: Due to the abundance of functional genomic methods available for mice, transgenic mouse models dominate modern studies into the pathogenesis of congenital

hydrocephalus. However, their small size inhibits the use of surgical and imaging procedures that could be performed in larger rodents. Emergence of CRISPR/Cas9 genome-editing technology provides an accessible method for generating transgenic rat models of congenital hydrocephalus that have been traditionally challenging to manipulate genetically. We sought to use CRISPR/Cas9 to knockout the L1cam gene in a rat model of X-linked hydrocephalus (XLH). **Methods**: Two guide RNA (gRNA) oligomers, designed to disrupt exon 4 of the rat L1cam gene on the X chromosome, were injected into SD rat embryos and transplanted into recipient rats. Rats born from these embryos were sequenced for evidence of L1cam mutation and monitored for the XLH phenotype. **Results**: Of the eleven rats born from CRISPR-modified embryos, seven exhibited mutation of the L1cam gene in the targeted region of exon 4. The types of mutations disrupting L1cam in each L1exon4CRISPR allele varied from nonsense mutations to large deletions up to 300 base pairs. Genotype analysis revealed heterozygous rats carrying one knockout allele of the L1cam gene and mosaic rats exhibiting a combination of wild type and mutant genotypes. Although all of the mutated animals were heterozygous females and thus did not show signs of XLH, they will be used to establish a homozygous line of L1cam knockout rats, which will be L1exon4CRISPR/y male rats and L1exon4CRISP/ exon4CRISPR female rats. **Conclusions**: CRISPR/Cas9 can be harnessed to efficiently disrupt the L1cam gene in rats for creation of a XLH model. This study suggests that CRISPR/Cas9 can be used to generate additional rat models of hydrocephalus involving other genomic dysfunctions, providing further opportunities to explore novel surgical and imaging techniques on a larger model organism.

P5 **Introducing a Realistic Operative Workstation for Educating Neurosurgical Apprentices, 'Rowena'**

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With changes in junior doctors hours and working practices exposure to operative neurosurgery is less than ever, and training opportunities have been commensurately reduced. Whilst other specialities rely increasingly on simulation for a part of training this is not yet widespread in neurosurgery, mainly due to the lack of a high quality simulator. I have therefore designed and had manufactured a realistic operative simulator for neurosurgery. The base of the unit consists of a plastic head and face, with realistic internal skull base anatomy. On this is fixed a 'cranial top', also in plastic, consisting of the skull vault bones, covered with plastic 'scalp' and lined internally by a plastic 'dura', complete with realistic vascular markings. Each layer is joined so as to 'dissect free' in a realistic way and the plastic vault similarly cuts and drills in like real bone. Inside is a realistic plastic brain, complete with a CSF filled ventricular system, which comes in two sizes, normal and enlarged. The whole simulator can be used to mimic a very wide variety of neurosurgical procedures; including positioning in head pins, basic burr holes, simple and complex flaps, ventricular cannulation, insertion of ICP monitors and external ventricular drains, and assembly and insertion of the upper end of VP shunts and Ommaya reservoirs.
Once the cranial top has been drilled, cut, sawn and screwed to destruction it can be inexpensively replaced for the next training course. The base is a permanent fixture, and the brains last for many courses worth of ventricular access if used carefully.
The ventricular system also means that it can be used as an endoscopy simulator, something much appreciated by trainees when getting to grips with this very safety critical procedure. It is fully MRI and CT compatible making it useful for image guidance training and we routinely perform image guided ventricular catheterisation on our courses. We have been running twice yearly 2 day courses using Rowena at QMC since 2012 and similar training

courses are now run in Sheffield, Manchester, Coventry, London, Scotland and the Royal College of Surgeons of England. A paediatric version with fontanelles and sutures is also available and most recently one has been used by the charity SHINE to take on a UK wide tour to help educate patients and their carers about hydrocephalus.

