SRHSB
Society for Research into Hydrocephalus and Spina Bifida

64th Annual Meeting Webinar, Doha, Qatar November 6th 2020

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Welcome to Webinar

Dear Friends and Colleagues,

We had been planning to host the 2020 SRHSB annual scientific meeting in Doha, Qatar on 5-7th November but due to COVID-19 restrictions a face to face meeting has not been possible. Instead we are holding a virtual annual meeting as a single day webinar on 6th November.

We have assembled some excellent local and international guest speakers to complement our usual scientific paper presentations which we hope you will all enjoy.

This webinar is a new venture for the Society which has traditionally relied on face to face networking and friendship, so please be patient with any technical problems that might arise during the course of the day and feel free to dip in and out of the virtual lecture hall for breaks!

We will try to make things up to members by hosting a proper face to face scientific meeting in Doha (with social events on Dhows and in the desert) next year - November 2021, if covid conditions permit.

So, salam alaiykum from Doha and see you online on 6th November!

Ian Pople MD FRCS
Local webinar host, Doha

Program

Friday November 6th 2020

NOTE: Times shown below are in Doha time (12:00 noon GMT / London time)

3:00 PM - 3:15 PM	**Introduction** Host Dr Ian Pople
3:15 PM - 3:25 PM	**President's welcome**. Professor John Pickard

SPECIAL SESSION. Improving Bladder Control & Quality of life

3:30 PM - 4:00 PM	Nerve root transfer continence surgery. the Xiao Procedure. Professor Xiao
4:00 PM - 4:30 PM	Bladder function investigations - the basics. Dr Santiago Andres Vallasciani
4:30 PM - 5:00 PM	Surgery for management of refractory incontinence. Dr Pippi Salle
5:00 PM - 5:30 PM	Spina Bidifa: How can we optimize Quality of Life? Dr Lisa Thornton

SESSION 1. **Spina Bifida research**

5:30 PM - 5:45 PM	Molecular similarity between the mechanisms of epithelial fusion and wound healing during the closure of the caudal neural tube in mouse embryos. Dr Noelia Sola-Idigora
5:45 PM - 6:00 PM	Prevention from NTDS linked with WNT-PCP signalling pathway. Dr Patricia Ybot-González
6:15 PM- 6:30 PM	Spina bifida and hydrocephalus: general overview and 30 years of collecting register data. Dr Liina Pappa

SESSION 2. Hydrocephalus clinical research

6:30 PM - 6:45 PM	Impact of antibiotic impregnated catheters and programmable valves on all-cause mortality following CSF shunt surgery in adults: results from the UK Shunt Registry. Dr Rocío Fernández Mende

6:45 PM- 7:00 PM	Lower breakpoint of intracranial amplitude-pressure relationship in NPH. Dr Marek Czsonyka
7:00 PM - 7:15 PM	Diffusion Tensor Imaging profiles can distinguish hydrocephalus vs. non-hydrocephalus using a strategy of a periodic table of DTI elements. Dr Nicole C Keong
7:15 PM - 7:30 PM	Rapid Drainage, irrigation, and Fibrinolytic Therapy (DRIFT) versus standard DRIFT for post hemorrhagic ventricular dilatation in premature infants - a research proposal for discussion and feedback. Dr Nada Mohamed
7:30 PM - 7:45 PM	25 years of single center experience in CSF dynamics testing. Dr Zofia Czosnyka
7:45 PM - 8:00 PM	Assessment of cerebrospinal compliance: comparison of three methods. Dr Agnieszka Kazimierska
8:00 PM - 8:15 PM	Ventriclulo-peritoneal shunt abdominal complications (pseudocyst), multiple presentations and different modalities of management. Dr Wesam Khalafallah
8:15 PM - 8:30 PM	Radiological Evaluation of posttraumatic hydrocephalus. Dr Nikolas Syrmos

SESSION 3. Pathophysiology of hydrocephalus

8:30 PM - 8:45 PM	Animal (*in vivo*) Models of hydrocephalus: a critical review. Dr Pat McAllister
8:45 PM - 9:00 PM	Is hydrocephalus a structural or a functional brain disease? Dr Eric Schmidt
9:00 PM - 9:15 PM	CSF metabolic signature of congenital hydrocephalus. Dr Alicia Requena-Jiménez
9:15 PM - 9:30 PM	Neocortical responses to neurodegeneration in experimental hereditary congenital hydrocephalus. Dr Betsaida Ojeda-Pérez
9:30 PM - 9:45 PM	Hydrocephalus condition associated to hypoxia and aging is partially reversed by reoxigenation. Dr Miriam Echevarría
9:45 PM - 10:00 PM	The cerebral folate delivery system shows a decline in dementia and Alzheimer's disease. Dr Syeda Farwa Naqvi and Dr Jaleel Miyan
10:00 PM - 10:15 PM	Activated gene pathways in Post-Infectious Hydrocephalus (PIH): Proteogenomics and the PIH expressome. Dr Albert M Isaacs

