54th Annual Meeting of the Society for Research into Hydrocephalus and Spina Bifida

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INTRODUCTIONS

S1 54th Annual Meeting of the Society for Research into Hydrocephalus and Spina Bifida

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The 54th Annual Meeting of the Society for Research into Hydrocephalus and Spina Bifida was held at the University of British Columbia, Vancouver, Canada at the invitation of the local organizing committee; Bill Arnold, Doug Cochrane, Paul Thiessen, Judi Haddy, Nicola Valentine, Bev Irwin and Carol King.

Proceedings began on Wednesday afternoon with the Annual General Meeting of Members. This was followed by a reception for all delegates and guests at the Museum of Anthropology where we were welcomed by Vancouver Dr. Ralph Rothstein, Acting Head of the Department of Pediatrics, Faculty of Medicine at the University of British Columbia. The scientific programme was opened on Thursday Morning by a welcome from Dr. Ross MacGillivray, Vice-Dean of Medicine, University of British Columbia, and included sessions on ‘Hydrocephalus’ (Two Sessions), ‘Urological Problems and Spina Bifida’, ‘Myelomeningocele: Management and Genetics’, ‘Spina Bifida: Sociological Issues’, ‘Choroid Plexus and Molecular Biology’, ‘Shunts and Infections’. This year we were pleased to have three excellent Invited Lectures, from Dr. Benjamin Warf (Boston Childrens Hospital, MA, USA), entitled ‘Endoscopic Management of Children with Hydrocephalus and Spina Bifida in East Africa’, from Professor Rima Rozen (McGill University, Montreal, Canada) on ‘Biochemistry and Genetics of folate Metabolism’ and from Dr. Margot Van Allen (Department of Medical Genetics, University of British Columbia, Vancouver, Canada) entitled ‘Prenatal diagnosis and Folic Acid in the Detection and Prevention of Neural Tube Defects’.

The Thursday afternoon social programme consisted of a First Nations Salmon Barbeque Luncheon, a coach trip through Vancouver and a Dinner Cruise departing from Coal Harbour and sailing in Indian Arm of Burrard Inlet. The return at dusk gave the amateur photographers some spectacular views of the Vancouver Skyline in the golden light. The final event of the social programme was a gala dinner in Cecil Green House on the campus of the University of British Columbia.

S2 Experimental Hydrocephalus Pre-meeting 7th July 2010, Ike Barber Centre, University of British Columbia, Vancouver, Canada

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This year was a milestone since it was the 10th anniversary of the first session on experimental studies on hydrocephalus held every year except one, since they were initiated in the SRHSB meeting in Atlanta, USA in year 2000. The aim has been to give researchers who are presenting experimental research at the main meeting, the opportunity to present their work in an informal atmosphere with time for feedback and useful discussion from the audience which usually amounts to 20 - 40 people.

The first speaker was Pat McAllister (University of Utah), who spoke on “Behavioral and neuroimaging correlates of white matter injury in experimental hydrocephalus”. He said that white matter tracts are known to be affected by ventriculomegaly and can be probed using diffusion tensor imaging (DTI), but not enough data have been accumulated to determine if this particular marker has reliable predictive power. He and colleagues have hypothesized that DTI and CSF pulsatility could serve as biomarkers to predict disease severity in experimental communicating hydrocephalus. This was investigated using their novel adult rat model of kaolin-induced communicating hydrocephalus, characterized by CSF flow impairments in the basal cisterns, marked changes in ventricular size, and variations in disease severity. Preliminary data has suggested that DTI changes in the corpus callosum and internal capsule were predictive of poor motor and cognitive outcomes, but that CSF pulsatility was not predictive. Ongoing analyses will correlate these non-invasive neuroimaging changes with specific cytopathology.

The second speaker was Weihong Yuan (Cincinnati Children’s Hospital) on “Validation of diffusion tensor imaging as a biomarker for neonatal hydrocephalus”. He described an ongoing project designed to validate diffusion tensor imaging (DTI) as a biomarker to identify injury to the developing brain as a consequence of hydrocephalus. They propose to use DTI at 7 Tesla in an animal (rat) model of neonatal hydrocephalus and to compare results with outcome measures using histological examination of brain tissues and behavioral tests. The data obtained is expected to help to a further understanding of pediatric hydrocephalus at the radiographic, pathologic and behavioral level.

The third talk was by Dorte Clemmensen and Mikkel Mylius Rasmussen (Aarhus University Hospital) on “Tethered Cord – our first long term results”
This year they presented their first long term survival results on six pigs that underwent either sham surgery (2) or kaolin-induced experimental tethered cord (4). At the point of sacrifice (3 months), magnetic resonance imaging showed what seemed to be an increased longitudinal CSF space due to thinning of the medulla of the induced tethered cord animals when compared to sham. This study supports their view that the model is useful and development of the tethered cord is possible. However, the main goal, to achieve clinical symptoms of tethered cord syndrome, has yet to be accomplished.

After a coffee break, Andrew Baird (UCSD) spoke on behalf of a small network of five research groups that collaborate in hydrocephalus research between San Diego, Providence (Brown University) and the UK (University of Birmingham), on “Can the Power of Zebrafish genetics be exploited to study hydrocephaly and CNS fluid balance?” He discussed their joint efforts to include investigating whether a zebrafish model might help understand the role of factors produced by the choroid plexus and ependyma in hydrocephalus. After describing the many advantages and the significant disadvantages of a fish model, he emphasized that zebrafish have been extensively exploited by developmental biologists to understand the genetic basis for disease and that the results are now widely recognized as relevant to man, within limitations. Zebrasfish can be used to selectively knockdown different genes in vivo including one they are studying called ECRG4 that produces augerin in the choroid plexus epithelium and ependyma.

Knockdown ECRG4 produces a gene-dependent specific hydrocephalus-like phenotype that developmental biologists call CNS “edema”. Because of its low cost, amenability to high throughput experimental analyses and its proven utility as a model for human diseases, the group propose that it should be considered as a complementary – albeit not stand alone – alternative to other animal models of hydrocephalus. If so, they believe it might be possible to ask very basic mechanistic, yet more physiological questions that cannot be addressed using either cells in culture or mammalian models of CNS injury and inflammation.

The next speaker was Alexander Shlyakov (University of Manitoba) who spoke on “Brain biomechanics during acute obstructive hydrocephalus in live rats”. He described how biomechanically, viscoelastic, nonlinear brain can accumulate strain with cyclic loading, in young more than in mature animals. In the normal state, intracranial pressure is maintained by vascular pulsation, and pulsating stress is mitigated by CSF oscillatory exits. In the case of CSF obstruction, due to Pascal’s principles, pulsating stress transmits undiminished to all parts of the enclosed fluid, resulting in a large multiplication of applied forces. CSF is a Newtonian (non compressible) fluid, the brain is viscoelastic, enabling accumulate strain (deformation) with cyclic, pulsating stress. Pulsating stress shrinks brain parenchyma (reducing extracellular space) leads to ventricular enlargement and hydrocephalus.

This talk was followed by Miles Miller (Brown University) who spoke on “A study of human choroid plexus mRNA reveals disease-related changes in gene expression”. To do this human lateral ventricle choroid plexuses from advanced Alzheimer’s disease patients, healthy aged controls, and diseased controls (frontotemporal dementia and Huntington’s disease) were obtained at autopsy. RNA was extracted and amplified, and human Affymetrix 48K gene arrays were utilized to investigate neurodegenerative disease-related changes in choroid plexus gene expression. The gene sets of most significance were separated into four experimental groups, revealing differences in choroid plexus gene expression when comparing the AD samples with both the normal and diseased control groups.

The final talk of the morning was by Mark Luciano and Steve Dombrowski (Cleveland Clinic) who spoke on “Pulsatility and cerebral blood flow in hydrocephalus”. They described how the movement of fluid through the cranial and spinal spaces appears to play a physiological role in cerebral compliance and therefore in blood flow. They suggest that the relationship between CSF flow and pressure pulsatility in altering cerebral blood flow is not clearly understood. In order to study the possible effect of cranial pulsatility on cerebral blood flow, they have developed a novel method and device to control CSF pulse amplitude via a cardiac-gated oscillating bladder which dynamically modulates the CSF space, either accommodating or opposing entering systolic waves of blood. In an experimental model of hydrocephalus, it was possible to either augment or reduce intracranial pressure wave amplitude without affecting systemic conditions. Preliminary findings from this study suggest a relationship between CSF and CBF that may be involved in the underlying pathophysiology of hydrocephalus.

Overall, this was a very interesting session with lively presentations of novel research. Throughout the morning there were many discussions among presenters and audience participants that we hope were beneficial to all present.

INVITED SPEAKER PRESENTATIONS

S3 Hydrocephalus treatment and outcome in African infants with myelomeningocele: what we have learned so far

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We estimate that around 2000 infants in Uganda develop hydrocephalus (HC) each year. Post-infectious hydrocephalus (PIH) accounts for 60% of all cases, and several lines of investigation are underway to determine the pathogens and their mode of transmission. HC associated with myelomeningocele (MMC) is the second most common etiology, accounting for 15% of cases.

Access to treatment for hydrocephalus in Africa is inhibited by poverty, politics, poor infrastructure, and a paucity of neurosurgeons. These also present obstacles to follow up and emergency care for treatment failure, making death from future shunt malfunction a serious enduring threat.

We explored the role of endoscopic treatment for hydrocephalus in African infants, and found that combined endoscopic third ventriculostomy and bilateral choroid plexus cauterization (ETV/CPC) was significantly more successful than ETV alone in those less than one year of age. Infants with myelomeningocele benefitted the most from this approach, with a 76% success rate. In contrast to shunt failure, nearly all ETV/CPC failures become evident within 6 months of surgery. We have demonstrated factors that are independently predictive of ETV/CPC outcome, and have generated a new outcome prediction score (the Uganda Score) that is currently being evaluated across several centers in Africa.

In addition to safety and long-term efficacy of ETV/CPC in the myelomeningocele population, we also demonstrated that those treated in this way performed as well or better on the Bayley Scales of Infant Development over the course of their early childhood development than those who were shunted. Furthermore, we found no correlation between performance and ventricle size. We recently investigated whether the presence of HC or its method of treatment affected 5 year survival in these children, and were surprised to find no difference. Importantly, the most important determinant of survival was involvement in a community-based rehabilitation program. The five year mortality for these children was close to that of their unaffected peers (16%); whereas the mortality for those with no access to such a program was more than triple (50%). Deaths were mostly from causes not directly related to the underlying neurological conditions.

ETV/CPC is a safe and effective alternative to shunt-dependence in children with myelomeningocele. In Africa, any long-term survival advantage of shunt-independence may be obscured by diseases of poverty and neglect. “Life-saving surgery” in these children must be wedded to community-based support programs that promote their access to adequate health care and nutrition.

