La Laguna 2019

Abstracts

Session 1: **Clinical Aspects of Hydrocephalus**

Current state of neuroendoscopy for the treatment of hydrocephalus.

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Background
During last decades neuroendoscopy has gained a crucial role in the treatment of the hydrocephalus not only in children but also in adult patients, with fewer overall complications than shunt insertion. The endoscopic technique has evolved and refined over past few decades, replacing traditional shunts insertion in most of obstructive and non-obstructive hydrocephalus. However, complications like hemorrhage or failure of the procedure requiring CSF diversion can occur.

Materials and Methods
We review the current state of neuroendoscopy, summarizing clinical indications and prognosis of the main techniques while illustrating with some surgical videos from cases treated at the Hospital Universitario de Canarias (HUC). Some technical aspects are discussed including complication avoidance and neuronavigation use.

Results
The literature review demonstrated that congenital hydrocephalus is the most common etiology treated by neuroendoscopy, being endoscopic third ventriculostomy (ETV) the most frequent technique performed. The role of ETV for the treatment of idiopathic normal pressure (iNPH) is discussed. Using the endoscope in patients suffering hydrocephalus has extended beyond third ventriculostomy, currently including cyst fenestration, tumor biopsy/removal, septostomy, aqueductoplasty…

Conclusions
The results indicate that ETV is very safe and reliable minimally invasive therapeutic option for all obstructive and most of communicating hydrocephalus, however the efficacy of ETV for iNPH remains controversial. Adjunctive procedures like aqueductoplasty, choroid plexus cauterization, cyst or tumour removal etc have significant role depending on the particularities of each clinical case.

Session 1: **Clinical Aspects of Hydrocephalus**

Correlations between brain stiffness, headaches and ventricular size using magnetic resonance elastography in children with hydrocephalus

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Background
Chronic headaches in treated hydrocephalus patients may be related to changes in brain elastance (stiffness, compliance), which may occur at the onset of hydrocephalus or develop chronically over the course of shunt treatment. Magnetic Resonance Elastography (MRE) is a new tool to measure brain elastance non-invasively. We employed MRE to test the hypothesis that brain tissue elastance is altered in hydrocephalus.

Materials and Methods
Twenty-seven shunt-dependent patients (age 14-35, median 19) who developed hydrocephalus as infants and had chronic headaches were selected and compared to 20 healthy controls (age 8-46, median 22). MRE was performed by inducing a 30Hz vibration transmitted through the zygomatic arches via MRI-compatible pneumatic pistons. Tissue elastance was calculated through Algebraic Helmholtz Inversion. The Headache Disability Index (HDI) and Hydrocephalus Outcome Questionnaire (HOQ) were collected in all patients, as well as other clinical data. Brain elastance (G*), averaged separately across white and grey matter masks and within lobar regions-of-interest, was compared to healthy controls, and linear associations of elastance with ventricular size, HDI and HOQ were investigated.

Results
Overall, brain tissue elastance was reduced in patients compared to controls (WM - $G^* = 1.83 \pm 0.18$ kPa vs. 2.01 ± 0.12 kPa, frontal GM - $G^* = 1.40 \pm 0.14$ kPa vs. 1.55 ± 0.12 kPa, occipital GM - $G^* = 1.18 \pm 0.20$ kPa vs. 1.36 ± 0.12 kPa, $p < 0.001$). Occipital grey matter elastance was negatively correlated with ventricular size ($R2 = 0.23$, $p < 0.001$). There was a weak positive correlation between occipital grey matter elastance and HOQ ($R2 = 0.16$, $p < 0.05$), and a negative trend correlation between occipital grey matter stiffness and HDI ($R2 = 0.14$, $p = 0.056$).

Conclusions
Brain elastance was reduced in hydrocephalus patients, possibly indicating impaired biomechanical integrity of brain tissue.

Session 1: **Clinical Aspects of Hydrocephalus**

Global cerebral autoregulation, resistance to CSF outflow and cerebrovascular burden in normal pressure hydrocephalus

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Introduction
We previously examined the relationship between global autoregulation pressure reactivity index (PRx), mean arterial blood pressure (ABP), the Resistance to CSF outflow (Rout) and their possible effects on outcome after surgery on 83 shunted patients. In this study, we aimed at quantifying the relationship between all parameters that influence Rout, their interaction with the cerebral vasculature and their role in shunt prognostication.

Methods
We studied a cohort of 88 shunted NPH patients. All patients had undergone a CSF infusion test in parallel with non-invasive ABP monitoring, the correlation between these two being PRx. After shunting, 6 months patients' outcome after was marked using a simple scale (improvement, temporary improvement, and no improvement). We explored the relationship between age, different CSF dynamics variables, and vascular parameters using multiple linear regression model, after which we sought the AUC for outcome prediction.

Results
There was a strong and significant relationship between the interaction of age, PRx, ABP and Rout (R=0.53 ; p= 7.28e-0.5). 69 patients responded to shunting, versus 19 non-responders. The AUC between the two groups and our linear model was 86.4% (80.5-92.3%). The overall sensitivity was 94%, specificity 75 % PPV 54%, and NPV 97%.

Conclusions
In patients with low Rout and high cerebrovascular burden, as described by high ABP and disturbed global autoregulation, response to shunting is less likely. The low PPV of high resistance, preserved autoregulation and absence of hypertension could merit further exploration.

Session 1: **Clinical Aspects of Hydrocephalus**

Principles of testing hydrocephalus shunts in vivo using infusion test

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Objective
Hydrocephalus shunts may fail after implantation. Patients may develop adverse symptoms, which are not always 100% specific for shunt failure, and brain imaging may be not always clear. Our recent study in mixed population (adults and children) showed that in approximately 50% of cases referred to Hydrocephalus Clinic for infusion test to check shunt system patency, blockage (either proximal or distal) or overdrainage is not confirmed. These patients, if revised surgically, would not benefit from surgery.

Methods
Infusion study can be performed via two 25G butterfly needles inserted into shunt prechamber. Almost all shunts with CSF sampling chamber placed before the valve (exception: burr-hole Flow Control Valve) can be tested this way. Free aspiration of CSF is important marker of ventricular inlet patency. One needle is connected to pressure transducer and second to syringe infusion pump with Hartman solution. After 10 minutes of steady state pressure monitoring, infusion starts with the rate of 1.5 or 1 ml/min. Pressure rises until reaching plateau, then infusion is stopped and pressure decreases towards baseline value. Afterwards patient is sat up (in bed or reclining chair) and pressure is monitored minimum for 10 minutes.