SESSION 4. Research into therapies for hydrocephalus

10:15 PM - 10:30 PM	Retrieval of germinal zone neural stem cells from CSF samples of patients with severe intraventricular hemorrhage. Dr Beatriz Fernández-Muñoz
10:30 PM - 10:45 PM	*In vitro* and *in vivo* experimental approaches to study the effects of a mesenchymal stem cell therapy in congenital hydrocephalus. Dr María García-Bonilla
10:45 PM - 11:00 PM	Ciliogenesis pattern alteration during treatment with mesenchymal stem cells following induction of hydrocephalus. Dr Patricia Páez-González
11:00 PM - 11:50 PM	**Final comments and close of meeting** Dr Ian Pople and Professor John Pickard

Doha Webinar 2020

Abstracts

SESSION 1. Spina Bifida research

Molecular similarity between the mechanisms of epithelial fusion and wound healing during the closure of the caudal neural tube in mouse embryos

Beatriz Fernández-Santos 1, José Manuel Caro-Vega 1, Noelia Sola-Idigora 1, Cecilia Lazarini-Suarez 1, Laura Mañas 1, Alejandro Fuerte-Hortigón 2, Patricia Ybot-Gonzalez 1,2

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Neural tube (NT) closure is a complex developmental process that takes place in the early stages of embryogenesis and that is a key step in neurulation. In mammals, the process by which the neural plate generates the neural tube requires organized cell movements and tissue folding and it terminates with the fusion of the apposed ends of the neural folds. Interference with any of neurulation steps can impair NT closure, resulting in neural tube defects (NTDs). By inducing a wound in embryonic day 9 embryos we describe how almost identical cellular and molecular machinery is used to fuse the spinal neural folds as that involved in the repair of epithelial injury in the same area of the embryo. Differential expression and production of several major components of the ECM like hyaluronic acid (HA), collagen and platelet-derived growth factor (PDGF) have been noted to contribute to the remarkable scarless healing ability of embryonic skin. For both natural and wound activated closure of caudal neural tissue, HA and PDGF signalling appear to be crucial for the final fusion step. There seems to be no general wound healing machinery for all tissues but rather, a tissue-specific epithelial fusion machinery that embryos activate when necessary after abnormal epithelial opening.

SESSION 1. Spina Bifida research

Prevention from NTDS linked with WNT-PCP signalling pathway

J.M. Caro-Vega(1), N. Sola-Idígora(1), B. Fernández-Santos(1), C. Mesa-Cruz(1), L. Cerrillos-González(2), A. González-Meneses(3), J. Marquez-Rivas(4), P. Ybot-González(1,5)

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Neural tube (NT) closure is a complex developmental process that is regulated to a great extent by the non-canonical Wnt signalling pathway (Wnt-PCP), which in turns regulates actin cytoskeleton responsible for cell shape, directs polarised cellular orientation within the plane and directional cell migration. Mutation of genes in this pathway yields embryos that exhibit severe NT defects owing to failure of initiation of NT closure. There is a clear evidence for the Wnt-PCP pathway to be involved in the final step in neurulation, the closure of the posterior neuropore. Mouse embryos homozygous for Wnt-PCP gene mutations exhibit craniorachischisis, making difficult to study the role of those genes during the later stages of the neural tube closure. Heterozygous embryos have offered instead better tool into the molecular and cellular study of caudal NT defects. Histological studies revealed that a high number of E11.5 Vangl+/lp embryos fail to fuse completely the neural folds in the most caudal region of the NT. This malformation is “rescued” by a cellular aggregate that seal the NT, however, although the closure occurs, the neural ectoderm remains morphologically altered. Our results suggest that the Looptail heterozygous embryo can be a mouse model for spina bifida occulta in humans. Thus, our lab we have focused in the study of the etiology and prevention of this NTD.

SESSION 1. Spina Bifida research

Spina bifida and hydrocephalus: general overview and 30 years of collecting register data

Liina Pappa 1, Andres Asser 2, Cristina Lõokene 3, Kirsti Pedak 4, Merle Poola 5, Tiit Nikopensius 1, Andres Metspalu 1, Ann Paal 5

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Neural tube defects (NTDs), including Spina bifida and hydrocephalus, are congenital birth defects of the nervous system which occur during early embryonic development. The worldwide incidence of NTDs is on average 1-2 per 1000 live births. NTDs have multifactorial etiology associated with additive effects of genetic variants and gene-environment interactions. In Estonia, a registry of patients with NTDs was established in 1985 on the basis of the paediatric surgical department of Tallinn Children's Hospital. The data from the registry has allowed us to present an overview of NTD patients in Estonia. In 2017, there were 127 alive patients with Spina bifida and 234 patients with hydrocephalus. The data from the past 30 years were used to calculate the birth prevalence of NTDs in Estonia. Data analysis, combined with genetic studies, has emphasized prophylactic consumption of folic acid during pregnancy. The data shows that from the beginning of 21st Century, the birth prevalence of Spina bifida has decreased whereas the birth prevalence of hydrocephalus has had a minor increase. The data have also broadened our knowledge of the epidemiology of NTDs in Estonia and have addressed the need for improvement in the healthcare of young adult patients. By summer 2020, all Estonian NTD patients were genotyped on Illumina microarrays, and individual gene cards were created. This will allow us to further investigate the genetic basis and the inheritance patterns of NTDs.