S4 Biochemistry and genetics of folate metabolism

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Folates serve in many critical one-carbon transfer reactions including nucleotide synthesis, amino acid synthesis and methylation. Methylation is important for gene expression (through methylation of DNA), neurotransmitter synthesis and maintenance of homocysteine (a potentially toxic amino acid) at low levels. Genetic and nutritional
deficiencies in folate metabolism may modulate risk for several complex traits including neural tube defects (NTD) and other birth defects, cardiovascular disease, pregnancy complications and some cancers. Inadequate dietary folate has been recognized as a risk factor in approximately 2/3 of NTD although metabolic disturbances in folate metabolism have emerged more recently as contributors to this common multifactorial disorder. Fortification of food with folate has been established in many countries to reduce the incidence of NTD; although NTD rates have in fact decreased in those countries, there are controversies regarding the impact of food fortification on other folate-related disorders. The first genetic risk factor identified for NTD is a common variant in methylenetetrahydrofolate reductase (MTHFR), the enzyme that synthesizes the primary circulatory form of folate, 5-methyltetrahydrofolate, which is utilized in the remethylation of homocysteine to methionine. This variant, present in the homozygous state in approx. 10% of many European and North American populations, is responsible for a fraction of the folate-responsive NTDs. Other variants in the pathway have been identified and may contribute although additional studies are required. A mouse model for MTHFR deficiency has been useful in studying the biochemical disturbances and mechanisms that could contribute to NTD and other complex traits. The presentation will focus on the impact of genetic polymorphisms/relevant enzymes on NTD risk, the use of mouse models to study mechanisms, and some aspects of the controversy surrounding high folate intake post-fortification.

**ORAL PRESENTATIONS**

**S5**
Role of urodynamics in diagnosing tethered cord in spina bifida patients

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**Background:** The aim of this study was to see how many patients with spina bifida aperta (SBA) had untethering or a myelotomy. In 70 cases secondary TC was suspected, based on a variety of symptoms: visible back anomalies, loss of strength, changes in lower urinary tract function, increase in scoliosis or a combination of these. Patients had a one day check-up by a multidisciplinary team, consisting of neurologist, orthopedic surgeon, neurosurgeon, physical therapist and urologist. Imaging (MRI) and urodynamic studies were done on the same day. At the end of the day the results were evaluated and a decision was made whether or not to operate for TC.

**Results:** 26 patients with SBA had untethering or a myelotomy. 18 patients had neurologic changes: 7 of these patients also had changes in urodynamics. None of the 26 patients had urodynamic changes without neurologic deterioration. This is probably because all spina bifida patients had hydrocephalus. Results: 26 patients with SBA had untethering or a myelotomy. 18 patients had neurologic changes: 7 of these patients also had changes in urodynamics. None of the 26 patients had urodynamic changes without neurologic deterioration. This is probably because all spina bifida patients had hydrocephalus.

**Conclusions:** In a population of 400 SBA patients, 70 patients were seen under the age of 18 years, were followed. In 70 cases secondary TC developed in 8 years time. In this study urodynamics did not contribute to the diagnosis, probably due to the use of antimuscarnics.

**S6**
Spinal dysraphism associated with OEIS complex: aspects of diagnosis and treatment

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**Background:** Associated neurospinal dysraphism in combination with anomalies of the genitourinary tract is well known in children with imperforate anus. There is a broad spectrum of concomitant anomalies with the OEIS Syndrome as the most serious endpoint. OEIS is an acronym for omphalocele, exstrophy (bladder exstrophy/cloacal exstrophy), imperforate anus and spinal defects. At present almost all cases of OEIS are diagnosed prenatally and the patients should be treated at a specialized center with a multidisciplinary team. The complex diagnostic procedures and surgical measures are addressed as well as the difficulties in achieving continence in these patients.

**Materials and methods:** We present data of six patients with imperforate anus and spinal dysraphism (4 with meningomyelecele, two with lipomeningocele) currently managed in the spina bifida clinic of the Children’s Hospital of Cologne. Two of them presenting the complete OEIS syndrome symptoms, another two with cloacal exstrophy without omphalocele and two with major renal malformations. Only two of six patients had hydrocephalus.

**Results:** The often complicated multiple reconstructive surgical procedures in these patients are described (e.g. creation of neo-bladder with catheterizable channel, colostomy, pull-through procedures, closure of omphalocele and neurosurgical procedures). Especially the management of incontinence is extremely complex in these patients. For instance there is no sufficient bladder capacity in patients following initial closure of bladder exstrophy and there is only a weak or no function of the anal sphincter following pull-through procedures.

**Conclusions:** OEIS syndrome is a devastating combination of anomalies resulting in a neurological deficit similar to myelomeningocele. In contrast to the functional problems arising in spina bifida patients, children with OEIS syndrome have functional impairment with additional problems due to the malformed urogenital tract and anorectal system. Management of children with OEIS syndrome demands a careful management plan starting already in the prenatal period and resulting in a life-long surveillance. Treatment of these patients should only be performed by a multidisciplinary team in a specialized center.
Conclusions: With careful preoperative evaluation and urinary work up including 6 months to 1 year prior to the proposed date of surgery, proper CIC training, anticholinergic medication and meticulous augmentation technique, most patients with neurogenic incontinence stand to benefit significantly by augmentation colostoplasty. Easy access to continent channels such as a Mitrofanoff makes CIC a simpler task. We recommend augmentation colostoplasty with adjunct procedures to achieve social continence in patients with neurogenic incontinence.

58 Management of neurogenic bladder in myelodysplasia patients: experience at our center
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Cerebrospinal Fluid Research 2010, 7(Suppl 1):58

Background: Myelodysplasia is the term used for lesions include Spina bifida occulta, lipomeningocele, meningocele and meningomyelocele. Meningomyelocele is by far the most common disease of this group. These patients are commonly having neurogenic bladder. The treatment of neurogenic bladder is not so easy [1]. We are presenting our experience of 68 cases with neurogenic bladders. The aim of our study is to achieve continence and preserve upper urinary tract from further damage. There are a battery of investigations to assess these patients for eg. renal biochemistry, ultrasonography of the urinary tract, Micturating cysto-urethrogram, isotope renal scans, Clinical and bedside assessment, and Urodynamics. Treatment options available for these patients are drug therapy in the form of prophylactic antibiotics and anticholinergic drugs. Clean intermittent catheterization advocated by Lapides plays major role in the treatment of these patients [2]. Operative procedure perform in these patients are bladder neck reconstructions like, Yeong Dees Leadbetter and rectus sling [3]. High pressure bladder can be converted to low pressure bladder by using bladder augmentation procedures. Bladder augmentation procedures are increasing bladder capacity also thus improving dry intervals. Continent urinary diversion can be done by using appendix [4] and segment of ileum [5]. Once these patients achieve social or urinary continence follow up is very important.

Material and methods: We at our center in India have evaluated 68 patients of spinal dysraphism following standard protocols. Out of these 68 patients 45 were having upper urinary incontinence. 34 patients were advised CIC and oxybutynin from second months onward. Nine patients underwent continent urinary diversion using Mitrofanoff’s (8 patients) and Monti’s 1 principle. Two patients underwent rectus sling bladder neck suspension and now on CIC.

Patients who underwent continent urinary diversion are doing well and maintaining good dry intervals. One patient who underwent Mitrofanoff’s procedure developed post-operative necrosis of the ileal patch along with appendix due to severe lordosis. 6 patients are totally dry, and one patient developed post-operative wound infection. The upper tract of these patients is okay, but long term follow up will be required to draw further outcome.

Conclusions: Proper assessment and appropriate medical and surgical intervention is must to achieve continence in neurogenic bladder patients.

References

S9 Spina bifida occulta in children: presentation and outcome
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Background: Occult spinal dysraphism (OSD) encompasses a wide spectrum of congenital anomalies. Since OSD can lead to irreversible neurological, urological and orthopedic dysfunction, early diagnosis and treatment is necessary. In this study we evaluated a selected cohort of patients with OSD with regard to presenting symptoms and clinical outcome. The main purpose of this project is to develop clinical guidelines for this condition.

Materials and methods: We retrospectively reviewed the medical records of all children with OSD referred to University Hospital Uppsala during the period 2000-2008. Fifty-six children (22 males and 34 females) aged from 3 days to 16 years were identified having OSD. All had MR scans carried out. The median observation time was 11 years.

Results: The first sign of neurological dysfunction was noticed at the median age of 2 years. The symptoms included deformities of feet, bladder dysfunction and gait disturbance. Retrospectively, cutaneous lesions in the back were found in 43 children. The MR scans demonstrated in all children various congenital anomalies such as diastematomyelia or lipomyelomeningocele. During the follow-up period deterioration was seen in approximately half of the patients. Twenty-eight children underwent detethering operation. Despite this operation the symptoms of eight of these children progressed. At follow-up at the median age of 11 years 38 children had clinical signs and symptoms of neurological dysfunction whereas 19 children had severe persistent symptoms.

Conclusions: In this study one third of the children with OSD developed persistent severe symptoms of neurological dysfunction. It is highly important to detect these lesions before the occurrence of neurological or urological manifestations. Urinary incontinence is often the first clinical symptom, but can be difficult to evaluate when the child is very young.

S10 Desmopressin in the treatment of nocturnal enuresis in patients with spina bifida
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Background: It was observed that some of our patients with spina bifida (SB) that became dry during daytime still suffered urine loss during the night. It was difficult to wake them up. It seemed that they suffered from normal nocturnal enuresis (NE).

Materials and methods: Of 241 SB patients that are in yearly follow-up in our institution, 203 patients were 5 years or older and 13 of them seemed to have true NE. These 13 patients were all treated with Desmopressin 0,4 mg ante noctem.

Results: Thirteen patients, 5 males and 8 females were treated with Desmopressin and they were evaluated. Nine patients were operated beforehand: 8 patients were treated with a bladder augmentation and bladder neck sling suspension and one boy had an urethral valve resection. All 13 patients were dry during daytime and 3 of them even did not need antimuscarnic agents. All 13 patients had normal kidney function and urodynamic studies showed compliant bladders without obstructive contractions. During nighttime however they wetted their beds. Desmopressin (0,4 mg a.n.) was successful in 12 patients: they became completely dry during the night. One of them however relapsed and he will be treated with an alarm clock system as an adjuvant therapy.

Conclusions: Until now NE was not recognised as a possible cause of nocturnal urine loss in SB patients because the incontinence was
considered to be caused by overactive neuropathic bladder behaviour. Desmopressin as a monotherapy was successful in 11/13 SB patients with recognised NE.

S11 Evaluation of prenatal diagnosis of isolated ventriculomegaly
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Cerebrospinal Fluid Research 2010; 7(Suppl 1):S11
Background: The prenatal management of hydrocephalus with myelomeningcele(MMC) has been established in recent years. However, other types of fetal hydrocephalus so called isolated ventriculomegaly show wide heterogeneity in prognosis, as various diseases are included. For the proper counselling, it is very important to clarify this entity.