Results
Around 2000 tests were performed in years 1993-2017 in shunted patients. Following principles were formulated: 1. Presence of detectable pressure pulse waveform at baseline and through the test is essential marker for patency of ventricular drain. 2. If during the infusion, pressure increases above ‘critical threshold’ established as shunt opening pressure plus shunt’s hydrodynamic resistance times infusion rate plus 5 mm Hg, the valve is judged to underdrain. 3. Normal outflow resistance during infusion test should not exceed 6 mm Hg/(ml/mi) (exception: Orbis Sigma Valve). Cases with normal resistance but baseline pressure elevated above shunt operating pressure plus 5 mm Hg, can result from abnormally elevated abdominal pressure. 4. If during the ‘tilting test’, pressure decreases below -10 mm Hg initially and then it further decreases gradually, overdrainage is possible.

Conclusion
Infusion test allows avoiding unnecessary shunt revision . Test is safe, with sterile mode of preparation of skin and tubing/needles, rate of infection is less than 1% avoiding unnecessary shunt revision.

Session 1: **Clinical Aspects of Hydrocephalus**

Epidemiology of cerebrospinal fluid shunt surgery in the UK and Ireland

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Background
There is no recent report on the epidemiology of CSF shunt surgery that is based on large populations of all ages followed over time, including all aetiologies. The aim of this study was to determine current epidemiology and clinical characteristics of CSF shunt surgery, including revisions.

Methods
A retrospective, multi-centre, registry-based study was conducted based on 10 years' data from the UK-Ireland Shunt Registry (UKSR). All primary and revision shunting procedures reported between 2004 and 2013 were included. Case ascertainment and data quality were explored. Incidence rates of primary shunts, shunt revision rates and descriptive statistics of clinical characteristics were explored, stratified by age group, geographical region, and year of operation.

Results
Between 2004 and 2013, the 41 UKSR participating institutions submitted 41036 shunt procedures in 26545 patients, including 20947 (51.0%) primary and 20089 (49.0%) revision procedures. Incidence rates of primary shunts in infants, children and adults were 39.5, 2.4 and 3.5 shunts per 100,000 person-years respectively, with some variation by geographical region and year of operation. Most common underlying aetiologies were perinatal intraventricular haemorrhage (35.3%) and malformations (33.9%) in infants, tumours (40.5%) and malformations (16.3%) in children, and tumours (24.6%), post-haemorrhagic hydrocephalus (16.2%) and idiopathic normal pressure hydrocephalus (14.2%) in adults. Shunt revision rates included 21.9%, 18.6% and 12.8% 90-day revision rates, and 31.0%, 25.2% and 17.4% first-year revision rates, for infants, children and adults respectively. Main reasons for revision included underdrainage (66.3%) and infections (12.2%), as single events or combined with other reasons.

Conclusions
Our conclusions inform patients, carers, clinicians, healthcare commissioners, researchers and industry about current epidemiology of CSF shunting, and potential complications.

Session 2: Spina Bifida a Life Style

Psychology adding value through partnership (PAVTP): Hydrocephalus screening a mental health screening and intervention pathway for children and young people with hydrocephalus (CYPwH)

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Rationale/Objectives
Hydrocephalus (seen in approx. 80% of Spina Bifida cases) is related to: poor quality of life (QOL); increased mental health (MH) problems and poorer long-term psychosocial outcomes. The PAVTP: Hydrocephalus Screening project developed a MH screening protocol and intervention pathway for CYPwH.

Methods
The Strengths and Difficulties Questionnaire (SDQ) and Hydrocephalus Outcome Questionnaire (HOQ) are completed by families prior to routine clinic appointments. Scores on the SDQ are then linked to a traffic light metaphor, indicating the level of MH concern, and potential route through the stepped intervention pathway. Interventions include: psychological self-help materials; support at home or school by SBH Scotland; referral to third sector workshops. Children already known to Child and Adolescent Mental Health or Learning Disability services are excluded from screening.

Results and Conclusion
Of the CYP screened, 36% of those with Spina Bifida and Hydrocephalus (n = 22) fell into the red zone compared to 10% with Spina Bifida only (n = 10) and 5% in the general population indicating that CYPwH are at significant risk of MH problems. ‘Overall Health Status’ on the HOQ negatively correlated with SDQ ‘Total Difficulties’ scores indicating that: as health status decreases, MH difficulties increase. Many CYPwH receive additional support for their physical needs however their psychological and cognitive needs can be neglected. SBH Scotland family support is found to have a positive impact on wellbeing indicators. The impact of child-specific interventions requires further evaluation. The data sample should also extend to include a ‘Hydrocephalus only’ group. These findings suggest that MH needs could be met using a partnership approach to detection and intervention between third sector and health services allowing access to timely, stepped, preventative interventions without significant increase in resource. Project funded by SBH Scotland and R S McDonald.

Session 2: Spina Bifida a Life Style

The impact of ageing on neurocognitive and emotional processing in hydrocephalus

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Background
Neuropsychological assessment has revealed a distinct pattern of cognitive and emotional sequelae associated with the neuroanatomical changes caused by hydrocephalus. This neuropsychological profile highlights executive function, memory and attentional deficits that have been linked to difficulties in everyday function, that are exacerbated by high levels of anxiety (Fletcher et al, 2004; Dennis et al, 2005; Loveday and Edginton, 2012). Subjective memory changes over time have been reported in individuals with hydrocephalus that may be atypical of healthy ageing. This study aims to explore the impact of ageing across cognitive domains in individuals with hydrocephalus who have had longitudinal neuropsychological follow up.

Materials and method
Longitudinal measures of cognitive, behavioural and emotional functioning were assessed in a group of patients (n=48) with hydrocephalus who had completed initial baseline assessments. Objective and subjective measures of cognitive function were analysed across a range of executive function, memory and attentional tasks and HADS questionnaires to assess anxiety and depression.

Results
Initial assessment confirmed the neurotypical pattern of cognitive deficits with impairments in memory, learning and executive function with abnormal levels of anxiety on the HADS. Analyses revealed that over 55% of patients declined on measures of memory and executive function and anxiety increased in over 56% of patients. Further analysis will explore individual patterns of change.