SESSION 2. Hydrocephalus clinical research

Impact of antibiotic impregnated catheters and programmable valves on all-cause mortality following CSF shunt surgery in adults: results from the UK Shunt Registry

Rocío Fernández-Méndez[1,2]*, Kim May Lee[3], Gordon Murray[4], John D Pickard[2,5], Alexis J Joannides[1,2,5], UKSR Collaborators

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Background: Failures in CSF shunt surgery are still common and can even lead to death. This study aimed to investigate the impact that antibiotic impregnated catheters (AIC), slit-ended distal catheters (SEDC), and programmable pressure valves may have on all-cause mortality of adults after their primary CSF shunt.
Methods: A retrospective, multi-centre study was carried out based on data from the UK Shunt Registry. Eligible patients were 17 years or older, undergoing a primary CSF shunt during the study period (01/01/2004 to 31/12/2013). Thirteen centres meeting strict inclusion criteria based on their average reporting rates were eligible. The primary outcome measure was patient survival after primary shunt surgery. Main variables of interest were the catheter type (3 categories: AIC, no-AIC no-SEDC, or no-AIC SEDC) and the valve pressure regulation type (2 categories: fixed or programmable). Cox proportional hazards modelling was used to estimate adjusted mortality hazard ratios (HR).

Results: 9276 adults (53% females), with a median (IQR) age of 57 (41, 69) years, and mostly operated for acquired hydrocephalus (33%), were included. Median follow-up was 49 months. After controlling for age, diagnosis, centre and whether surgery was performed out of hours, based on complete case analysis from 3603 subjects, adjusted mortality HRs (95% CI) were 2.0 (1.2, 3.4) and 1.9 (1.3, 2.9) with no-AIC no-SEDC and no-AIC SEDC respectively, as compared to AICs ($p<0.01$); and 2.0 (1.3, 2.9) in fixed as compared to programmable pressure valves ($p<0.01$).

Conclusions: All-cause mortality hazard was halved in patients with AICs, as compared to those with no-AICs (with or without SEDC), and in patients with programmable pressure valves, as compared to those with fixed pressure valves. The impact of shunt device components should be regularly monitored, and medical registries are a powerful resource for this.

SESSION 2. Hydrocephalus clinical research

Lower breakpoint of intracranial amplitude-pressure relationship in NPH

Marek Czosnyka 1 , Zofia Czosnyka 1, Afroditi Lalou 1, Eva Nabbanja 1, Matthew Garnett 1, Eric Schmidt 2, Olivier Baledent 3, Dong-Joo Kim 4

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The relationship between intracranial pulse amplitude (AMP) and mean ICP has been previously described; generally stating that AMP increases proportionally to rise in ICP. Such an increase in AMP can be observed particularly often (but not exclusively), if the rise in ICP is provoked by controlled CSF volume increase during the infusion test. We studied lower breakpoint (LB) of amplitude-pressure relationship below which pulse amplitude stays constant when ICP varies. Theoretically, below this breakpoint, the pressure-volume relationship is linear (good compensatory reserve) and above- exponential (brain compliance decreasing with rising ICP).
169 infusion tests performed in patients diagnosed for idiopathic NPH (2004-2013) were available for analysis. Inclusion: patients had lumbar infusion test performed before surgery, raw data of ICP digitally recorded (ICM+ software) available for post-hoc processing and response to shunting was assessed in follow-up clinic.
Lower breakpoint was observed in 62 patients diagnosed for NPH. Improvement after shunt surgery in patients in whom lower breakpoint was recorded was 77% versus 90% in patients where LB was absent ($p<0.02$). In patients with detected LB, the distance between baseline ICP and LB was lower in those who improved (not-improved: 4.1+/-2.1 mmHg versus improved: 1.2+/-2.7 mmHg; $p<0.02$). There was no correlation between improvement and slope of amplitude-pressure line above LB.
The detection of lower breakpoint is associated with less frequent improvement after shunting in NPH. It may be interpreted that CSF dynamics of patients working on flat part of pressure-volume curve and having a ‘luxurious’ compensatory reserve, is more frequently caused by brain atrophy, which is not responding to shunting.