Materials and methods: Our objective is to evaluate how to estimate the appropriate clinical outcome prenatally in isolated ventriculomegaly.
Method Retrospective study, single institute (Osaka National Hospital) Materials One hundred and seventeen cases with fetal hydrocephalus were treated at Osaka National Hospital from 1992 to 2010. As 35 cases with MMC and fetal brain tumor are excluded, 82 cases were selected for this study.
Results: Final diagnosis was as still isolated ventriculomegaly in 30 cases. Other anomaly are detected in 19cases(X-linked hydrocephalus in5, atresia of Monro in 2, corpus callosum agenesis in 3, lissencephaly in 2, other type of hereditary hydrocephalus in 2, chromosomal anomaly in 4 and a EEC syndrome). Final diagnosis were categorized in secondary hydrocephalus in 9 cases (virus infection in 2 and fetal intracranial hemorrhage in7) and 24 cases are diagnosed as other type of malformation( holoprosencephaly in 4 ,Dandy Walker syndrome in 3 cases, Jobert syndrome in a case, arachnoid cyst in 9 cases and encephalcele in 7cases). With exclusion of 6 aborted cases and fourteen unknown cases due to too young to evaluate or lost of follow-up, final outcome are analyzed in 62 cases. Of 62cases, 11% was dead in utero or after birth, 26% showed severe retardation, 11% moderately retarded, 16% mild retarded, and 35% of case showed good outcome.
Conclusions: For the accurate counselling to detect accompanied anomaly, fetal sonography by expert obstetricians, fetal MRI,TORCH screening test were useful for the final diagnosis. Prospective and retrospective studies to evaluate prenatal detections by using several kinds of tools and long term outcome in isolated ventriculomegaly is required.

S12 Direct control of CSF pulsatility and its effect on CBF: initial findings using a novel method and device
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Cerebrospinal Fluid Research 2010; 7(Suppl 1):S12
Background: Over the past several years, there has been new emerging and overlapping fields of research investigating CSF pressure and flow pulsality (CSFP), and cerebral blood flow (CBF). It is not known whether CSFP is merely a passive epiphenomena or alternatively, plays a physiologically significant role in cerebral compliance and blood flow. Thus, the relationship between CSFP and CBF is not clearly understood. In order to study the effect of CSFP on blood flow, we have developed a novel method and device for controlling (i.e., reducing or augmenting) pulsatility.

Materials and methods: In 15 canine subjects, a small (0.3-3.0cc), custom-made polyurethane bladder was surgically implanted in either the cranial or spinal epidural space such that it would alter the underlying CSF space. CSFP were controlled via an oscillating air pump gated to the cardiac cycle timed to deflate (ICP reduction) or inflate (ICP augmentation) during systole. Measures for ICP (fiberoptic probes) and CBF (laser-Doppler and thermal diffusion probes, microsphere injection, and SPECT-Tc-99) were obtained intra-operatively under different acute and chronic conditions.
Results: CSFP reduction or augmentation was successfully achieved via cardiac-gated oscillation of a bladder device. Alteration of CIP-waveform was global and measured remotely on the contralateral side and with device activation in the spinal space. Under specific inflation cycles and physiological conditions, operation of the system increased CBF up to 15 mL/min*100gm, or by as much as 40%. Mean systemic pressure, cardiac output, and mean ICP did not significantly change with system activation.
Conclusions: We have developed a method of altering CSFP pressure pulsatility using cardiac-gated oscillating bladder which dynamically alters CSF space volume. The ability of the system to increase CBF without affecting cerebral perfusion pressure (MAP or ICP) suggests it may work through alteration of cerebrovascular compliance and impedance. Understanding the effect of CSFP on cranial compliance may ultimately allow a new therapy for increasing blood flow in acute and chronic states, including hydrocephalus, where CBF and CSFP are abnormal.
Competing interests: SMD, MGL serve as Scientific Advisors for CSF Therapeutics, Inc.
patients who are symptomatic, reconstruction of the subarachnoid space by extensive supratentorial cranial expansion may be effective based on relief of transtentorial brain shifts and consequent venous congestion.

S14 Ventriculoperitoneal shunt after previous endoscopic third ventriculostomy: does ETV improve shunt survival?
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Background: Endoscopic Third Ventriculostomy (ETV) has been used as an alternative to Ventriculoperitoneal Shunt (VPS), but some patients “fail” ETV and subsequently require VPS insertion. However, little is known about the subsequent need for shunt revision in these patients. The current study aims to determine if there is a difference in shunt failure rates in patients who have had previous ETV, as compared with patients who have never had previous ETV.

Materials and methods: A case-control study was performed. We identified all patients treated with ETV at our institution who subsequently required VPS. Control subjects were selected, matched for age and hydrocephalus etiology. A survival analysis was performed for the VPS, to determine if there was any difference in shunt survival in ETV patients vs. non-ETV patients.

Results: We identified 17 patients with “failed” ETV who went on to require VPS, and selected 34 control subjects. Age and hydrocephalus etiology were similar in the case and control groups. There were 8 deaths (3 in the ETV group and 5 the non-ETV group), generally in brain tumor patients, and these cases were excluded. Of 14 ETV patients, 71% (10 patients) never required a subsequent revision (mean follow-up 5.9 years), and 29% (4 patients) required revisions (mean time to first revision was 1.5 years). In 29 control subjects, 34% (10 patients) never required subsequent revision (mean follow-up 8.9 years), and 66% required revisions (mean time to first revision was 1.5 years). The shunt after ETV was significantly more likely to survive (p=0.023) than the shunt in the non-ETV group.

Conclusions: VPS in patients with previous “failed” ETV appear to have better survival than VPS in patients who have never had ETV. This has interesting implications in considering the potential benefit of ETV, even when a VPS is subsequently necessary.

S15 Multiple surgeries in paediatric patients with myelomeningocele. Can we define quantitative and qualitative evolution patterns according to the level of spinal lesion?
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Cerebrospinal Fluid Research 2010. 7(Suppl 1):S15

Background: Children with myelomeningocele are usually submitted to multiple surgeries, since first days of life to late adolescence, with long stays in hospital and family life disruption. However the number and type of surgeries are not the same in every child with myelomeningocele across the time and from child to child. We have attempted to define a pattern of surgeries in patients with myelomeningocele and Chiari II malformation across the time (0-18 years), according to the spinal level.

Materials and methods: Data of all patients with myelomeningocele, followed actually in our centre, were analysed retrospectively. The inclusion criteria were: child with both myelomeningocele and Chiari II malformation, aged 0-18 years, alive and observed during 2009. The factors analysed were: date of birth, sex, spinal level, Chiari II malformations with and without shunt and the number and type of surgical interventions. The spinal level was classified in thoracic, upper lumbar level, lower lumbar level and sacral using "The International Myelodyplasia Study Group” criteria for assigning motor level. Three age groups were considered: 0-5 years; 6-12 years; 13-18 years. We analysed the associations across the time between the frequency of each type of surgical intervention (neurosurgical, orthopaedic, urinary and ulcers repair) and the level of motor involvement. Statistical analysis was done using the statistical package SPSS.

Results: From a total of 153 patients with neural tube defects, 72 fulfilled the inclusion criteria, 57 with shunt (all but one ventriculoperitoneal) and 15 with arrested hydrocephalus. The median of ages was 10 years. Neurosurgical interventions predominated in the first five years of life, mostly in patients with shunts, with no relation to cord level. Orthopaedic surgeries were more frequent in the second age group (6-12 years) and in those with upper lumbar level lesions. Urological surgeries were done mainly in the 6-12 years group with lower lumbar level impairment. Surgical repair of ulcers were more frequent in ambulant adolescents (lower lumbar and sacral levels).

Conclusions: The construction of an evolution pattern of the type and frequency of surgeries across lifespan of an important subgroup of children born with Spina Bifida and its relation with the spinal level, can be challenging for the comparison of Spina Bifida populations from different centres. Methodologies of treatment and results could be better compared among centres by benchmarking of best practices.

S16 Congenital myelomeningocele – do we have to change our management?
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Cerebrospinal Fluid Research 2010. 7(Suppl 1):S16

Background: Eagerly awaiting the results of the Management of Myelomeningocele Study (MOMS) with an increasing interest in setting up intrauterine myelomeningocele repair (IUMR), the optimal management of patients suffering from congenital myelomeningocele (MMC) has become a matter of debate again. We performed a cross-sectional study at our referral-center for MMC to compare the outcomes of our expectantly managed patients with the results of IUMR and historical controls on which the MOMS trial has been based on.

Materials and methods: A computed chart review revealed 71 patients suffering from spina bifida. Of those, 10 have been lost for follow-up and 2 were excluded because they had undergone IUMR. A retrospective analysis was performed only in patients that underwent MMC repair within the first two days of life and were seen at our outpatient clinic between 2008 and 2009 for a regular interdisciplinary follow-up. Data were collected on: gestational age (GA) and weight at birth, shunt status at the first year of life and age at shunt placement, radiological presence of Arnold-chiari II malformation (ACMII) and tethered cord (TC), bladder function, lower leg function and educational level. Data were compared to published results for IUMR and historical controls [1,2]. Data are given in percent or mean (standard deviation).

Results: We analyzed the data of 43 patients born with mainly lumbar sacral MMCs between 1979 and 2009 that are now 13.3 (8.9) years of age. At birth, mean GA was 264.5 (16.3) days and mean weight was 2921.3 (760.3) g, both significantly than in IUMR patients. 69.8 % required a shunt placement at a mean age of 16.0 (10.7) days, which was significantly better than historical controls. In 57.1 % an ACMII and in 41.9% a TC was observed radiologically. Only two patients underwent a surgical correction for TC. 69.7% of the patients perform clean intermittent catheterization. 56.4% are (assistant) walkers and 64.1% attend regular classes, both comparable to historical controls.

Conclusions: With a close and interdisciplinary management by pediatric surgeons, neurologists and urologists, long-term outcomes of patients suffering from MMC can currently be considered satisfying. With respect to the known drawbacks of fetal interventions for mother and child, especially preterm delivery, the results of the MOMS trial should be awaited with caution before jumping on a complex intervention like IUMR.
S17

Is it possible to use specific IgE to single latex allergens to discriminate between spina patients with natural rubber latex allergy and sensitization?

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Cerebrospinal Fluid Research 2010, 7(Suppl 1):517

Background: Eleven characterized allergens of Hevea brasiliensis are available as recombinant proteins for in vitro IgE diagnosis. Hb b 2 and Hb b 13 are only suitable as native proteins. By testing patient sera against this panel of recombinant and native allergens of Hevea brasiliensis individual sensitization profiles and the relevance of single allergens can be assessed.

Materials and methods: Sera of 30 spina bifida patients with specific IgE to NRL were tested for allergen-specific IgE antibodies (sIgE) to natural rubber latex (NRL) and 13 single Hb b allergens using the ImmunoCAP system. The results of the specific IgE values against single allergens were plotted (frequency of antibodies against the single allergen vs. the percentage of the total latex-specific IgE-response). Minor and major allergens for spina bifida patients sensitized or allergic against NRL could be identified.

Results: Regarding all 30 spina bifida patients with sIgE Hb b 1, 2, 3, 5, 6.01 and 13 were identified as major Hb b allergens. In the patients without latex-related symptoms Hb b 2 and Hb b 6.01 were found only in small percentages of the latex-specific IgE response and low frequencies (minor allergens) whereas in patients with latex-related symptoms these allergens were found in high concentrations and frequencies. Hb b 5 represents the allergen with the highest percentage of the latex specific IgE response in all groups of patients, Hb b 1 is the allergen with the highest frequency of sensitization (about 80%) in all groups.