Conclusions
This study suggests that subjective reports of cognitive decline are revealed with longitudinal neuropsychological follow up. We discuss the impact of ageing on cognitive and emotional processing and attentional capacity and discuss the implications for everyday function over time for individuals with hydrocephalus and spina bifida and their caregivers.

Session 2: Spina Bifida a Life Style

Functional aspects of spina bifida in childhood: a cross-sectional analysis of a nationally represented sample

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Background
The aim of the study was to investigate the clinical and psychosocial outcomes of spina bifida (SB), as well as relationships between pathology, participation, environment, and health-related quality of life (HRQOL).

Materials
A cross-sectional study of a nationally representative sample of 99 children with SB aged 5 to 18 years. Methods. The questionnaires used in the study were the Spina Bifida HRQOL instrument, developed by Parkin et al. (1997), and the Participation and Environment Measure for Children and Youth. Clinical data related to SB were obtained from the medical files and the clinical examination.

Results
Children with SB were experiencing a high number of secondary health conditions (mean ± SD = 6.23± 3.316). Participation restrictions were found mostly in school and the community. The environmental factors consistently explained at least one dimension of participation across all settings. Cognitive abilities had a significant impact on participation at home and school, while bowel incontinence influenced participation in school. The most potent predictors of the HRQOL in children aged 5 to 12 years were the community overall environmental supports, a number of health conditions, access to personal transportation, and supplies, explaining 80% of the variance in the SB-HRQOL scores. The most significant predictors of the HRQOL in adolescents aged 13 to 18 years were a number of health conditions, cognitive demands of activities at home, supplies, money, physical layout at school, and access to public transportation, explaining 90% of the variance in the SB-HRQOL scores.

Conclusions
Our findings highlight the role of the neuropsychological functioning and environment in explaining participation and the HRQOL of children with SB and, therefore, support the development of interventions to train executive functions, as well as the development of compensatory strategies and environmental modifications.

Session 2: Spina Bifida a Life Style

Quality of life (QOL) in children with Spina Bifida (SB) in South East Asia need not to be gloomy -as generally believed: A short report

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Aim
To assess current quality of life in SB children who were treated at a single center. Materials and Methods: The study included children with SB from different parts of India. Of 100 SB patients, 50 patients were selected randomly, and questionnaires sent to them. Out of 50, 39 patients/families replied. The questionnaire included information about socio-economic status, patient's education status, quality of treatment, personal and social life. A score was assigned to each question, and the total score was tabulated, cross-tabulated and analysed for assessing the QOL.

Results
N=39, F=23, M=16, <10Y=6,10-20=23, >20Y=10 Results summary of QOL questionnaire: Rural Urban LI MI HI WCB AWS A Treatment quality 76% 88% 75% 87% 92% 86% 87% 87% Educational level 52% 85% 50% 82% 92% 77% 77% 88% Social life 67% 82% 58% 75% 92% 74% 74% 87% Personal life 62% 79% 54% 82% 83% 70% 73% 86% LI-low income MI-middle income HI- high income WCB- Wheel chair bound AWS-Ambulatory with support A-Ambulatory

Conclusions
After analyzing the results, some striking findings were- QOL in wheel chair bound SB was as good as others. The quality of treatment and the personal lives in SB individuals in rural areas was as good as those in urban areas. However, the educational level and social life in SB in rural area was slightly inferior to those in urban area (which is generally true for entire rural population). The QOL in SB individuals is co-related with incomes as can be expected (which is generally true for entire population). The paper will discuss above in detail. Thus, we conclude that the QOL of SB individuals in SEA need not to be gloomy- as generally believed in this part of the world.

Session 3: Basic Aspects of Hydrocephalus and Spina Bifida

Ventriculoperitoneal shunting and endoscopic third ventriculostomy with choroid plexus cauterization in a piglet model of infantile communicating hydrocephalus

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Background
Large, clinically-relevant animal models of hydrocephalus in which neurosurgical devices and novel procedures could be tested are lacking. To meet this unmet need, we developed a porcine model of juvenile communicating hydrocephalus, in part to test safety of the Microbot Self-Cleaning Shunt (SCS), and report our experience in performing ventriculoperitoneal shunting (VPS) and endoscopic third ventriculostomy with choroid plexus cauterization (ETV-CPC) on this model.

Materials and Methods
Hydrocephalus was induced in 30-day old piglets by percutaneous intracisternal injection of kaolin. Pre- and post-kaolin and pre- and post-treatment anatomic MRIs were obtained to document ventriculomegaly and guide the neurosurgical procedures. VPS was performed with standard Medtronic (n=4) or experimental Microbot SCS (n=5) systems. Terminal ETV-CPC (n=4) was performed using a frontal approach, visualization of the foramen of Monro (FoM), and opening the floor of the 3rd ventricle with balloon expansion. Animals survived 1-84 days (median 41) post-kaolin untreated and 5-30 days (median 12.5) post-shunt. Cytopathology was evaluated with histology and immunohistochemistry.

Results
Lateral ventricle volumes progressed from 1291+188 mm3 SEM pre-kaolin to 2455+1067, 2821+1139, 2280+1836, and 3538+2043 at post-kaolin days 1-5, 8-15, 22-29, and 42-69, respectively. Ventriculomegaly continued to progress post-shunt (mean 4051 mm3). ETV-CPC was performed successfully and the path through the FoM, and the ETV-CPC could be confirmed grossly with minimal damage to adjacent tissue.

Conclusions
The juvenile piglet represents a clinically-relevant large animal model of communicating hydrocephalus, with moderate-severe ventriculomegaly, ependymal disruption and reactive astrogliosis. VPS and ETV-CPC can be performed with

clinical instrumentation and hardware. This model can be used for a variety of studies, including the physiological effects of removing the choroid plexus.

Session 3: Basic Aspects of Hydrocephalus and Spina Bifida

The H-Tx rat has a heritable methylation error affecting all tissues including the germline which underlies the congenital hydrocephalus of its offspring and is corrected by folate supplementation

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Background
We have previously described a folate imbalance in the cerebrospinal fluid of affected hydrocephalic H-Tx rat fetuses and neonates. We further showed that this responds to maternal folate supplementation to reduce the incidence of hydrocephalus and generally improve brain development. We have been investigating two issues, firstly how to get the incidence to zero and secondly what is the origin of the methylation folate imbalance.