SESSION 2. Hydrocephalus clinical research

Diffusion tensor imaging profiles can distinguish hydrocephalus vs. non-hydrocephalus using a strategy of a periodic table of DTI elements

Nicole C Keong[1,2]*, FRCS MD; Christine Lock[1], BA; Shereen Soon[1], BSc, Aditya Hernowo[3], PhD, Zofia Czosnyka[4], PhD, Marek Czosnyka[4], PhD, John D Pickard[4], FMedSci, Vairavan Narayanan[3], FRCS and the Alzheimer's Disease Neuroimaging Initiative†

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Background: The aim of this study was to create a simplified model to reduce the complexity of interpreting diffusion tensor imaging (DTI) profiles in white matter disruption, using a novel strategy of a periodic table of DTI elements. We sought to examine if DTI profiles could characterize white matter changes specific for hydrocephalus vs. non-hydrocephalus and to distinguish cohorts of neural injury by their differing potential for reversibility.

Methods: DTI datasets from cohorts representing reversible to irreversible brain injury were compared to those of healthy controls at baseline, over time and with interventions. The final dataset comprised patients vs. controls in the following: mild traumatic brain injury (mTBI), n=62 vs. 27, normal pressure hydrocephalus (NPH), n=16 vs. 9 and Alzheimer's disease (AD), n=45 vs. 47. We generated Pareto graphs of DTI profiles from fractional anisotropy (FA) and mean, axial and radial diffusivity measures (MD, L1 and L2and3 respectively), then constructed a periodic table of DTI elements by arranging white matter injury patterns according to their common diffusivity and neural profile properties.

Results: Mapping their profile properties to a periodic table of DTI elements helped rapidly characterize cohorts by their differing patterns of white matter injury. In NPH, the magnitude of changes was dependent on "familial" DTI neuroanatomy, i.e. potential for neural distortion from risk of ventriculomegaly. It was possible to reproduce at least three distinct patterns of white matter injury. In patients with Alzheimer's disease, progressive white matter damage was evident. By contrast, patients with mTBI showed contrasting trends suggesting both loss of integrity and pathophysiological processes of neural repair. In NPH, some patterns of injury, such as "stretch/compression" and "compression" were more reversible following intervention than others; these neural profile properties suggested a form of "microstructural resilience" to injury.

Conclusions: Using the novel strategy of a periodic table of DTI elements, our study has demonstrated that it is possible to distinguish different cohorts along the

spectrum of brain injury by describing neural profile properties of white matter disruption. Further work is needed to further explore this strategy.

Acknowledgements/ Disclosures

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MTBI data from the University of Malaya was partially funded by a University Malaya Research Grant (UMRG; RG008C-13HTM) and a High Impact Research Grant of University of Malaya (HIR-UM.C/625/1/HIRMOHE/12).

Data for the Alzheimer's Disease cohort used in this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) † database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

SESSION 2. Hydrocephalus clinical research

Rapid Drainage, irrigation, and fibrinolytic therapy (DRIFT) versus Standard DRIFT for post hemorrhagic ventricular dilatation in premature infants – a research proposal for discussion and feedback

Nada Mohammed, Khalid Alkharazi, Sahar Algam, Wesam Khalafallah, Wagdy Al-Kadasi, Mary Dinan, Ian Pople

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Improving long term outcomes and reducing the need for insertion of a shunt in 6 months. A proposal for a phase II randomized pilot study, for a single-center, open-label with a blinded rater, parallel randomized, and controlled superiority trial.

Background: Premature infants are prone to suffering intraventricular hemorrhage (IVH) especially those in the very low birth weight group, in whom the percentage risk is 20-25%. These hemorrhages may be associated with significant complications such as post hemorrhagic hydrocephalus (PHH) and periventricular leukomalacia, and the majority of infants will develop varying degrees of neurodevelopmental disability. There is a now level one evidence for the efficacy of standard DRIFT technique in reducing long term cognitive disability in these premature babies, but the technique is time-consuming and labor-intensive. A more rapid one stop DRIFT technique using an on-table washout of blood using a neuroendoscope was recently developed at Great Ormond Street Hospital in London so we propose a comparative small scale study of this newer technique with the standard DRIFT technique to determine if there are significant benefits in this new technique over standard DRIFT.

Methods: This will be a parallel-group, randomized, open-label with a blinded rater, controlled clinical trial, with a superiority design, for 24 months. It will be conducted in Sidra Medicine, Doha/Qatar 2021-2023.

Participants: will be premature infants with PHH below 37 weeks, who will meet the inclusion and exclusion criteria.

Intervention: The intervention group will consist of rapid DRIFT management, and the control group will receive the standard DRIFT management.

Objective: The primary objective of this phase is to test the study safety and feasibility (recruitment and retention rate) of the rapid DRIFT.

Outcome: Reducing the need for insertion of a shunt is an important goal and work as our primary outcome, while maintaining equivalence improvement in cognitive outcomes. The secondary outcomes which will compare the relative safety of the two techniques are: CSF infections rates, neurological complications, bleeding, and frequency of seizures.