Conclusions: Latex extracts for skin prick testing or in vitro allergosorbents should contain the major allergens Hb b 1, 2, 3, 5, 6.01 and 13. In spina bifida patients Hb b 6.01 and Hb b 2 could be useful to distinguish sensitized from allergic patients.

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S18

Does fetal endoscopic closure of the myelomeningocele prevent loss of neurologic function in spina bifida aperta?

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Cerebrospinal Fluid Research 2010, 7(Suppl 1):518

Background: Spina bifida aperta (SBA) is associated with shunt-dependent hydrocephalus and with meningomyelocele (MMC). Fetal endoscopic closure of the MMC may reduce shunt-dependency, but the benefit upon motor function in individual patients is still unclear.

Methods: In a matched-pair study between SBA children treated by fetal endoscopic closure (fSBA) and by neonatal closure (nSBA) of the MMC, the effect of intrauterine repair on the incidence of shunt-dependent hydrocephalus was assessed. Results: Among 42 SBA children treated in the study period (2006-2009), 22 were treated by fSBA and 20 by nSBA. All 22 fSBA patients were delivered by caesarean section, all 12 nSBA patients by vaginal delivery. To compensate for the effect by delivery mode, we also compared separate (age- and level of MMC-) matched pairs of SBA children born by caesarean section (nSBA-SC; n=13) and by vaginal delivery (nSBA-VD; n=13). Neurological parameters consisted of dMUD (defined as: [MUD caudal to the MMC] minus [MUD cranial to the MMC]); motor- and sensory function and shunt-dependent hydrocephalus and Chiari-II (C-II) malformation. fSBA and nSBA patients were treated at Bonn and Groningen/Cologne, respectively.

Results: dMUD was significantly lower in fSBA than in nSBA [15 (-9 to 68) vs. 22 (-1 to 13)] and in control fetuses (median gestational ages 37 and 40 weeks, respectively) [p<0.05]. Assessment of motor and sensory function indicated a lower segmental spinal function in fSBA than in nSBA [p<0.05]. Shunt-dependent hydrocephalus appeared less frequent in fSBA than in nSBA [4/12 vs. 11/12; p<0.05], whereas the incidence of C-II malformation did not significantly differ between fSBA and nSBA [10/12 vs. 12/12, respectively]. Comparing the neurological parameters between nSBA-SC and nSBA-VD revealed no significant differences.

Conclusions: Assessment of dMUD and neurological function in fSBA and nSBA children indicates a moderately improved neuromuscular outcome in fSBA. It remains to be established by long-term functional and cognitive outcome parameters to determine whether the suggested neurological benefit is maintained and outweighs the risks of iatrogenic complications by the fetal endoscopic surgery.
formation of rosettes and macrophage invasion); and (IV) completed ependymal denudation (with astroglial reaction).

Conclusions: In full-term SBA fetuses, intra-individual concurrence of imminent, ongoing and completed ependymal denudation implicates that ependymal denudation would continue after birth. At the areas associated with imminent ependymal denudation, the abnormal expression of junction proteins suggests that abnormal formation of gap and adherent junctions precedes defective ependymal coupling, desynchronized ciliary beating, ependymal denudation and hydrocephalus.

S20 Submicroscopic chromosome abnormalities associated with spina bifida (myelomeningocele)
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Cerebrospinal Fluid Research 2010. 7(Suppl 1):S20

Background: Visible chromosome abnormalities have been commonly reported in patients with spina bifida (myelomeningocele), particularly when associated with other malformations. Newer technologies such as array comparative genomic hybridization (CGH) have made it possible to identify smaller (submicroscopic) DNA deletions/duplications, also referred to as copy number variants (CNVs). Submicroscopic CNVs have been identified as the cause of a variety of disorders, substantially increasing the diagnostic yield in patients with intellectual disability and multiple congenital malformations. Submicroscopic CNVs have not been commonly reported in patients with spina bifida, but given the high frequency of visible chromosome rearrangements, we hypothesize that submicroscopic CNVs also contribute to the genetic etiology of spina bifida.

Materials and methods: We reviewed all array CGH results at a single children’s hospital laboratory for which neural tube defect was included in the indication for the test. During 2007–2009, array CGH was performed by the laboratory on a total of 1988 patients.

Results: Fourteen patients with spina bifida were evaluated by array CGH during the study period. CNVs were identified in two patients: 1) A 14 year old male with thoracoscopic myelomeningocele, diastematomyelia, shunted hydrocephalus, bilateral clubfoot, bilateral subependymal heterotopias, bilateral closed-lip schizencephaly, seizures and polyarticular juvenile rheumatoid arthritis, had normal high-resolution karyotype (550-650 band), but array CGH revealed a 1.3 Mb interstitial deletion in 16p13.11. Of note, the patient’s brother has Gorlin syndrome, but no neural tube defect, and carries the same deletion. Parents have not been tested. 16p13.11 deletion has been reported in patients with autism, intellectual disability, epilepsy, holoprosencephaly and other malformations, but also in a few phenotypically normal individuals. 2) A 14 year old female with thoracic myelomeningocele, shunted hydrocephalus, bilateral hearing loss and caudal regression with imperforate anus had a normal high-resolution karyotype (600-650 band), but array CGH revealed a 0.4-2.1 Mb duplication in 15q13.3. Mutter does not carry the duplication, father has not been tested and a 17 year old sister with learning disabilities and ADHD has not been tested. 15q13.3 duplication has been reported in patients with intellectual disability, autistic behaviors and dysmorphic features.

Conclusions: Newer technologies for detecting smaller chromosome abnormalities may identify the cause of spina bifida in a proportion of patients. We hypothesize that atypical presentation may be associated with increased risk of an underlying CNV. Larger studies are required to determine the prevalence of CNVs in patients with spina bifida and whether patients with CNVs display atypical clinical features.

S21 Dysfunction of the antisiphon device, SiphonGuard, due to rupture of the shell
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Cerebrospinal Fluid Research 2010. 7(Suppl 1):S21

Background: Codman Hakim programmable valves are used in treating hydrocephalic children in many countries. To prevent or treat over drainage with slit ventricle syndrome an antisiphon device (ASD) can be added. The ASD can be included in the valve or separate as the SiphonGuard.

Materials and methods: A hydrocephalic boy shunted with a programmable Codman Hakim valve and a SiphonGuard has had two episodes of shunt dysfunction. The reasons were rupture of the ASD shell, which was difficult to detect. The medical records and x-rays were investigated.

Results: At the first episode the boy was irritated and developed a minor swelling around the valve and the ASD. No disconnection of the shunt system was found at the plain x-ray. The symptoms accelerated and the boy was sent to a neurosurgical department for further investigation. A new plain x-ray verified the defect ASD even notable at the first investigation. At the second episode the symptoms were diffuse with variations in severity. Investigations showed no disconnection and normal CT scan. At the subsequent follow up, the symptoms became more pronounced especially in the mornings and a mild papilloedema was found. The valve was easy to press and filled quickly, why another follow up after adjusting to a lower opening pressure was recommended. At this follow up papilloedema with a little hemorrhage in the optic disc and a slight change in sensation at testing the valve was noticed. Exploration was decided and a rupture of the ASD shell was found. When aware of it, it was detectable on previous plain x-ray even if the picture was not perfect.

Conclusions: In children with symptoms of shunt dysfunction it is important to have a plain X-ray of the whole shunt system, appropriate projections and be aware of how it should look, to be able to detect a defect SiphonGuard.
conditions in the past year: skin breakdown (43%); overweight (37%), pain (47%); or scoliosis (40%). 64% had UTIs in past 3 years. 19-41% of participants reported these secondary conditions interfered with school, job or recreation with pain having the highest interference and overweight the least. The average AYA needs some assistance with bladder/bowel program and has accidents (1-2 or less a month). Parent and AYA satisfaction with bladder program was not associated with amount of assistance needed nor LOL but was related to number of bladder accidents \(=39.29\) respectively. The same pattern was found with satisfaction with bowel program.

Conclusions: Parents report a substantial number of AYA with at least one secondary condition. Pain appears to interfere most with activities and overweight the least. Prevention and effective treatment of secondary physical conditions are important for full participation in society.

Acknowledgment: This study was funded by the Association for University Centers on Disabilities.

S24

Testing a model of adaptation in adolescents and young adults (AYA) with spina bifida (SB)

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Background: Little is known about physical health (PH), mental health (MH) and health-related quality of life (HRQOL) adaptation outcomes in AYA with SB, and the factors associated with them. The purpose of this presentation is to 1) describe the PH (functional status [FS], self-management, secondary conditions), MH (depression, overall self-worth, and internal/external behavior problems [IBP, EBP]), and HRQOL outcomes; and 2) delineate the direct and indirect relationships of risk and protective variables in the Ecological Model of Secondary Conditions and Adaptation in SB associated with these outcomes. This model includes SB Context (SES, shunt status and level of lesion [LOL]), neuropsychological risk (NPR), and protective processes (adolescent resilience and family resourcefulness).

Material and methods: This is an interdisciplinary descriptive cross-sectional study. AYA were between 12-25 years of age and from 4 clinical programs in the USA. They had no other major medical condition, no mental retardation, were English speaking and functioned at approximately grade levels. Parent and AYA report of PH and MH and AYA report of HRQOL outcomes were included. Study measures had reliability and validity data and most had been used in our previous studies. Structural Equation Modelling (SEM) analyses were used to assess the model.

Results: Mean parent and AYA basic functional status scores reflect need for supervision; self-management reflects need for substantial assistance. Mean parental report of IBP are higher than EBP and both are in the normative range. However, 13-18% of parent or AYA reports of AYA depressive symptoms were in the clinically significant range.

Self-worth and HRQOL were both moderately high. Three SEM analyses revealed different predictive patterns for PH, MH, and HRQOL constructs. In the PH model only LOL was significantly related to FS. NPR mediated the impact of shunt status and LOL on self-management, and age, NPR, and functional status had direct relationships to self-management. In the MH model, SES and family resourcefulness had indirect paths to MH; whereas AYA resilience, secondary conditions, and age had direct paths to MH. In the HRQOL model SES, age, and family resourcefulness had indirect paths to HRQOL through AYA resilience and MH; whereas AYA resilience and MH had direct paths.

Conclusions: Different direct and indirect relationships of the conceptual framework variables were identified for the three outcomes. Clinical interventions should be differentiated by outcome and targeted to risk and protective variables.

S25

Knowledge on and intake of Folic acid supplementation in pregnant women in Denmark

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Background: Folic acid (FA) deficiency is related to neural tube defects (NTDs). In a non risk pregnancy The Danish National Board of Health
recommends a FA supplementation from planned pregnancy until 3 month after conception. We looked into pregnant women’s knowledge about and actual supplementation of FA and related this to education, number of pregnancies and age.

**Materials and methods:** Eighty four consecutive pregnant women with a midwife consultation were included from the 25th - 28th of August 2008. All filled out a unified questionnaire.

**Results:** 82% had knowledge of FA supplementation and 89% had a FA supplementation. 51% followed national recommendations. We found statistically significant correlation between higher educational level and knowledge about FA supplementation, actual supplementation of FA and FA supplementation in correlation with national recommendations. No statistical relations were found between number of pregnancies or age and FA related parameters. Family, friends, general practitioner (GP) and the internet were main information sources.