Materials and Methods
10 male female adult H-Tx rats were given daily subcutaneous injections of a combination folate supplement for 1 month before mating. After mating the males were sacrificed for analysis and the females continued on supplements throughout gestation. Heads of neonates and tissues from the dams were frozen for sectioning. Untreated male and female H-Tx as well as Sprague-Dawley control rats were also taken for analysis. Tissues including brain, liver, testis and ovaries were fresh frozen in isopentane cooled with dry ice, cut into 25μm thick sections and stained for immunofluorescence using antibodies for 5-methyl cytosine, 5-hydroxymethyl cytosine, folate binding proteins and folate.

Results
We found a general reduction in methylation in all tissues in the HTx rats including the brain and with a greatly reduced methylation in the testes compared to normal Sprague-Dawley rats. Folate supplemented rats showed improved/normal methylation in tissues including the brain and testes. Staining showed an apparent block to folate entry into the tubules of the testes compared to control rats. Moreover there was a block of entry into the nuclei of cells, including in the brain, of the folate enzyme 10-formyl tetrahydrofolate dehydrogenase (FDH) associated with the methylation error.

Conclusion
Our data indicate a germline methylation error may be causative in the general folate issue leading to hydrocephalus in the H-Tx rat. A failure of FDH to enter the nucleus may be responsible for the failure of the methylation process. Our combination folate formulation fixes the methylation error in all tissues and prevents hydrocephalus completely when given to both males and females.

Funded by a Nuffield Research Placement

Session 3: Basic Aspects of Hydrocephalus and Spina Bifida

IV ventricle choroid plexus study in several cases of hydrocephalus human fetuses

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Background
The choroid plexuses, under normal conditions of development, are formed by a specialized ependymal epithelium. This epithelium consists of a layer of cubic cells with rounded nuclei in the central position and microvilli on the surface. The choroid plexus is mainly involved in the production of cerebrospinal fluid. The aim is to analyze the expression of aquaporin-1 (AQP1) and transthyretin (TTR) during fetal development and hydrocephalus.

Material and methods
In this study, the pattern of development of the expression of AQP1 and TTR in the choroid plexuses (ChP) of the IV ventricle was analyzed by histological and immunocytochemistry methods in control embryos from 10 to 24 GW and hydrocephalic from 19-22 GW.

Results
In embryos with tetraventricular hydrocephalus, the nuclei of the ChP epithelium are located in the basal position, while in the control the nuclei are centrally located. In the Arnold Chiari fetus, the nuclei are rounded and larger than in the controls and centrally located. In the other cases of hydrocephalus of unknown origin, the epithelium presents an appearance pseudostratified. The AQP1expression was lower in the cases of hydrocephalus than control and was observed in the apical and basolateral zone. The expression of TTR was located in the cytoplasm and membranes of the epithelial cells, but in hydrocephalus, the TTR intensity was high in the apical pole of the cells.

Conclusions
The increasing expression of AQP1 and TTR protein reflects a progressive increase in filtration capacity, which probably reflects the functional maturation of these cells during the prenatal development period. In the fetus with hydrocephalus, the amount of AQP1 in the fetal brain could restraints the production of CSF and contributes to maintaining water balance.

Session 3: Basic Aspects of Hydrocephalus and Spina Bifida

Role of AQP4 in brain barriers and functional interfaces during systemic hypertension and ventriculomegaly

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Background
Systemic arterial hypertension produces alterations of the circumventricular structures, ventricular dilation and changes in the protein composition of the CSF, the aim of the present work is to analyze the expression of aquaporin-4 (AQP4) in the CSF-brain interface (CSF-Bi) and blood-brain barrier (BBB) in a rat model of hypertension.

Materials and Methods
Brains and CSF from rats of 26 and 52 weeks of age were used, divided into two groups: a control group Wistar-Kioto (WKY) and a hypertensive group (SHR). The brain sections containing lateral ventricle, striatum, hippocampus and frontal cortex were processed by immunohistochemistry and immunofluorescence with anti-AQP4. AQP4 in the CSF was also analyzed by ELISA.

Results
CSF-Bi AQP4 was located at the feet of the astrocytes and in the ependymal cells of the lateral ventricles. Lateral ventricle presented AQP4 differences, showing a decrease of almost half in the expression of AQP4 in SHR with respect to WKY. BBB AQP4 was also located at the feet of the astrocytes surrounding the cerebral capillaries in hippocampus and frontal cortex. At six months a 1.5 fold increase in the expression of AQP4 was observed in the hypertensive rats compared to the controls, while at 12 months this increase was double in the quantification of AQP4. CSF The mean value of the concentration of AQP4 CSF of the SHR tend to be higher than WKY, but not significant at 6 months. However, at 12 months, an average concentration of AQP4 CSF of the SHR was significant higher than WKY.

Conclusions
Hypertension in these rats produces an AQP4 decrease in the CSF-Bi and an AQP4 increase in the BBB and CSF. We could surmise that, given that BBB and CSF-Bi are areas involved in the passage of water from the blood to the brain and the brain to CSF, that transport would be altered in systemic hypertension and ventriculomegaly and the AQP4 variations could be a compensation mechanism to avoid or slow the brain edema and the ventriculomegaly.

Session 3: Basic aspects of hydrocephalus and spina bifida

Exome sequencing establishes dysregulation of neural progenitor cell fate as a critical mechanism in human congenital hydrocephalus

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Congenital hydrocephalus (CH), thought to arise from failed cerebrospinal fluid (CSF) homeostasis, is treated with lifelong surgical CSF shunting with substantial morbidity. CH pathogenesis is poorly understood. Our recent genomics study of 180 probands with CH identified four novel CH genes, each implicated in regulating neural stem cell fate (Furey et al., Neuron, 2018). Nonetheless, less than 10 percent of studied cases are solved by these genes.

To expand our understanding of CH genetics, we doubled the size of our cohort via robust domestic and international collaborations and exome sequenced a total of 361 radiographically confirmed CH probands, including 216 case-parent trios, 14 familial cases, and 2 brain tissue-germ line paired samples.