Randomization: The allocation will be concealed and will occur in 1:1 ratio either to the intervention or the control group. The randomization will be performed by a randomization software using randomization sequences of blocks of either four or six. The block size will not be informed to ensure concealment.

Blinding: it will be an open-label with a blinded rater.

Sample size: 15 participants will be in each group.

Recruitment: The recruitment will be done in the neonatal ICU by direct meeting of the neurosurgeons with the caregivers of the participants.

Trial registration: trial will be registered in ClinicalTrial.gov

Funding: we will apply for a local research grant to fund this pilot trial. A description of the techniques and the proposal will be presented at the SRHSB annual meeting for discussion and critical evaluation and feedback prior to submission to the Grant-giving body.

SESSION 2. Hydrocephalus clinical research

25 years of single center experience in CSF dynamics testing

Zofia Czosnyka 1, Marek Czosnyka 1, Piotr Smielewski 1, Matthew Garnett 1, Afroditi Lalou1, Eva Nabbanja 1, Slawomir Barszcz 2, Eric A. Schmidt 3, Peter JA Hutchinson1, John D Pickard 1

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Disturbed CSF dynamics is an important component of hydrocephalus. Lumbar infusion test supported with computer identification of Marmarou's CSF dynamics model was for the first time used in Child's Health Centre in Warsaw, Poland in 1985. Since 1992 over 5000 infusion studies has been performed in both shunted and non-shunted hydrocephalus patient in University Hospital in Cambridge.

1. Infusion test is safe. There were no fatal complications. Infection rate is estimated as less than 1%

2. Knowledge of compensatory parameters helps in making decision about patients' management. Increased resistance to CSF outflow (Rout) is positively correlated with better outcome following shunting ($p<0.004$).

3. In adults, Rout increases with age, while estimated CSF production rate decreases ($p<0.01$).

4. In patients with disturbed CSF dynamics positive response to shunting in our center was observed to rise in time ($R=0.205$; $p<0.0003$) from 62% in 1992 to reach 80-90% at present

5. In shunted patients, reservoir infusion study helps to objectively assess shunt function and therefore avoid unnecessary revisions. Yearly savings are estimated to amount to £1 million.

6. Defective CSF dynamics may overlap existing cerebrovascular disease with both contributing to poor clinical status. It has been shown that in patients with normal CSF circulation autoregulation of CBF estimated with transcranial Doppler was worse ($p<0.002$).

7. In adults with idiopathic NPH, white matter CBF (PET) decreases towards surface of lateral ventricles. Also autoregulation of CBF is worse in this region. This may illustrate transependymal route of CSF absorption and its interference with regional CBF around ventricles.

8. Even small rise in ICP during infusion study, slightly but significantly increases heart rate variability, suggesting possible existence of 'brain baroreceptors'.

In conclusion, continuing studies in CSF dynamics elucidate pathophysiology of hydrocephalus and other CSF disorders and helps in better management of patients.

SESSION 2. Hydrocephalus clinical research

Assessment of cerebrospinal compliance: comparison of three methods

Agnieszka Kazimierska [1], Magdalena Kasprowicz [1], Marek Czosnyka [2,3], Michal M. Placek [2], Olivier Baledent [4], Peter Smielewski [2], Zofia Czosnyka [2]

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Background. Cerebrospinal compliance describes the ability of the cerebrospinal space to buffer changes in volume. Diminished compliance is associated with elevated risk of potentially threatening increases in intracranial pressure (ICP) when changes in cerebrospinal volume occur. However, despite various methods of estimation proposed so far, compliance is seldom used in clinical management. This study aimed to compare three measures of cerebrospinal compliance: a) based on a model of cerebrospinal fluid (CSF) dynamics (CCSF), b) based on evaluation of changes in cerebral arterial blood volume (CCaBV), and c) based on the amplitudes of peaks P1 and P2 of ICP pulse waveform (CP1/P2).

Materials and methods. ICP, cerebral blood flow velocity (CBFV), and arterial blood pressure (ABP) recordings from 17 normal pressure hydrocephalus patients who underwent infusion studies were analysed retrospectively. Three methods were used to calculate compliance estimates during changes in mean ICP induced by infusion of fluid into the CSF space.

Results. The increase in ICP associated with infusion caused a significant decrease in all compliance estimates (Wilcoxon signed rank test p-value < 10-4). Time courses of compliance estimates were strongly positively correlated (group-averaged Spearman correlation coefficients: 0.90 for CCSF vs. CCaBV, 0.82 for CCSF vs. CP1/P2, and 0.74 for CCaBV vs. CP1/P2).

Conclusions. Our results show that indirect methods, CCaBV and CP1/P2, allow for assessment of relative changes in cerebrospinal compliance and produce results exhibiting good correlation with the direct method of volumetric manipulation. This suggests the possibility of monitoring compliance based on the ICP waveform alone.

Conflicts of interest:
MC and PS have a financial interest in licensing fee of ICM+ software (https://icmplus.neurosurg.cam.ac.uk) used in this study. Other authors have no conflict of interest to declare.