**Conclusions:** Correct FA supplementation is quite low, correspondingly ambulation scale. We developed a 'In relation to EuroQol, patients referred no problems in walking

Graduates of up to 10 years (1999-2008) from 2010, between higher educational level and

physical and financial

phalus, spinal surgery, faecal and

included from the 25th - 28th of August

Cerebrospinal Fluid Research

questionnaire with 15 secondary conditions associated with SB, which had

urological reeducation and Hoffer

neurological level, shunted hydroce

Myelomeningocele (MMC), Meningocele, Sacral anomalies associated with

MMC and Meningocele regularly controlled in our interdisciplinary SB Unit

with normal or borderline intelligence quotient (IQ). We collected the data

from the medical history and performed an interview with each patient

included in this study. The medical data included diagnosis, functional

neurological level, shunted hydrocephalus, spinal surgery, faecal and

urological reeducation and Hoffer amputation scale. We developed a questionnaire with 15 secondary conditions associated with SB, which had to be filled in order of importance by all patients. In order to measure their health outcome we administered the EuroQol and the HRQL.

**Results:** In relation to EuroQol, patients referred no problems in walking about (35.7%), self-care (72.9%), usual activities (64.1%), pain (64.3%) and anxiety/depression (81.4%). Mean EQ VAS in the EuroQol and HRQL were 66.30 and 196.63 respectively. A higher EQ VAS in the EuroQol was found statistically associated with having boyfriend/girlfriend (p=0.017), and not having some of the conditions of the personal questionnaire such as obesity (p=0.008), urinary infections (p=0.004), and scoliosis (p=0.014). A higher score in the HRQL was associated with a better faecal reeducation (p=0.046), gait level (p=0.043), use of gait aids (p=0.017), family economic level (p=0.020), mobility, self-care, and usual activities. A lower score in the HRQL was related to had undergone spine surgery (p=0.016), having anxiety/depression (p=0.000), and having some of the conditions of the personal questionnaire such as pressure ulcers (p=0.010), and low self-esteem (p=0.024). In the regression model, determinant factors of having worse quality of life measured with EQ VAS were anxiety/depression, obesity, having boyfriend/girlfriend, and urinary infection. Determinant factors of having worse quality of life measured with HRQL were self-care, anxiety/depression, IQ and low self-esteem.

**Conclusions:** Almost two thirds of the series referred no problems in the health outcome. The determinants factors related to young SB patients personal perception of quality of life are not those related to disability.

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**S26 Measuring health outcome in young adults with spina bifida**

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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S26

**Background:** Most young adults with spina bifida (SB) face various impairments and activity limitations and decreased community acceptance which may affect their quality of life and confront young SB patients with additional barriers in the transition from adolescence to adulthood compared to their typically developing peers.

**Materials and methods:** We conducted a cross sectional study in 70 adult patients born between 1982 and 1989 with the diagnosis of Myelomeningocele (MMC), Meningocele, Sacral anomalies associated with MMC and Meningocele regularly controlled in our interdisciplinary SB Unit with normal or borderline intelligence quotient (IQ). We collected the data from the medical history and performed an interview with each patient included in this study. The medical data included diagnosis, functional neurological level, shunted hydrocephalus, spinal surgery, faecal and urological reeducation and Hoffer amputation scale. We developed a questionnaire with 15 secondary conditions associated with SB, which had to be filled in order of importance by all patients. In order to measure their health outcome we administered the EuroQol and the HRQL.

**Results:** In relation to EuroQol, patients referred no problems in walking about (35.7%), self-care (72.9%), usual activities (64.1%), pain (64.3%) and anxiety/depression (81.4%). Mean EQ VAS in the EuroQol and HRQL were 66.30 and 196.63 respectively. A higher EQ VAS in the EuroQol was found statistically associated with having boyfriend/girlfriend (p=0.017), and not having some of the conditions of the personal questionnaire such as obesity (p=0.008), urinary infections (p=0.004), and scoliosis (p=0.014). A higher score in the HRQL was associated with a better faecal reeducation (p=0.046), gait level (p=0.043), use of gait aids (p=0.017), family economic level (p=0.020), mobility, self-care, and usual activities. A lower score in the HRQL was related to had undergone spine surgery (p=0.016), having anxiety/depression (p=0.000), and having some of the conditions of the personal questionnaire such as pressure ulcers (p=0.010), and low self-esteem (p=0.024). In the regression model, determinant factors of having worse quality of life measured with EQ VAS were anxiety/depression, obesity, having boyfriend/girlfriend, and urinary infection. Determinant factors of having worse quality of life measured with HRQL were self-care, anxiety/depression, IQ and low self-esteem.

**Conclusions:** Almost two thirds of the series referred no problems in the health outcome. The determinants factors related to young SB patients personal perception of quality of life are not those related to disability.

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**S27 Evaluating functional and health outcomes for patients with spina bifida 5 and 10 years post-transition into adult care**

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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S27

**Background:** In BC, pediatric patients with spina bifida are followed by a multidisciplinary clinic at BC Children’s Hospital. Upon graduation, patients transition into the adult healthcare system where they must coordinate their own care. The purpose of this study is to determine the functional and health outcome of graduates transitioning from the spina bifida clinic at BC Children’s Hospital.

**Materials and methods:** Graduates of up to 10 years (1999-2008) from the pediatric spina bifida clinic were mailed a questionnaire. It consisted of 11 sections, including two standardized questionnaires on quality of life (QOL), the Medical Outcomes Study 36-item short-form (SF-36) and Spina Bifida-specific Health Related QOL (SBHRQOL).

**Results:** 113 graduates were identified; 19 were lost to follow-up. 27 (29%) questionnaires were returned. 96% graduated from high school; 63% went on to post-secondary education. 30% had never been employed. 85% lived with parents. 48% had never been in a relationship. 81% were satisfied with their present bowel care; 38% were always clean and 15% had no bowel control. 85% were satisfied with their present bladder care; 22% were always dry and 11% had no bladder control. 19% voided independently and 78% self-catheterized. The wheelchair (38%) was most commonly used for community ambulation. 74% drove or utilized public transit. 93% were satisfied with life in general. The SF-36 physical function domain had the lowest average score (56/100). SBHRQOL mean score was 191. Overall, 89% were satisfied with their ambulation. 96% were satisfied with the care from the pediatric clinic; 52% were satisfied with their adult care. 96% of patients had a family physician; of these, 61% felt that their physician understood spina bifida.

**Conclusions:** Health and functional outcomes may indicate the level of independence of adults living with spina bifida. Physical and financial dependence may limit these graduates from full independence. Most patients completed high school; fewer pursued higher education. Many patients demonstrated independence in the community by driving or using transit. Although largely satisfied with their bladder and bowel function, patients continued to have episodes of incontinence. Bladder function was mostly managed by self-catheterization. Overall, the majority of patients were satisfied with life in general, however, our results suggest that more physical support is required for adult graduates. Our results show that fewer adults were satisfied with adult care than in the pediatric clinic; this may result from a perception that their adult healthcare providers inadequately understood spina bifida.

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**S28 A Comparison of parenting stress between mothers of children with spina bifida and able-bodied controls**

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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S28

**Background:** To compare parenting stress between mothers of children with spina bifida and mothers of able-bodied controls, and to explore factors other than the disease that moderate stress.

**Materials and methods:** 81 mothers of children with spina bifida and 69 mothers of children with acute, non-disabling illnesses aged 1-18 years completed the Parenting Stress Index Short Form (PSI/SF) and General Health Questionnaire-12 (GHQ). Each child’s adaptive skills was assessed using the Vineland Adaptive Behaviour Scales (VABS). Medical and sociodemographic data were collected from a combination of case notes’ reviews and direct interviews. Multiple regression analysis was used to determine factors related to Parental Distress (PD), Parent-Child
Dysfunctional Interaction (P-CDI) and Difficult Child (DC) sub domains of the PSI.

Results: Compared to controls, mothers of children with spina bifida had lower educational levels and were more likely to be the main caregiver and not working. They also had significantly higher mean scores for the GHQ. Total PSI/SF and the PD (Parent Domain), DC (Difficult Child) and P-CDI (Parent-Child Dysfunctional Interaction) sub scales. Children with spina bifida had lower VABS scores, indicating poorer adaptive skills, than controls. Single parent status, having a child with spina bifida and higher Life Stress scores were associated with higher PD scores. Single parent status, higher Life stress and GHQ scores were associated with higher DC scores. The only factor associated with higher P-CDI scores was lower VABS scores.

Conclusions: Factors such as life stress events, single parent status, maternal mental health status and the child’s adaptive skills appear to moderate the impact of spina bifida on various aspects of parenting stress.

S29
Long-term effects of arterial hypertension on the choroid plexus, blood to cerebrospinal fluid barrier and CSF proteins and their involvement in certain types of dementia

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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S29

Background: The correlation of hypertension with vascular dementia has long been established and it is becoming increasingly clear that hypertension is also a reversible risk factor in the development of Alzheimer’s dementia (AD). Aging, AD and hypertension are major determinants of cognitive dysfunction which are associated with profound alterations in the structure and function of cerebral blood vessels. The aim of the present work is to analyze cerebrovascular blood flow in the middle cerebral artery (MCA), the integrity of blood to CSF barrier (BCB), choroid plexus (CP) structure and protein secretion as well as cerebrospinal fluid (CSF) protein composition.

Materials and methods: Choroid plexus (CP) structure, CSF and serum from hypertensive (SHR) and control (WKY) rats of 8, 26 and 52 weeks of age were used. Blood flow was measured by transcranial Doppler sonography on MCA. Brain sections containing CP were processed by immunohistochemistry using antibodies against transhyretin (TTR), caspase-3 (CAS-3), proliferating cell nuclear antigen (PCNA) and immunoglobulin G (IGG). CSF from 26 weeks of age was used by 2D electrophoresis and western-blot.

Results: CP immunohistochemistry: TTR increased during aging in SHR with respect to WKY. CAS-3 was undetectable at 8 weeks in SHR and at 8 and 26 weeks in WKY, at 26 weeks the SHR showed a slight reaction which was increased at 52 weeks of age, a soft reaction was also observed at 52 weeks in WKY rats, SHR also expressed a significant number of cells marked by CAS-3. PCNA results were similar to CAS-3; IGG was mainly expressed in the basolateral membrane of the CP and in CP cells at 52 weeks of age in SHR. 2D electrophoresis and Western-blot: By 2D, we found differences in the CSF protein profile of the SHR when compared to CSF of the WKY, these variations were similar to variations found by other authors in AD. By Western-blot (WB) the TTR was found to be higher in blood and lower in the CSF of SHR with respect to WKY groups.

Conclusions: Long-term effects of hypertension cause a degeneration and hypertrophy of the CP producing variations in protein secretion to the CSF that could influence the maintenance of neurons and functions in the brain. Variations in CSF proteins in AD could similarly cause a CP disruption and support the close connection between cerebrovascular risk factors and AD in light of the fact that they could share common pathogenic etiological processes.