Exome sequencing revealed multiple new causative mutations in genes we previously identified (e.g., *TRIM71* and *SMARCC1*), along with at least four novel CH genes, each of which is known to regulate ventricular zone NPC cell fate. Strikingly, three of these novel CH genes encode interacting enzymes of a signal transduction pathway targetable with available drugs.

These findings implicate new genes in CH and demonstrate related pathophysiology among sporadic and familial patients. These findings have implications for diagnosis, prognosis, and treatment, and suggest that in a subset of patients the risk of adverse neurodevelopmental outcomes may be unaltered whether or not shunting is performed.

Session 4: Hydrocephalus; a Cytological Disease

The progression of kaolin-induced hydrocephalus: light and electron microscopic features in rats

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Hydrocephalus is a common neurological disorder caused by an abnormal accumulation of cerebrospinal fluid within the brain which results in injury to the surrounding brain tissue with neurological deficits. A major factor not usually accounted for is the progressive change over time. In this study, we examined, the changes that occur with time in neurons, glia and neuropil in the brain parenchyma; and ependymal lining of the ventricles in neonatal rats with kaolin-induced hydrocephalus. We induced hydrocephalus in 18 three week-old Wistar rat pups by intracisternal injection of 0.05ml of kaolin solution (250mg/ml in normal saline) while 18 controls had sham injection. The hydrocephalic rats were divided into three groups consisting of six rats each which were sacrificed at one, four and eight weeks post-induction of hydrocephalus along with their age-matched controls. Following sacrifice, 24 of the brain samples were stained with haematoxylin and eosin, cell counts were determined and data analysed using ANOVA at α0.05. The remaining 12 were processed for Transmission and Scanning Electron Microscopy (TEM and SEM) and the images analysed descriptively. The laminar organisation of the cerebral cortex was disrupted in all hydrocephalic rats, but neuronal density was significantly increased at 8 weeks (127.80±8.68 / HPF vs 85.50±5.42 / HPF in controls). An initial denudation observed in the ependymal cell cilia of the ventricular wall was followed by gradual restoration of cilia size and population over time. Ultrastructural changes in the brain parenchyma including enlargement of extracellular space, disruption of intracellular architecture, neuronal degeneration and hydropic changes in cell organelles like the mitochondria were observed with increasing severity as the duration of hydrocephalus increased. Hydrocephalus produces significant structural injury within the brain parenchyma which increases with duration and severity, but there is also evidence of partial structural recovery on the ventricular wall over time.

Session 4: Hydrocephalus; a Cytological Disease

Long-time effects of an experimental therapy with mesenchymal stem cells in congenital hydrocephalus

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Introduction
Bone marrow-derived mesenchymal stem cells (BM-MSC) are a potential therapeutic tool due to their ability for migrating and producing neuroprotector factors when they are transplanted in other neurodegenerative diseases. Moreover, some investigations have shown that BM-MSC are able to modulate astrocyte activation and neuroprotector factor production. The aim of this study was to evaluate the long-time effects of a BM-MSC experimental therapy in the hyh mouse model of congenital hydrocephalus.

Methods
BM-MSC were characterized in vitro and then transplanted into the ventricles of young hydrocephalic hyh mice, before they develop the severe hydrocephalus. Non-hydrocephalic normal mice (wt) and hydrocephalic hyh mice sham-injected (sterile saline serum) were used as controls. Samples were studied by analyzing and comparing mRNA, protein level expressions and immunoreaction related with the progression and severity of hydrocephalus.

Results
Fourteen days after transplantation, hydrocephalic hyh mice with BM-MSC showed lower ventriculomegaly. In these animals, BM-MSC were found undifferentiated and spread into the periventricular astrocyte reaction. There, BM-MSC were detected producing several neuroprotector factors (BDNF, GDNF, NGF, VEGF), in the same way as reactive astrocytes. Total neocortical levels of NGF, TGF-β and VEGF were found increased in hydrocephalic hyh mice transplanted with BM-MSC. Furthermore, astrocytes showed increased expressions of aquaporin-4 (water channel protein) and Slit-2 (neuroprotective and anti-inflammatory molecule).

Conclusions
BM-MSC seem to lead to recovery of the severe neurodegenerative conditions associated to congenital hydrocephalus mediated by reactive astrocytes.

Supported by PI15/0619 (ISCIII/FEDER) to AJJ.

Session 4: Hydrocephalus; a Cytological Disease

Grafting of subcommissural organ cells improves neurological deficits in the hydrocephalic brain

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Introduction
It is now understood that hydrocephalus is not only a disorder of CSF dynamics, but also a brain disorder, and that derivative surgery does not resolve most aspects of the disease. Indeed, 80-90% of the neurological impairment of neonates with fetal onset hydrocephalus is not reversed by derivative surgery. We have begun to explore new strategies for diminishing such deficits, including the grafting of subcommissural organ (SCO) in the cerebrospinal fluid (CSF). Why SCO? Because SCO cells release neurotrophic compounds such as SCO-spondin, transthyretin (TTR), and the fibroblast gtowth factor (FGF-2). Goal of this research was to dilucidate if grafting of SCO cells diminish neurological deficits in the hydrocephalic brain.

Methods
Hydrocephalic HTx rats (n=10) were grafted at postnatal day 7 (PN7). Ventriculomegaly was studied by computed tomography (TC) and histology. Neurological and cognitive condition was evaluated by standardized tests, such as the Object Recognition and Spontaneous Alternation in T Maze, at PN30. Non hydrocephalic HTx rats and sham- HTx rats were used as control.

Results and conclusions
Grafting of SCO-cells significantly improved neurological and cognitive condition in the hydrocephalic animals. It was not associated to a reduction of ventriculomegaly. Histological studies of grafted brains showed SCO cells integrated in the wall of the lateral ventricules. They were strongly reactive with antibodies against SCO-spondin and TTR, supporting that effects reported on neurological and cognitive conditions are mediated by SCO secretory compounds. These findings open an avenue for the development of a neurotrophic therapy for hydrocephalus.

Supported by grant from Fondef (Chile) 14I10236 to MG.

Session 4: Hydrocephalus; a Cytological Disease

iPSC differentiation into ependymal progenitors to treat ventricular damage during hydrocephalus

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Introduction
During both obstructive congenital hydrocephalus and post-hemorrhagic hydrocephalus additional pathological events are intimately associated with their ethiology: a) a detrimental inflammatory response; b) severe damage of the underlying periventricular nervous tissue, including white matter, and c) damage on the ventricular wall. Therapeutic approaches have been directed to overcome a) and b), however recovery of damaged neuroepithelium/ependyma is, in our present, an important therapeutic gap.