P6 **Role of primary cilia in the developing chick.**

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Introduction: Impairment of cilia function underlies a number of human diseases including hydrocephalus. However, the role of cilia in the developing embryo is not well understood. Chloral hydrate is known to have an adverse effect on the cilia formation. In this paper, the possible role of cilia in developing chick embryos will be described mainly by focusing on the formation of the nervous system. **Materials and Methods**: White Leghorn chicken eggs were incubated until embryos reached Hamburger and Hamilton stages 4 to 10. Chick embryos were prepared for both in vitro culture and in ovo culture. For in vitro, embryos were then removed from the shell and cultured on agar plates. After staging, embryos were treated with a chloral hydrate solution for 20 minutes, after which excess solution was removed and the embryos were washed with saline and reincubated. For in ovo culture, after making a small window on the shell, embryos were treated with a chloral hydrate solution for 20 minutes. Air space was filled with the saline solution then embryos were reincubated. Embryos were collected from the incubator and examined morphologically after approximately 24 hours. **Results**: In vitro cultured: The embryos treated with chloral hydrate developed neural tube defects, reversed-sided heart looping, and an abnormally shaped primitive cerebral ventricle in a dose dependent manner. In ovo culture: The embryos had more severe anomaly compared to the embryos cultured in vitro such as divided cardiac system. Rostral part of the neural system including primitive ventricle did not developed normally in some embryos. **Discussion**: The importance of motile cilia in normal function of the cerebral ventricular system, including its role in circulation of cerebrospinal fluid, is widely recognized, but the role of primary cilia in early embryonic development is not well understood. In this study we found that embryos treated with chloral hydrate have many types of anomalies depending on the cultured system. Our results suggest that cilia also have an important role in early development of the ventricular system in addition to a role in axial development.

P7 **Hydrocephalus based procedures in an adult/transition Spina Bifida Clinic: a 5 year experience**

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Introduction: There are more adults than children living with Spina Bifida yet there are limited resources and clinics to support their unique needs. To address this need in our region we initiated an Adult Spina Bifida Clinic in 2010 and report here a 5-year experience with the management of hydrocephalus in this cohort. **Methods**: Retrospective review of a prospectively collected institutional database. IRB approval obtained. Shunt procedures were stratified into single revisions (shunt revision with 1 year of revision free survival) and those

which occurred in clusters (those procedures requiring multiple revisions and prolonged hospitalization) and were evaluated by age. **Results**: Since 2010 198 unique adult (age>=18 years) patients with a past medical history of open Myelomeningocele or Occult Spinal Dysraphism (Lipomyelomeningocele, Split Cord Malformation or Dermal Sinus Tract) were evaluated in our adult Spina Bifida Clinic (ASBC). From this group we identified 61 patients who underwent 176 Neurosurgical procedures. All procedures not related to hydrocephalus management were excluded to yield a cohort of 51 adult patients who underwent a total of 151 procedures for hydrocephalus. The average number of procedures was 2.04 (STD=1.9) but those occurring in clusters ranged from 2-11 shunt revisions. Clustered events tended strongly to occur in younger patients. Patients 25 and under demonstrated an 85% rate of clustered procedures whereas only 1 patient over 35 had a cluster of shunt procedures. The inflection point occurred around age 25. **Conclusion**: In this cohort of adult SB patients younger patients exhibited a higher rate of complex clustered shunt procedures compared with older patients. If corroborated at other centers these data may impact clinic choices of the age for transition. Procedures for shunt intervention occur throughout the life span but decrease in frequency.

P8 Practice Preferences for Neurosurgical Management in Spina Bifida: a survey of the American Society for Pediatric Neurosurgery - Issues of Childhood through Transition

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Introduction: To better quantify the difference is Neurosurgical practice preferences we developed a survey that widely explored common Neurosurgery issues in Spina Bifida and utilized Survey Monkey to distribute it to 232 members of the American Society of Pediatric Neurosurgery (ASPN). **Methods**: A broad based survey was developed by a neurosurgical working group that widely surveyed practice preferences for a variety of Neurosurgical problems encountered across the lifespan in patients with SB. The survey was distributed via Survey Monkey. There were 32 ASPN members who were not available by e mail or had retired from clinical practice. Of the remaining 200 members there were responses from 80 members (40% response rate). All results are self reported and non-validated. **Results**: Eighty percent of ASPN surveyed Neurosurgeons obtain routine brain imaging on patients with SB. Symptoms of shunt failure without radiographic change prompt revision in about 1-25% of cases. This cohort was more willing to perform shunt revision for symptoms alone compared with images alone. For an intact shunt with increased ventricles and no symptoms 60% of respondents would observe while 25% would revise. An asymptomatic broken shunt without ventricular enlargement produced evenly divided responses between observation, intervention and further investigation. Operative shunt exploration is always performed before Chiari II decompression (C2MD) in 56% and performed sometimes in 40%. **Conclusion**: This cohort of academic pediatric neurosurgeons emphasized symptoms above imaging changes in making shunt revision decisions. The role for shunt exploration before C2MD is widely but not universally embraced. Criteria that cross thresholds to trigger C2MD and tethered spinal cord release (TSCR) will be reviewed.