S30
Augurin production in the mammalian choroid plexus: Implications for CSF and hydrocephalus

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Background: Whereas augurin, a protein encoded by the ecrg4 gene, is highly conserved across species, bioinformatic algorithms predict the existence of several other potential hormone-like peptide products transcribed from the same gene. With gene expression highest in the mammalian choroid plexus (CP) compared to all other tissue types however, we deemed it critical to know which peptide(s) is produced by the CP so as to determine its potential release into, and activity in, cerebrospinal fluid (CSF). Our previous data has shown that gene knockdown in developing zebrafish causes severe and dose-dependent hindbrain edema/hydrocephalus. Accordingly, we suggested a novel function for ecrg4 gene products in CP physiology and implicated them as new hormone(s) regulating CSF and CP function. Immunohistochemical staining showed protein in CP epithelium in vitro and in vivo, and ligand-targeting shows internalization into ependymal cells.

Materials and methods: Ecrg4 gene products were detected by immunoblotting and immunofluorescence with chicken and rabbit polyclonal or mouse monoclonal antibodies that we raised. DNA sequences for fragments (31-148), (31-70) and (71-148) were cloned into pET11b vector, expressed in BL21DE3pLysS and purified. The human gene was cloned into the pLVx-IRES-ZsGreen vector and virus generated using the Lentix kit (Clontech) while siRNA lentivirus was obtained from Santa Cruz Biotechnology. Human primary epithelial CP cells were purchased from ScienCell Research Laboratories.

Results: Immunoblotting of CP tissue and lentivirus-transduced primary epithelial CP cells reveals a single 14 kDa immunoreactive band that comigrates with recombinant augurin (ECRG4(31-148)) indicating that the predicted signal peptide for secretion (ECRG4(1-30)) is removed with no additional predicted processing. Immunostaining of both rodent epithelial CP and primary human CP cells shows that immunoreactivity is present and localized at least in part, to the plasma membrane. These data suggest that, while secreted, augurin may remain cell associated and not released. If so, it may act in an autocrine fashion on CP epithelia and ependyma. Thus, we tested for augurin in conditioned media and found very little peptide, even when over-expressed.

Conclusions: The presence of the 14 kDa band in the CP and its localization at the cell surface indicates that augurin may be a ligand that is either tethered to the cell surface or secreted and bound to an unidentified receptor on the CP in an autocrine/paracrine fashion. With this in hand, we can begin to develop a model to explain the function of CP-derived augurin in ependyma, the CP and in brain fluid balance.

S31
Expression of aquaporins in a transgenic mouse model of Alzheimer’s disease

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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S31

Background: Several studies reported altered expression of the water channels, aquaporins (AQPs), in brains of Alzheimer’s disease (AD) but the relevance of the observed changes with respect to the neuropathology of AD is poorly understood. Because aberrant processing of the amyloid precursor protein (APP) to amyloid beta-peptide (A-beta), the principle component of amyloid plaques, is central to the pathogenesis of AD, we
sought to determine the temporal and spatial expression of AQPs in the cortex and hippocampus of the triple transgenic mouse model of Alzheimer’s disease (3xTg-AD) and to elucidate whether AQPs contribute directly to the aberrant processing of APP into A-beta.

Materials and methods: We used a mutant strain 3xTg AD mice, which harbor the human presenilin1 (PS1 M146V), APP (APPSwe) and tau (tauP301L) transgenes and develop age-dependent accumulation of both plaques and tangle pathologies in a pattern consistent with AD. Cortex and hippocampus (free of choroid plexus) were harvested from 2, 6 and 14 month-old 3xTg AD and wild type (C57) mice. APP1 and APP4 protein expression was quantified by immunoblotting, and immunohistochemistry was performed on frozen sections probed with anti-AQP1 and anti-AQP4 antibodies. AQPI and AQP4 mRNA expression was measured by real-time PCR.

Results: AQP1 but not AQP4 was detected at significantly higher levels in 3xTg-AD mice at 12 months when compared with younger mice at 2 and 6 months of age. No significant changes in the expression of AQP1 and AQP4 were observed at any ages in non-transgenic control mice. Immunohistochemical analyses to determine co-localization of AQP1 with APP in neurons (in 12 month-old 3xTg-AD mice) are being undertaken. Our findings correlate with published data suggesting amyloid clearance abnormalities in chronic and normal pressure hydrocephalus.

Conclusions: Our findings show increased expression of AQP1 in the brains of older 3xTg-AD but not non-transgenic control mice. This finding is consistent with published data of AQPI in AD, and maybe related to abnormalities in chronic and normal pressure hydrocephalus. Increased AQP1 expression in late stages of AD may possibly contribute to aberrant APP processing, and warrants further study.

Competing interests: The authors have no conflict of interest to declare.

S32
ECRG-4 expression in normal and neoplastic choroid plexus
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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S32

Background: The choroid plexus is a major site of gene expression of esophageal cancer-related gene (ECRG-4) during development, suggesting that its gene product may be involved in cerebrospinal fluid (CSF) homeostasis. Yet, ECRG-4 is also a novel candidate tumor suppressor gene whose expression is downregulated and is inversely associated with a worse prognosis in several different cancers. Reduced expression of ECRG-4 has been demonstrated in most tumors, including colorectal carcinoma and malignant glioma, to be mediated by hypermethylation of its promoter.

Materials and methods: In this study, samples of normal human choroid plexus (both fetal and adult) and choroid Plexus neoplasms (WHO grade I papilloma, grade II atypical papilloma, and grade III carcinoma) were stained with antibodies that we generated to augurin, the gene product of ECRG-4. DNA was then extracted from the tissue, treated with bisulfite, and subjected to PCR using a 217-base pair region encompassing the ECRG-4 promoter to detect methylation.

Results: Both fetal and adult human choroid plexus cells demonstrated a robust positive immunostaining at the apical surface that is consistent with our prior results in human, rat, and mouse brains. In contrast, there was a near-complete absence of immunostaining in all of the choroid plexus neoplasms examined. The choroid plexus carcinoma demonstrated significant methylation of the ECRG-4 promoter region.

Conclusions: Taken together, these data suggest that ECRG-4 is downregulated in neoplasms of the choroid plexus just as has been observed in other central nervous system (CNS) and non-CNS cancers. This is likely due to hypermethylation of the ECRG-4 promoter, as shown in the choroid plexus carcinoma. Further analysis is underway to determine the (1) physiologic and (2) pathophysiologic consequences of ECRG-4 over- and under-expression in the choroid plexus on CSF formation, function, and composition.
10 min, the supernatant frozen immediately and stored at -70°C until used. PC12 cells were cultured in RPMI-1640 with 10% FBS, 100 unit/ml of penicillin, 100 mg/ml of streptomycin and 5% CO2 at 37°C. For culture experiments, 2*10E4 PC12 cells were added to each well of a 96-well plate that had been coated with Poly-D-Lysine. After attachment, the cells were exposed to CSF at different ages with dissimilar concentration of 7, 10, 25% (v/v). The cell viability and cell proliferation were measured by MTT assay. The neuronal differentiation of PC12 cells were considered by changes of neurite outgrowth. Results: Viability and cell proliferation were significantly elevated in PC12 cells cultured in CSF supplemented medium in E18 compared with control ones. A significant neurite-like outgrowth appeared as early as Day 3 after the application of the CSF supplemented medium E17. Conclusions: It was shown that CSF neurotrophic factors can support normal neurogenesis and promotes proper brain development, neuronal differentiation. It has been reported that CSF can be a survival material on its own with any medium for cerebral cortex primary cultures. Our data are in the same line with previous studies that clarify crucial role of CSF neurotrophic factors in neuronal differentiation and cell proliferation. Taken together we address PC12 neuronal differentiation and cell proliferation to CSF induction by its components especially growth factors.

S35 The effect of decompressive craniectomy on CSF pulsatility in experimental communicating hydrocephalus Mark E Wagshul1,*, Shams Rashid, James P McMallster II, Martin U Schuhmann1

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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S35

Background: It has been well established that intracranial pulsatility, whether measured as parenchymal/intraventricular pressure or as cerebrospinal fluid (CSF) flow in the cerebral aqueduct, is often markedly elevated in patients with hydrocephalus. Attempts have been made to use this measure to predict outcome from shunt surgery, but its specificity is still questionable. The question of whether or not intracranial pulsatility plays a causative role in hydrocephalus or is merely an epiphenomenon related to intracranial compliance is similarly an unanswered question. As a first step toward answering this question, we hypothesized that aque ductal pulsatility would be reduced after increasing compliance following decompressive craniectomy.

Materials and methods: Communicating hydrocephalus was induced by injection of kaolin into the basal cisterns in five (n = 5) adult Sprague-Dawley rats; controls received similar saline injections. Flow pulsatility was studied at two weeks post-injection by cine phase contrast MRI prior to and immediately following bilateral craniectomy. Aque ductal stroke volume before and after craniectomy were compared. To minimize effects of extended anesthesia, the craniectomy was started prior to the first imaging scan without breaking through the bone completely. Animals were then moved to the scanner, imaged for the pre-craniectomy pulsatility measurements, and returned to the bench to complete the craniectomy. A bone flap (4 x 10 mm) was taken from each side over the parietal lobe. The dura mater was left intact, although small tears in the dura were noticed in some cases. A second scan was then obtained to measure post-craniectomy pulsatility. To ensure similar physiological state for the two materials, and methods: All HASTE MRIs obtained at Seattle Children’s Hospital over two-years were reviewed by two evaluators on scales of overall image quality, catheter visualization, motion artifact, and ventricular size. Relationships among these factors were sought.

Results: Overall image quality was rated very good or excellent in 94% of the studies reviewed, while only one study was graded as poor. Significant motion artifact was noted in 7% while 77% had little or no motion artifact. Catheter visualization was rated as good or excellent in 57% of studies reviewed, poor in 36%, and misleading in 7%. Small ventricular size showed a significant correlation with poor catheter visualization (Pearson correlation coefficient = .575; p<0.0001). Ventricular enlargement concerning for shunt malfunction on HASTE imaging correlated with operative findings of shunt malfunction in 100% of cases taken to the OR based on HASTE imaging.

Conclusions: Our study adds further support to the emerging evidence that HASTE MRI is an adequate substitute for CT scanning allowing for reduced utilization of CT imaging and resultant exposure to ionizing radiation. Visualization of catheter position remains suboptimal with HASTE MRI, particularly when ventricles are small; however, shunt malfunction can be adequately determined based on ventricular size alone in the majority of cases.


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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S36

Background: Recent reports and our clinical experience have shown the usefulness of rapid-acquisition MRI in evaluating children with hydrocephalus. An axial HASTE (i.e. Half-Fourier Acquisition Single-shot Turbo Spin Echo Magnetic Resonance Imaging) MRI study acquires clinically useful images in seconds without exposing children to the risks of ionizing radiation or sedation. The current report review the Seattle Children’s Hospital experience with rapid acquisition MRI in shunted children with attention to ventricular size, overall image quality, motion artifact, and catheter visualization.

Materials and methods: All HASTE MRIs obtained at Seattle Children’s Hospital over two-years were reviewed by two evaluators on scales of overall image quality, catheter visualization, motion artifact, and ventricular size. Relationships among these factors were sought.