Methods
Human and mouse induced pluripotent stem cells (iPSC) have been artificially differented into ependymal progenitors. Intracerebroventricular (ICV) injections of iPCS are performed ex vivo and in vivo in the damaged ventricular wall. Their integration and differentiation has been studied by immunohistochemistry and histopathological analysis. Also, the effect of TNF-alpha on the recovery of the ventricular wall will be tested.

Results
Mice and human ependymal progenitors are able to integrate and differentiate into ependyma in damaged ventricular wall. Stage of ependymal differentiation by the time of the injection defined different degrees of integration.

Conclusions
iPSC appear to be a good ependymal progenitor source with no ethical controversy associated.

Session 4: Hydrocephalus; a Cytological Disease

Temporal changes in the brain in neonatal hydrocephalic mice: structural and neurobehavioural findings

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In hydrocephalus, the circulation of cerebrospinal fluid is altered leading to its accumulation in the ventricles and subarachnoid space. The impact of this disease on neurobehaviour and the structure of the cellular organelles of pyramidal neurons and their synapses in the neonatal hydrocephalic mouse brain overtime are not fully understood.

Hydrocephalus was induced in day-old mice by intra-cisternal injection of sterile kaolin suspension. The pups were tested for reflex developments prior to sacrifice on postnatal days 7,14,21. Cortical thickness and neuronal density in the sensorimotor cortex were evaluated using hematoxylin and eosin and Nissl stains while ultrathin stained sections were also assessed.

Surface righting reflex (3.08±0.48 vs 1.27±0.16;2.49±0.10 vs 1.06±0.05) and cliff avoidance activities (17.15±2.18 vs 10.50±2.00) were significantly impaired in hydrocephalic pups. The cortical thickness (μ m) of the hydrocephalic mice was significantly reduced on PND 7 (2409±43.37 vs 3752±65.74), PND 14 (2035±322.10 vs 4273±67.26) and PND 21 (1676±33.90 vs 4945±81.79) compared to controls. Compared with age-matched controls (129.60±3.72x10^{-6} μm^2; 230.0±44.1x10^{-6} μm^2), the neuronal density of the sensorimotor cortex in hydrocephalic mice was significantly increased on PND 14 (157.70±21.88x10^{-6} μm^2) and PND 21 (373.20±21.54x10^{-6} μm^2). The TEM of the hydrocephalic mice brains showed loss of structural integrity of cellular organelles and depletion of synaptic junctions. The synaptic densities (per μm^2 x10^{-5}) of the hydrocephalic mice were significantly lower (188.0±22.67;120.0±21.68;72.0±0.66) than their age-matched controls (336.0±37.09;486.0±18.60;600.0±17.61) on days 7, 14 and 21 respectively.

The quantitative changes and ultrastructural findings seen in the neuronal population of the hydrocephalic mice may provide supportive data for the structural basis of the neurological disabilities associated with neonatal hydrocephalus.

Session 5: Hydrocephalus as an Inflammatory Disease

Neuropathological events in an animal model resembling human fetal post-hemorrhagic hydrocephalus

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Introduction
In premature newborns, intraventricular hemorrhages (IVH) probably trigger the disruption of the neurogenic ventricular zone. Most of the cases with severe IVH develop post-hemorrhagic hydrocephalus (PHH). A mouse model with IVH has been developed to research into the common neuropathological events present in PHH and into possible therapies.

Methods
In two-day-old mice, the blood serum from littermates was injected into the ganglionic eminence of one hemisphere or both hemispheres. Fourteen days later, a histopathological analysis was carried out. In the case of injection in one hemisphere, the effects were compared with the contralateral non-injected hemisphere.

Results
Mice with IVH developed the following neuropathological effects. The ependyma was found denuded and replaced by reactive astrocytes. A reaction of astrocytes over-expressing aquaporin-4 and of NG2 cells was also found developed in the white matter. Alterations in the neurogenesis were also common in the ventricular zone and in the white matter.

Conclusions
The animal model of IVH developed shows similar neuropathological events to other forms of congenital hydrocephalus and can be used to research into therapies for PHH.

Supported by PI15/0619 (ISCIII/FEDER) to AJJ.

Session 5: Hydrocephalus as an Inflammatory Disease

Post-infectious and post-hemorrhagic hydrocephalus may have a common pathway that triggers ventricular zone disruption

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Background
Hydrocephalus is a neurological condition characterized by abnormal dilatation of the cerebral ventricles. The main etiological factors in neonates are central nervous system infections and hemorrhage, which leads to post-infectious (PIH) and post-hemorrhagic (PHH) hydrocephalus, respectively. We have found that PIH and PHH share common pathophysiological mechanisms such as ventricular zone (VZ) disruption. VZ disruption is implicated in the etiology of neonatal hydrocephalus as a result of N-cadherin (N-cad) cleavage. Adam10 is a metalloproteinase responsible for the regulation of N-cad-dependent cell junctions; increased ADAM10 activity causes VZ disruption by loss of cell junctions. We hypothesize that Adam10-N-cadherin cleavage is a common pathway in PIH and PHH, and its modulation may prevent VZ disruption and other hydrocephalic events.

Materials and Methods
Progenitor cells from newborn mice were cultured as a monolayer of VZ cells that received either blood to mimic PHH or alpha-hemolysin (Hl-α), a bacterial toxin released in infections, to mimic PIH. Treatments included: (1) DMSO (vehicle control), (2) syngeneic blood, (3) syngeneic blood + ADAM10 inhibitor (Ad Ih), (4) Hl-α, (5) Hl-α + Ad Ih. Cell cultures and media, were evaluated with immunohistochemistry, ELISA and western blots.

Results
In vitro treatments were associated with significant disruption of N-cad expression ($p<0.05$), reduction in the percentage of VZ cells ($p<0.01$) and increased ADAM10 activity ($p<0.05$) in PHH and PIH conditions. However, when the cells were pre-treated with ADAM10 inhibitors, cytological structure and N-cad expression were preserved in PHH and PIH conditioned cells; no significant differences were seen when compared to control.