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SESSION 2. Hydrocephalus clinical research

Ventriclulo-peritoneal shunt abdominal complications (pseudocyst), multiple presentations and different modalities of management

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A case series of 6 children of abdominal CSF pseudocyst occurring in children with hydrocephalus due to different causes with an indwelling ventriculo-peritoneal managed by pediatric neurosurgery team in Sidra hospital, Doha is presented, together with a review of available literature of abdominal complications in similar children with CSF shunts undergoing elective or emergency abdominal surgery by pediatric surgeons. Increasing the use of laparoscopic fenestration or marsupialization has reduced the need for externalization of the distal catheter and repeated surgeries on the shunt.

SESSION 2. Hydrocephalus clinical research

Radiological Evaluation of posttraumatic hydrocephalus

Nikolaos Syrmos, Georgios Gavridakis

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Radiological Evaluation of posttraumatic hydrocephalus in young male patients after severe craniocerebral injuries due to road traffic accidents

Aim of this study was to present cases of posttraumatic hydrocephalus in young male patients (<40 years) after severe craniocerebral injuries due to road traffic accidents.

Methods-10 cases are presented, 10 male patients, range of age was from 16 to 40 and mean age was 29,5.

Results-In all of them we performed CT and MRI studies.5 of them -50%-they developed post traumatic hydrocephalus after subdural brain hematoma evacuation, 1 of them-10%- after extradural brain hematoma evacuation and 4 of them-40%- after combined trauma cases (traumatic subarachnoids hemorrhage, contusions etc).

Conclusions-Radiological appropriate evaluation is essential in order to plan an optimal approach of such cases.

Radiological Evaluation of posttraumatic hydrocephalus in elderly male patients after severe craniocerebral injuries due to falls

Aim of this study was to present cases of posttraumatic hydrocephalus in elderly male patients (>65 years) after severe craniocerebral injuries due to falls

Methods-10 cases are presented,10 male patients, range of age was from 65 to 85 and mean age was 75.

Results-In all of them we performed CT and MRI studies.4 of them -40%-they developed post traumatic hydrocephalus after subdural brain hematoma evacuation, 1 of them-10%- after extradural brain hematoma evacuation and 5 of them-40%- after combined trauma cases(traumatic sub arachnoids hemorrhage, contusions etc).

Conclusions-Radiological appropriate evaluation is essential in order to plan an optimal approach of such cases.

SESSION 3. Pathophysiology of hydrocephalus

Animal (*in vivo*) models of hydrocephalus: a critical review

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Although the pathophysiology of hydrocephalus is extremely multifactorial and thus difficult to model, important contributions to our understanding of the mechanisms involved in hydrocephalus rely on studies with animal models. Unfortunately, no single model mimics all of the injury mechanisms prevalent in hydrocephalus; thus, evaluations of appropriate animal models are important. This review attempts to critically compare and contrast historical models as well as the most popular models currently in use. At the outset, investigators must realize that both congenital and induced ventriculomegaly is highly variable, both in terms of extent and progression; thus, quantification (e.g. ventricular volume) is essential. Many congenital and neonatal models (mice, rats, felines) are short-lived with ventriculomegaly so severe it prevents optimal neuroimaging and may not be clinically relevant. Gyrencephalic animal models are more homologous to humans and allow interventions with clinical instrumentation (e.g. ventricular shunting, endoscopic third ventriculostomy with or without choroid plexus cauterization) but they are expensive and complicated. Mechanical induction methods, especially those that employ kaolin injected into the cisterna magna or basal cisterns, are reliable with high yields, but the "side-effects" may be criticized (e.g. wide-spread intracranial inflammation and sudden-onset). Learning or developing an animal model always takes much more time than expected, and investigators must be prepared to modify their induction methods and experimental design, especially survival periods. Finally, investigators must be prepared to defend the use of their model. Comparisons to other models are very

important, especially with regard tp age-matching in neurodevelopmental studies; a complete knowledge of the various animal models will enhance credibility amongst investigators and funding sources.

SESSION 3. Pathophysiology of hydrocephalus

Is hydrocephalus a structural or a functional brain disease?

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Hydrocephalus is primarily considered as an intracranial fluid problem, yielding biomechanical constrains that alter brain tissue (ventricular enlargement and parenchymal deformation) but also compress brain vessels (blood supply reduction and oxygen/energy crisis). However, the impact of hydrocephalus is rarely addressed in terms of neuronal circuitry derangement. Is hydrocephalus a structural or a functional brain disease?

Several recent and independent experimental studies demonstrated in mammals and humans a novel physiological mechanism linking intracranial pressure with sympathetic discharge via a possible novel intracranial baroreflex. Intracranial pressure does not solely define brain perfusion; it is also a physiological trigger of a neuronal reflex. Hence we hypothesize that brain intrinsic barosensitivity could be involved in the onset and development of the neurological dysfunction related to hydrocephalus.