Results: Overall image quality was rated very good or excellent in 94% of the studies reviewed, while only one study was graded as poor. Significant motion artifact was noted in 7% while 77% had little or no motion artifact. Catheter visualization was rated as good or excellent in 57% of studies reviewed, poor in 36%, and misleading in 7%. Small ventricular size showed a significant correlation with poor catheter visualization (Pearson correlation coefficient = .575; p<0.0001). Ventricular enlargement concerning for shunt malfunction on HASTE imaging correlated with operative findings of shunt malfunction in 100% of cases taken to the OR based on HASTE imaging.

Conclusions: Our study adds further support to the emerging evidence that HASTE MRI is an adequate substitute for CT scanning allowing for reduced utilization of CT imaging and resultant exposure to ionizing radiation. Visualization of catheter position remains suboptimal with HASTE MRI, particularly when ventricles are small; however, shunt malfunction can be adequately determined based on ventricular size alone in the majority of cases.

S37 Brain biomechanics during acute obstructive hydrocephalus in live rats Alexander V Shulyakov1,*, Richard Bunt1, Stefan S Cenkowski1, Marc R Del Bigio1,2

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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S37

Background: Predicted transmante pressure gradients are not found in humans or in animals with hydrocephalus [1,2]. We hypothesize that pulsatile forces transmitted through incompressible cerebrospinal fluid (CSF) into viscoelastic brain tissue results in slowly accumulating strain that leads to subsequent ventricular enlargement. As a first step to proving this hypothesis, we have measured viscoelastic properties in living rat brain.

Materials and methods: Young adult rats (age 56-70 days; n=18) had hydrocephalus induced by kaolin injection into the cisterna magna. Ventricle size, cerebral blood flow (CBF) before and after craniotomy was
assessed by magnetic resonance imaging (MRI). At several time points after kaolin injection (on 3-4, 7-9 and 12-15 day) a craniotomy was performed and vice versa. The ventricles were determined in live brain with intact dura using microindentation testing. Contact cortical CBF was also measured using a laser Doppler device incorporated into the indention sensor. Brain intraparenchymal pressure (IPP) was measured simultaneously.

Results: MRI showed progressive ventricular enlargement after kaolin injection. There was a significant increase of the cortical cerebral blood flow (measured by MRI arterial spin labelling) following craniotomy. Cortical CBF ascertained by laser Doppler did not change appreciably as hydrocephalus developed, however it decreased up to 30% at the site of indentation testing. A 2-fold IPP increment was observed at days 3-4 and 7-9 relative to the normal value (8-10 mm Hg). Instrumented brain indentation with low loading force (0.07-0.09 N) and loading-unloading rate of 0.140-0.18 N/min revealed a decrease of brain elasticity 3-4 and 12-15 days after kaolin injection. Viscoelastic creep increased at 3-4 days and was double the normal value at 12-15 days. Brain softening on multicycle indentation was increased 7-9 days after kaolin injection.

Conclusions: Living brain exhibits mechanical properties consistent with a viscoelastic nature. During the early development of hydrocephalus, the mechanical properties are modified at a time when overt histopathological changes would not be expected. The act of measuring the properties results in physiological changes, which must be considered as this series of experiments progresses.

References

S38
Comparison of mild and severe forms of hydrocephalus using diffusion tensor imaging in neonatal rats
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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S38

Background: Abnormal diffusion tensor imaging (DTI) measurements have been found in human and experimental subjects with severe hydrocephalus (HCP) [1-3]. Because ventriculomegaly can often be variable, the present study aimed to investigate the degree of DTI abnormality in neonatal rats with less severe HCP.

Materials and methods: Seventeen Sprague-Dawley rats were divided into three groups: (1) HCPM - 5 rats with intracerebral kaolin injections leading to severe hydrocephalus; (2) HCPM - 5 rats with the same kaolin injection procedure that developed mild HCP; (3) Control - 7 rats with intracerebral saline injections. Either kaolin or saline injection was performed at P2. DTI were acquired at P9-10 on a 7T Bruker MRI scanner. Evan’s ratios of ventricular size and DTI metrics (Fractional anisotropy (FA) and mean diffusivity (MDI)) were calculated and compared using ANOVA and other statistical comparisons.

Results: The three groups were significantly different (p<0.0001) in Evan’s ratios with HCPM rats (Mean+/−STD = 0.38+−0.07, Range: 0.31-0.48) slightly higher than controls (Mean+/−STD = 0.29+−0.01, Range: 0.27-0.31, p=0.02) but lower than the HCP group (Mean+/−STD = 0.85+−0.04, Range: 0.80-0.90, p=0.0001). Both FA and MD values were significantly different among the three groups in cortex, corpus callosum and internal capsule (ANOVA, p<0.05). Post-hoc comparisons showed that the HCPM group was not significantly different from the control group, while the HCP group was significantly different (lower FA and higher MD, p<0.05) from the control group (with the exception of FA in the internal capsule) and the HCPM group. In the HCPM group, it was found that the FA values in the internal capsule increased proportionally with ventricle size (R=0.94, p=0.016), while FA values in the internal capsule decreased with increasing ventricle size (R=−0.98, p=0.005).

Conclusions: Although the DTI measurements in the HCPM rats with mild ventriculomegaly were not significantly different from normal controls, the correlation between ventricle size and DTI values in this group suggested that different levels of abnormality in brain tissues can be detected with DTI during various stages of hydrocephalus. Our results demonstrate that DTI is potentially a sensitive biomarker for monitoring the progression of ventricle enlargement and may help to determine the optimal window for surgical intervention.

S39
Definition and classification of hydrocephalus
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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S39

Background: To present a consensus on an updated definition and classification of hydrocephalus and discuss how this new classification will serve to focus research and improve the process of decision making in patients with hydrocephalus.

Materials and methods: Over the last two years we have had a series of meetings among leaders in basic science research into hydrocephalus as well as clinicians actively involved in assessing treatment of this complex condition. While many thoughts were voiced, a general agreement among these researchers was reached and a plan for its distribution was agreed upon.

Results: It was agreed that there would be two definitions as seen in all dictionaries. One would be for general use (1) and the second would be for those involved in pathophysiological studies (2). Definition 1. Hydrocephalus is a dynamic imbalance between the formation and absorption of cerebrospinal fluid resulting in an excessive accumulation of the CSF within the ventricles of the brain. Definition 2 Hydrocephalus is a dynamic imbalance between the formation and absorption of cerebrospinal fluid resulting in accumulation of excess CSF associated with ventricular dilatation and/or enlargement of the subarachnoid space. The classification would be based on the presence or absence of a point of obstruction and if there is a point of obstruction where that obstruction is located. The various types of hydrocephalus could then be modified by subclassification as to chronicity and as to treatment options.

Conclusions: Use of a new classification scheme is essential since the latest classification dates to 1914. Use of a classification based on a point of obstruction will lead to a common language among clinicians and researchers which has been absent generally and assure that animal models used in the laboratory can be compared to appropriate clinical conditions.

S40
Are adjustable valves effective in all ages of patient? Data from the UK Shunt Registry
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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S40

Background: Adjustable CSF valves have been developed by several manufacturers. These valves are more expensive, but have an advantage in that the operating pressure of the valve can be altered by the use of an external magnet. We have used data collected by the UK Shunt Registry to assess the effectiveness of these valves in reducing valve replacement for under and over-drainage using a case-control design.

Materials and methods: The UK Shunt Registry contains data on over 55,000 CSF shunt-related procedures. Our data suggests that primary factors involved in shunt revision are patient age, diagnosis and the number of revisions a patient has had. Procedures were identified where an adjustable valve was used in a ventriculoperitoneal shunt. Of these 3,682 had an accurate diagnosis and age entered and we were able to determine the exact number of shunt revisions. A database search was performed for procedures matched for these risk factors but using a
fixed-pressure valve. Matches were found for 3,262 procedures. The was dataset was further divided by the age of patient. There were 966 matched pairs aged 70 and over, 1569 matched pairs aged 17 to 69 and 727 matched pairs aged 16 and under. The cumulative valve revision rate (CVRR) for up to 5 years was calculated. Only revisions where the valve was replaced for a given reason of under- or over-drainage were considered. A Logrank test was used for comparison of CVRR between adjustable and fixed-pressure valves.

**Results:** In the over 70 age group, adjustable valves performed significantly better (P<0.05) from week 16 up to the 5 years of calculation. In the 17-69 age groups there was a significant lower CVRR from week 7 up to 5 years. However in the younger age group (0 to 16 years) there was no significant improvement in CVRR with an adjustable valve.

**Conclusions:** Our data suggest that adjustable valves may be effective in overcoming problems due to incorrect pressure selection in adult patients. However, although appears to be no significant advantage in using an adjustable valve in the majority of paediatric patients.

**S42**

**Complications and management of ventriculostomy-related infections in patients with hydrocerephalus and ventriculoperitoneal shunt failure.**

**Background:** Ventrillostomy related infections are strongly associated with longer in-situ stay of ventricular catheters. Bactiseal catheters may be considered in efforts to reduce the incidence of infections after VP shunt placement in neonatal patients. In an effort to generalize to an asymptomatic population of patients with risks ranging from medication interactions to hemorrhage. Given the prevalence of subclinical thromboembolism however, pharmacologic anticoagulation remains a consideration that must be individualized. Currently the American Heart Association finds no convincing evidence that peri-procedural prophylaxis is indicated in VA shunt patients. Finally, surgical conversion of VA shunts may be considered in efforts to reduce the potential for life-threatening complications of VA shunts. In conclusion, clinically evident and subclinical thromboembolic disease is known complication of VA shunts. Management and surveillance of these patients is largely left undefined in the current literature. Long term anticoagulation, thrombophilia screening, vigilant follow up, and surgical revision remain considerations.

**Materials and methods:** A literature review of VA shunt complications and long-term management was performed. Paediatric infectious disease, cardiology and neurosurgery were consulted. Long term anticoagulation with warfarin was instituted.

**Results:** Peri-procedural antibiotic prophylaxis was not recommended. Neurosurgery plans to reevaluate and possibly convert the shunt to a ventriculopleural shunt in the future.

**Conclusions:** There is a paucity of literature regarding the complications and long-term management of VA shunts. Reviews suggest the rate of clinically evident PE and pulmonary hypertension in patients with VA shunts is only 0.4 and 0.3 percent respectively. Autopsy studies however have demonstrated rates as high as 59.7 and 6.3 percent. Progressive cor pulmonale occurs in a small percentage of patients with VA shunts, but carries a high mortality rate. The contribution of subclinical infection or occult thrombophilia in subsequent thromboembolic disease is unknown. This begs the following questions. 1. Should all patients with VA shunts be anticoagulated, to what extent? 2. Is there a role for thrombophilia screening to detect at risk subjects? 3. Does prophylactic antibiotic use have a role? 4. What type of surveillance for asymptomatic PE and pulmonary hypertension is prudent? 5. Is surgical conversion of VA shunts recommended? Long-term anticoagulation is a difficult recommendation to generalize to an asymptomatic population of patients with risks ranging from medication interactions to hemorrhage. Given the prevalence of subclinical thromboembolism however, pharmacologic anticoagulation remains a strong consideration that must be individualized. Currently the American Heart Association finds no convincing evidence that peri-procedural prophylaxis is indicated in VA shunt patients. Finally, surgical conversion of VA shunts may be considered in efforts to reduce the potential for life-threatening complications of VA shunts. In conclusion, clinically evident and subclinical thromboembolic disease is a known complication of VA shunts. Management and surveillance of these patients is largely left undefined in the current literature. Long term anticoagulation, thrombophilia screening, vigilant follow up, and surgical revision remain considerations.
in newborns without symptomatic Hydrocephalus at birth when we had a wait and watch policy (late shunt placement) compared to newborns with prompt shunt placement. The relative risk (RR 95%) of having a infection was highly significant: RR = 6.8 (3.31415 - 13.95228) (P= 1.235e-07) and also neuroinfections RR = 4.76 (2.043019 - 11.09025) (P =0.0044478) if the child presented MMC wound CSF leakage before VP shunt insertion.