Conclusions
In vitro results indicate that ADAM10 plays a prominent role in the pathogenesis of PHH and PIH and pharmacological modulation of ADAM10 reduces VZ disruption in both cases.

Session 5: Hydrocephalus as an Inflammatory Disease

Persistent ventriculomegaly in hydrocephalic rat brains: neuroinflammatory response

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Hydrocephalus is especially prevalent in countries with limited resources, where its treatment is still a challenge. However, long-term neuropathological changes in untreated hydrocephalus largely remain to be explored. The present study examined whether neuroinflammation persists in acquired, chronic hydrocephalus. Intracisternal kaolin injections were performed in 3 week-old rats, followed by 1, 4 and 8 weeks survival. Ventriculomegaly has been previously reported to stabilize by the third week in this model. Matched control rats received saline injections. Single and triple immunocytochemical approaches were used to visualize astrocytes, microglia, and the pro-inflammatory cytokine interleukin (IL)-1beta in the parietal cortex, pursuing cell counts and densitometry. Microglial protein ionized calcium binding adaptor molecule 1 (Iba1) and IL-1beta expression was monitored with Western blotting in the parietal cortex and hippocampus. In the cortex, which showed progressive disruption of cytoarchitecture, neuronal cell density was significantly increased at 8 weeks post-induction but not at earlier time points, indicating ongoing cortical damage in chronic hydrocephalus. Astrocyte and microglia hypertrophy and quantitative analyses indicated sustained glial cell activation with a trend that persisted at 8 weeks. Iba1 expression showed at 4 weeks an increase that persisted at 8 weeks. IL-1beta expression peaked at 4 weeks and was then down-regulated. Overall the findings indicate that neuro-inflammatory features build up in the first month after hydrocephalus induction implicating marked IL-1beta up-regulation, and show that astrocyte and microglia activation persists in the presence of ventriculomegaly. The data also show that astrocytes are the main source of IL-1beta in this disorder.

Session 5: Hydrocephalus as an Inflammatory Disease

Quantification and differentiation of periventricular white matter injury in post-hemorrhagic hydrocephalus using diffusion basis spectrum imaging

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Background
Periventricular white matter (PVWM) disruption is a dominant pathology in post-hemorrhagic hydrocephalus (PHH), and accounts for long-term morbidity. Diffusion Tensor Imaging (DTI), which is frequently used to assess PVWM integrity, is unable to differentiate complex cellular pathologies such as edema, inflammation and axonal loss. We used Diffusion Basis Spectrum Imaging (DBSI), which has been validated to be more effective for assessing complex WM pathologies in multiple sclerosis, spinal cord injury and brain tumors to address the PVWM pathology associated with PHH.

Materials and Methods
PHH was induced in 20-day-old ferrets by intraventricular injection of autologous blood (n=7). Controls (n=6) received intraventricular PBS. At about 50-days-old, brains were fixed in 4% PFA and scanned ex vivo in a Varian® 4.7T MRI for T2W, multi-echo, spin-echo, and diffusion weighted sequences in 99 directions. Regions of Interest and voxel intensities for corpus callosum (CC), anterior (ALIC) and posterior (PLIC) limbs of the internal capsule were statistically analyzed using R package v3.4.1. Immunohistochemistry was done to assess PVWM.

Results
The PHH group had a 68% ($p<0.005$) proportional increase in hindered fraction: 120% ($p<0.005$) and 51% ($p<0.005$) in the CC and ALIC, respectively. CC and ALIC demonstrated proportionally decreased fiber density by 7% ($p<0.05$) and 10% ($p<0.05$), respectively. ALIC demonstrated axonal injury with decreased axial diffusivity of 8% ($p<0.05$). While similar trends were observed in the PLIC, none were statistically significant. Immunohistochemistry demonstrated significantly higher PVWM damage in PHH.

Conclusions
DBSI demonstrated marked edema, neuroinflammation, axonal injury and axonal loss in the PVWM of the PHH cohort. DBSI is a versatile tool for differentiating and

quantifying the different components of WM disruption, and can be used as a novel non-invasive biomarker for PVWM integrity in PHH.

Session 5: Hydrocephalus as an Inflammatory Disease

A role for inflammation: TLR-4-mediated cerebrospinal fluid hypersecretion in post- hemorrhagic and post-infectious hydrocephalus

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Hydrocephalus is a devastating disease commonly occurring secondary to intraventricular hemorrhage (IVH) or bacterial meningitis. The standard of care, cerebrospinal fluid (CSF) shunting, is an invasive neurosurgical procedure that is prone to complications, requiring multiple revision surgeries, and dramatically decreases quality of life. A fundamental obstacle in developing novel therapeutics for hydrocephalus has been a relative lack in our understanding of the pathophysiology of the choroid plexus epithelium (CPe) following IVH and bacterial meningitis. Recently, our group has demonstrated a novel role of TLR-4-mediated CSF hypersecretion following IVH that causes acute post-hemorrhagic hydrocephalus (PHH). CSF hypersecretion is secondary to an increase in the functional expression of the NF-κB- regulated Ste20-type stress kinase STK39 (SPAK), binds, phosphorylates, and stimulates the ion co-transporter, NKCC1 (critical for CSF secretion) at the apical CPe membrane. Strikingly, PHH could be attenuated by genetic and pharmacological manipulation of TLR-4, NF- κB, SPAK or NKCC1. Interestingly, post- infectious hydrocephalus (PIH) exhibits non- obstructive ventriculomegaly, CPe inflammation, and a positive response to endoscopic choroid plexus cauterization. Lipopolysaccharide (LPS), the canonical TLR-4 ligand, is a component of many PIH-causing bacteria. Here, we begin to show that PHH/PIH may share a common pathogenic mechanism of TLR4-dependent CSF

hypersecretion and acute hydrocephalus via a similar up-regulation of TLR-4-regulated ion transporters in the inflamed CPe. We propose instead of being classified as "secondary" forms of hydrocephalus, PHH/PIH may be better termed "inflammatory hydrocephalus" to highlight overlapping disease mechanisms and potential therapeutic vulnerabilities

Session 6: Spina Bifida: Clinical Aspects

Urinary incontinence is a major factor in determining the quality of life in Spina Bifida patients

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Aim
To assess the quality of life in SB individuals before and after incontinence management.