We review the eventual impact of hydrocephalus and intracranial pressure on central autonomic network, with particular interest in autonomic/somatomotor activity and arousal/action circuit. The central autonomic network is a regulation system that includes the insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus tractus solitarius, and ventrolateral medulla. With respect to hydrocephalus, paraventricular and hypothalamic nuclei are of interest since they are close to ventricles and contain neuronal population that control subset of preganglionic sympathetic and parasympathetic neurons. The rostral ventrolateral medulla is also of interests since it contains neurons that determine sympathetic outflow and is driven by various regulatory afferent inputs.

Despite traditional views of the structural impact of hydrocephalus, its functional impact on the brain has to be explored further. We have to understand the actual impact of intracranial pressure on the neural control of the sympathetic and somatomotor systems.

SESSION 3. Pathophysiology of hydrocephalus

CSF metabolic signature of congenital hydrocephalus

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Congenital hydrocephalic CSF proteome was analysed by LCMS and the biocomputing tool Ingenuity Path Analysis (IPA) to identify alterations in metabolism represented in CSF. Abnormal versus normal CSF were contrasted and top regulators and mechanistic networks retrieved. The differences between the CSF's metabolic patterns were striking, with hydrocephalic CSF showing a unique array of metabolic pathways controlled by specific top regulators involved in DNA and Histone Methylation as well as Histone Deacetylation. This analysis shows that major changes in metabolism occur during hydrocephalus, which may explain the complex pathophysiology of this condition and the distinct hydrocephalic CSF composition.

Ultimately, we propose that the devised CSF metabolic pattern may prove useful as a clinical tool for early detection of disease.

SESSION 3. **Pathophysiology of hydrocephalus**

Neocortical responses to neurodegeneration in experimental hereditary congenital hydrocephalus

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SESSION 3. Pathophysiology of hydrocephalus

Hydrocephalus condition associated to hypoxia and aging is partially reversed by reoxygenation

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AQP4 abundantly expressed in ependymal cells flanking the intraventricular compartments, glial limiting membranes and in pericapillary astrocytes foot processes has been indicated to play an important role in the cerebrospinal fluid (CSF) production and has a key role in hydrocephalus development produced by hypoxia in aged animals. Here we analyzed whether exposure of animals to normal oxygen levels (30 days, 21% O2; ReNx) can recover the alterations produced by hypoxia (5 days, 8%O2, Hy) in parameters such as ventricular volume, intraventricular pressure (IVP), CSF outflow rate and compliance of ventricular surrounding wall. Novel object recognition analysis was performed to evaluate cognitive stage of animals. Experiments were done using young and aged wild type (WT) mice and knock out animals for AQP4 (AQP4-/-), and were analyzed either under normoxia (Nx), after hypoxia treatment (Hy) or after a ReNx period following a Hy treatment. An additional group of aged WT animals were submitted to a second round of Hy+ReNx period to investigate the effect of repetitive exposure to Hy over the ventricle parameters mentioned above. IVP, outflow rate of CSF and compliance of ventricular surrounding membrane were measured by intra ventricular recordings in live animals, as well as total ventricular volume, that was measured by resonance magnetic images. Our results prove that alterations in ventricle volume, IVP and cognitive function produced by Hy were reversed by ReNx, but the reduction produced on the outflow rate and the ventricular complianza were permanent and never re-stablished after ReNx in the aged WT animals. Surprisingly, in the absence of AQP4, the changes in the outflow and complianza remained reversible by ReNx, indicating that AQP4 place a structural role in chronification of those changes. Repetitive exposure to Hy of aged animals did produce a permanent cognitive deterioration basically derived of the large ventriculomegaly produced in these animals.

SESSION 3. Pathophysiology of hydrocephalus

The cerebral folate delivery system shows a decline in dementia and Alzheimer's disease

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Background: Previous research has highlighted a CSF volume change associated with amyloid deposition and dementia/Alzheimer's disease. MRI scans show increasing fluid spaces around the deeper sulci and smaller gyri and significantly, also demonstrate enlarged ventricles. This latter observation indicates a potential CSF drainage issue at some point in the aetiology of dementia and AD. We hypothesised that such a drainage issue would result in a similar cerebral folate imbalance/deficiency we have previously reported in hydrocephalus.

Methods: We obtained CSF from the Manchester Brain Bank, collected from participants in their ageing study at death or some hours after, for 10 individuals who had no diagnosed neuropsychiatric condition (normal ageing), 10 individuals with mild cognitive impairment (MCI) and 10 with severe Alzheimer's disease (AD) diagnosis. Each brain was assessed by a neuropathologist and given a Braak score of I-II, III-IV or V-VI (for normal, MCI and AD respectively). CSF was analysed using Western and dot blots and bands and dots measured and analysed using densitometry.