Materials and method
Retrospectively, between 2000-2017 we analyzed 50 spina bifida patients who underwent incontinence management (medical and surgical) at our hospital. The quality of life pre and post continence management was assessed under the following parameters: psychological aspects (behavior, personal life, self-esteem, confidence), educational aspects (class, scores and interest in school and studies), social aspects (interaction with peers, participation in group activities). A score was given for each parameter.

Results
Of the 50 individuals, 32 were male and 18 were females. 5 were below 10 years, 38 were between 10-20 year and 7 were above 20 years. The dry intervals were between 15 min and 60 min before the continence management. After continence management the dry interval increased to 1-2 hours in 5 patients, 2-3 hours in 13 patients, 3-4 hours in 26 patients and > 4 hours in 6 patients. Psychological aspects Educational aspects Social aspects Pre-Contn Rx Post- Contn Rx Pre- Contn Rx Post- Contn Rx Pre- Contn Rx Post- Contn Rx Mean score * 2.0 2.79 1.97 2.85 1.88 2.73 SD 0.43 0.41 0.39 0.36 0.33 0.51 p-value <0.0001 <0.0001 <0.0001 *Mean score arrived by compiling scores for each parameter/patient. This will be discussed during presentation.

Conclusions
We noticed a statistically significant improvement in quality of life (for each parameter and in the overall quality of life) after successful urinary continence management. Hence successful continence management in children with Spina Bifida, greatly improves the quality of life.

Session 6: Spina Bifida: Clinical Aspects

Factors affecting outcomes of Bladder Augmentation Surgery in Spina Bifida patients

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Aims
To study factors affecting outcomes of bladder augmentation.

Materials and Method
A retrospective analysis of pre, intra and post-operative factors affecting bladder augmentations was done A protocol was followed for patients and outcomes were assessed with regard to complications, improvement in bladder capacity and dry intervals. Bowel preparation was in the form of enemas and liquid diet; this did not have any impact on results. De-tubularized sigmoid was used in 20 patients. We progressed from using the augment as a cap to a patch preventing an hour glass configuration. A thorough check for leaks minimized the occurrence of post-operative complications. Leaks seen in 3 patients were managed conservatively. We now keep only the Mitrofanoff and supra-pubic catheters and no indwelling ureteric catheters. This allowed early bladder cycling and prevented mucous accumulation. Bladder washes were started on 5th POD to prevent catheter blockage with mucous. Following a strict protocol for post-operative catheter care, preventing catheter kinking and use of urine collecting boxes rather than bags in smaller children showed reduction in complications due to mechanical causes.

Results
In all patients, the bladder capacities showed significant improvement and the dry intervals achieved were > 4hrs in 3 cases, 3-4 hrs in 10 cases, 2-3 hrs in 3 cases and < 2hrs in 4 cases.

Conclusion
The factors found to be important for improving outcomes and preventing complications after bladder augmentation were using a patch (rather than a cap) of colon, non-usage of ureteric catheters and thorough check for leaks.

Session 6: Spina Bifida: Clinical Aspects

Management of feet skin breakdown in spinal lipoma patient

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It is well known that Spina Bifida patients are ailed with complications such as walking difficulty, deformity of the feet, sensation loss of the lower extremities, urinary and fecal incontinence. It is further known that reports of skin breakdown of the feet are relatively rare in spinal lipoma patients compared to the open neural tube patients. During the last four years, there were three patients that suffered skin break down on the feet in our institution. Spinal lipoma was the cause of the skin break down for the two amount the three and myelomeningocele was the cause for the remaining one. Case presentation: Case.1 Twelve-year-old girl. Her back lipoma was removed surgically when she was one year old, and was also treated for urinary incontinence by the same surgeon. She had acquired a foot infection on the left little finger and was referred to our institution for further treatment where the decision to amputate the finger was made by the orthopedic surgeon as the infection had reached the bone. She was further referred to us for spinal lipoma and received operation without any complication. She experienced another case of intractable skin breakdown on the right lower feet two years later. Case. 2. Fifteen-year-old girl. She was treated in several different institutions for her urinary incontinence without any surgery for spinal lipoma. Her spinal lipoma was operated on in our institution to prevent further neurological deterioration. As the patient in case one, this girl also had to revisit our institution due to an intractable skin breakdown on the right foot. Discussion: There is no consensus that early prophylactic operation for spinal lipomas have better outcome, yet. We presented two cases here who had long history of urinary incontinence without untethering surgery for spinal lipomas. It seems that the ambulatory was good and the deformity of the lower extremities were mild in those cases. We will discuss the importance of patients' education and the management of spinal lipomas.

Session 6: Spina Bifida: Clinical Aspects

A sociological study of mothers' knowledge towards hydrocephalus and spina bifida in The Children Hospital, Lahore, Pakistan

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Background
In Pakistan hydrocephalus and spina bifida are becoming two of the most common birth defects but no effective organizational structure or educational program exists to create awareness about these in society. The main purpose of this research was to explore the knowledge of women regarding hydrocephalus and spina bifida both before and after birth of children affected by these conditions.

Methods
This study was carried out in paediatric neurosurgery outpatient department (OPD) in The Children Hospital, Lahore, Pakistan. 500 mothers with babies suffering from hydrocephalus and spina were selected using a non-probability purposive sampling technique. Data was analysed SPSS v19.

Results
Of the 500 babies 44.5% were suffering from hydrocephalus, 28.2% spina bifida and 27.3 hydrocephalus and spina bifida. 90.6% of the mother had no awareness about any vitamins preventing birth defects. The majority did not know what medicines (including vitamins) doctors/health workers had prescribed for them, remembering only their colours. Based on tablet colours and samples we deduced that 22% were taking folic acid but 89.4% of these did not know about folic acid preventing spina bifida, 10.6% did know, but only 2.6% knew the dose of folic acid to take and only 1% knew when to stop taking folic acid. Only 9.6% of the women said they could find folic acid available in medical stores.

Conclusion
The study findings show that women attending hospital with children suffering hydrocephalus and/or spina bifida had a very low knowledge of the importance of vitamins/supplements during pregnancy. There is therefore an urgent need to intervene with a complete program to focus on women and health professional to create awareness about hydrocephalus and spina bifda and how maternal health and simple supplements can prevent severe developmental defects. International and national programs may then have a better chance of making an impact.