Results: CSF analysis demonstrates a similar decreased concentration of ALDH1L1 (AKA 10-formyl tetrahydrofolate dehydrogenase (FDH)) in severe Alzheimer's disease (AD) compared to normal ageing. Mild cognitive impairment (MCI) showed a decrease not as great as AD. Other folate related proteins and metabolites showed decrease in CSF except for homocysteine that was raised.

Conclusions: The CSF analysis demonstrates two things. Firstly that the CSF folate supply system appears to be maintained throughout life. Secondly that this going wrong may be partly responsible for the aetiology, or be a consequence of the pathology in dementia and AD. It may present a novel target for prevention and/or treatment.

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SESSION 3. Pathophysiology of hydrocephalus

Activated gene pathways in Post-Infectious Hydrocephalus (PIH): Proteogenomics and the PIH expressome

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Introduction
The pathophysiologic basis of postinfectious hydrocephalus (PIH), a major complication of neonatal sepsis worldwide, is poorly understood. Variation in host response likely contributes to which infants with neonatal sepsis develop PIH. Further, advancing the molecular understanding of the host response in PIH could identify therapeutic targets for hydrocephalus prevention. Integration of deep-scale proteomics and RNA sequencing (RNA-Seq) provides an opportunity to discover genes and gene networks active in PIH pathophysiology. Previous metagenomic analysis in a cross-sectional cohort of sub-Saharan African infants with PIH reported Paenibacillus spp. as a dominant pathogen in PIH and cytomegalovirus (CMV) as a frequent co-infection.

Methods
Ventricular CSF samples of 100 infants ≤ 3 months of age with PIH (n=64) and non-postinfectious hydrocephalus (NPIH; n=36) were analyzed with proteomics and RNA-Seq. Genes with differential RNA and/or protein abundance were analyzed for functional enrichment.

Results
Genes with differential RNA and protein abundance among PIH samples were enriched for functions related to the immune response, cell-cell junction signaling, extracellular matrix structure and response to oxidative stress. Presence of Paenibacillus spp. in CSF was associated with enrichment of biological functions related to neuroinflammation, particularly neutrophil-mediated inflammation, negative regulation of metalloprotease activity and extracellular organization. There were 33 genes that were differentially expressed in both proteomic and RNA analyses, and these were enriched for processes involved with response to host recognition of microbes and for functions predominantly associated with the innate immune system, including interleukins (IL)-4, IL-12, IL-13, interferon and platelet-activating factors. CMV co-infection was associated with a differential RNA abundance enriched for functions related to host response to viruses, but CMV status did not significantly alter the gene ontology enrichment based on Paenibacillus spp. status.

Conclusions

Integration of proteomics and RNA-Seq enabled identification of critical biological pathways that underlie PIH pathophysiology. Proteogenomic clustering identified a subset of PIH patients with severe disease at time of hydrocephalus surgery that have differential expression of genes involved in neuroinflammation and maintenance of ependymal barrier integrity. Further studies of infants prior to the development of PIH are needed to identify biomarkers and therapeutic targets relevant to PIH pathogenesis.

SESSION 4. Research into therapies for hydrocephalus

Retrieval of germinal zone neural stem cells from CSF samples of patients with severe intraventricular hemorrhage

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Introduction: Intraventricular hemorrhage (IVH) is a common cause of morbidity and mortality in premature infants commonly leading to posthemorrhagic hydrocephalus (PHH). The rupture of the germinal zone (Gz) into the ventricles entails loss of neural stem cells (NSC) that can be easily and robustly retrieved from the hemorrhagic cerebrospinal fluid (CSF) of severe IVH patients.
Aim: To fully characterize these cells looking forward to possible clinical applications.
Methods: We performed a transcriptomic analysis to study the differences and similarities between isolated NSC and foetal forebrain NSC, currently used in different clinical trials. We have compared the cell growing rate and CD133 expression of these cells in different matrices and cell culture media. Finally, we have analyzed cell recovery upon cryopreservation with different media and cell viability after intracranial delivery with several conditioning media.
Results: Isolated NSC are similar to human foetal cell lines but display distinctive hallmarks related to their regional and developmental origin in the Gz of the ventral forebrain. These ventral Gz-NSC express more integrins than cadherins in contrast to fetal NSC and this correlates with faster cell growing in adhesion than in suspension as neurospheres. CSF-derived Gz-NSC cells can be expanded, cryopreserved and differentiated in vitro and in vivo in the brain of nude mice and show no sign of tumoral transformation 6 months after transplantation.
Conclusions: CD133+ CSF-NSC could be useful for the development of an autologous therapy for preterm infants with IVH and PHH.

SESSION 4. **Research into therapies for hydrocephalus**

In vitro and in vivo experimental approaches to study the effects of a mesenchymal stem cell therapy in congenital hydrocephalus

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SESSION 4. Research into therapies for hydrocephalus

Ciliogenesis pattern alteration during treatment with mesenchymal stem cells following induction of hydrocephalus

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