Conclusions: Centres with a conservative antibiotic policy should be even more careful to avoid CSF leakage before shunt placement as this gives a highly significant increased risk of both infections in total and neuroinfections and they should reconsider this conservative policy in newborns with MMC due to the significant high infection rates.

S44
The use of ASET (Anti Staph Epidermidis Titre) in the diagnosis of ventriculo-atrial shunt infection
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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S44

Background: Infection is an important and not infrequent complication for patients with shunted hydrocephalus, with a reported incidence of 3-20%. Shunt infections can present in a non-specific manner and can be difficult to diagnose. Inflammatory markers may in rare cases be normal and CSF culture can also be negative, especially in Staph epidermidis infection. Ventriculo – atrial shunt infections are particularly prone to presentation with subtle clinical features and diagnosis may be delayed as a result. Since 1972, a simple serological test has been available for diagnosis of VA shunt infection, but is not widely used.

Materials and methods: Casenotes were reviewed. The method of ASET testing was as published previously. Briefly, serial dilutions of patient’s serum and controls were reacted with S epidermidis antigen at 4degC and the antibody titre recorded.

Results: A 38-year old male with hydrocephalus secondary to a Dandy Walker cyst had a ventriculoperitoneal shunt inserted as a child. Following numerous revisions and replacements, the shunt was revised to a ventriculo-atrial shunt in June 2008. There was no growth on CSF culture at this time. Following this he was well for seven months but re-presented with severe headaches and occasional night sweats. ICP monitoring showed no evidence of raised pressure. He was readmitted one month later complaining of night sweats and back pain, in addition to ongoing headaches. He was aperistalsis, white cell count was normal and CRP was 30mg/L. CSF from lumbar puncture was sterile. Blood cultures grew Staphylococcus epidermidis, which our microbiologists thought to be a contaminant. However, shunt infection could not be excluded, blood was sent for Anti Staph Epidermidis Titre (ASET). Antibiotics were then started. ASET was >40,000 (normal range 160-640), confirming our suspicions of shunt infection. The shunt was removed, at which time, CSF and shunt tip grew S epidermidis. A new ventriculopleural shunt was inserted following a course of antibiotics. His headaches resolved and he was well following this.

Conclusions: Our patient presented with non-specific symptoms. Initial CSF culture was normal and his symptoms were thought not to be due to infection. However, ASET confirmed S epidermidis shunt infection. This was then successfully treated and his symptoms completely resolved.

S45
A simple method to reduce infection of ventriculoperitoneal shunts
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Background: Post-operative shunt infection is the most common and feared complication of ventriculoperitoneal shunt placement for treatment of hydrocephalus. The rate of shunt infection is highest in the first postoperative month. The most common organisms responsible for shunt infection include coagulase-negative staphylococcus and staphylococcus aureus. This suggests a transfer of patient’s skin flora via the surgeon’s glove as a possible means of infection. This led to our hypothesis of changing gloves before handling the shunt catheter as a simple way to reduce post-operative shunt infections.

Materials and methods: A total of 111 neonates born with congenital hydrocephalus requiring VP shunt placement were prospectively enrolled and divided into two groups. Group A, the control, had 54 neonates treated with standard protocol VPS placement while Group B had 57 neonates in which gloves were changed before the shunt catheter was handled. Shunt infection rates were compared up to six months postoperatively.

Results: There was a statistically significant reduction of infection rate from 16.33% in Group A; the control, to 3.77% in Group B.

Conclusions: Our study shows that a change of gloves before handling the shunt catheter may be a simple and cost effective way to reduce the burden of postoperative shunt infections. Our study was limited by a small sample size. A larger study is required to evaluate the effectiveness of this simple measure to reduce post operative shunt infections.

S46
The development of an antimicrobial EVD catheter to protect against multi-resistant hospital “superbugs”
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Cerebrospinal Fluid Research 2010, 7(Suppl 1):S46

Background: External Ventricular Drainage (EVD) infections are a serious complication, and the period of risk extends until the device is removed. The causative bacteria of EVD and shunt infections are similar but there are more multi – resistant strains such as MRSA and gram negative bacteria in EVD infections, particularly when the patient is in intensive care. To counter this, we have developed an antimicrobial EVD catheter with a broad spectrum to protect against these multi-resistant bacteria. Thus, the aim of this study was to evaluate the antimicrobial activity of this catheter against multi-resistant Staphylococcus epidermidis, MRSA, and gram negatives using clinically predictive in vitro tests.

Materials and methods: Medical grade silicone catheter tubing (Codman) was impregnated with antimicrobials: 1% triclosan, 1% trimethoprim and 0.2% rifampicin respectively. Three methods were used to evaluate the antimicrobial activity of the catheter. The Serial Plate Transfer Test (SPTT) is a screening test for duration of antimicrobial activity and to monitor resistance. Impregnated catheter segments were placed onto agar plates seeded with bacteria and incubated. Segments were removed daily and placed on fresh plates and reincubated. The inhibition zone was measured across the short axis. This was repeated until no inhibition zones were seen. The time taken to kill 100% of bacteria attached to catheter segments (tK100), was determined by first coating the catheter segments with a protein conditioning film, then allowing the bacteria to adhere to plain and antimicrobial catheter segments and incubating them. Samples were retrieved daily, sonicated to remove the adherent bacteria, and the sonicate cultured quantitatively to detect bacterial growth. Thirdly, a simulated in vitro model was used to determine the ability of the antimicrobial catheter to resist successive bacterial challenges every 14 days under constant perfusion, designed to mimic the CSF flow.

Results: The SPTT showed duration of antimicrobial activity for more than 80 days. The tK100 showed that it takes between 24-48 hours to kill all the bacteria attached to the catheter. The in vitro model showed that the catheter protected against bacterial colonization after 7 successive challenges (ie more than 80 days), without developing resistance.

Conclusions: The catheter demonstrated a broad spectrum of antimicrobial activity and a prolonged duration of activity against multi-resistant bacteria. The clinically predictive tests indicate that the catheter is likely to reduce significantly EVD infections caused by multi-resistant superbugs found among patients on intensive care and high-dependency units.

Competing interests: RB holds a patent for the catheter described, and receives consultancy fees from Codman but not for personal gain. WA and OS have no interests to declare.
**S47**

Immunohistochemical study of human embryonic brain choroid plexuses and Subcommissural Organ

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**Background:** The choroid plexus is involved in a variety of neurological disorders, including neurodegenerative, inflammatory, infectious, traumatic, neoplastic, and systemic diseases. We observed that choroid plexus epithelial cells and tanycytes of the lateral ventricle choroid plexuses were excised from 10 to 30 weeks of gestation (WG), -brain barrier. The choroid plexus epithelium constitutes the structural basis of the blood-cerebrospinal fluid barrier which is important for maintaining an optimal homeostatic environment for the brain. We immunohistochemically investigated the expression of the proliferation cell nuclear antigen (PCNA), p73, TTR and caspase in the choroid plexus and the SCO.

**Methods and materials:** Brains from 10 to 30 weeks of gestation (WG), from the collection of the Department of Anatomy of the University of La Laguna, were used. Brains were processed using p73 (1:1000), TTR(1:400), PCNA (1:15,000) and caspase (1:200) as primary antibodies.

**Results:** We observed that choroid plexus epithelial cells and tanycytes of circumventricular organs presented immunohistochemical changes. Pro-apoptotic p73 protein was detected in all parts of the SCO throughout the investigated period. TTR (pre-albumin) was found in the basal and apical process and in the secretory granules located in the ventricular cell pole. The antibodies to proliferating cell nuclear antigen (PCNA) were observed in the choroid plexus and the SCO. The immunoreactive material was located in the nuclei forming condensations in both the ependymal and hypendymal layer.

**Conclusions:** These proteins are detected in the SCO and the choroid plexuses suggesting that their expression is related with secretion of CSF by the choroid plexus and the development subcommissural organ.

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**S48**

Alterations in choroid plexus gene expression in Alzheimer’s disease provide inferences for CSF composition and dynamics

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**Background:** Alterations in CSF composition are associated with normal aging and the pathophysiology of Alzheimer’s disease and NPH. These changes may contribute to modified choroid plexus function in these states. Disease-related changes in choroid plexus gene expression were investigated using human Affymetrix 48K gene arrays.

**Materials and methods:** Lateral ventricular choroid plexuses were excised at autopsy from healthy aged controls (mean age/mean PM: 58 years/22 hours) and patients with advanced (Braak & Braak stage V-VI) Alzheimer’s disease (79/18). Diseased control patients with frontotemporal dementia (72/NA) and Huntington’s disease (71/19) were also sampled. All tissue specimens were snap frozen in liquid nitrogen and stored at −80°C until use. RNA was extracted from choroid plexuses with Trizol followed by NuGEN Ovation amplification, and cDNA was hybridized to custom chips at Rosetta/Merck. RNA normalization was performed, and data were analyzed using one way ANOVA to identify the gene sets of greatest significance. These sets were then analyzed further for biological enrichment using individual (Ingenuity) and combined (Target and Gene Information System) pathway tools.

**Results:** Differences on the level of gene expression were seen in the choroid plexuses of Braak & Braak V-VI AD patients when compared to both the normal and diseased (FTD, HD) control groups. Four experimental groups could significantly be separated out based on the analyses of 648 sequences (p<0.001, FDR<8%), with close to fifty percent of those sequences being up-regulated in neurodegenerative disease states. There was a significant increase in immune response noted in advanced AD patients, while amyloid processing and oxidative phosphorylation were both down-regulated in these cases. In addition, cellular adhesion function and extracellular matrix re-modeling were highly enriched in the advanced AD patients when compared to both the healthy and diseased controls. Other important observations that were made in analyzing these data include: decreases in PPARα/RXRα nuclear receptor/retinoid acid, a-adrenergic, glucocorticoid and melanin signaling, as well as N-glycan, glutathione (antioxidant) and ubiquinone metabolism in AD choroid plexuses.

**Conclusions:** These gene expression profiles may serve as valuable resources to investigators working in the fields of aging CSF dynamics and hydrocephalus. It is readily available and can be shared with interested investigators to address specific questions pertaining to their area of investigation.

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**S49**

Ventricular lavage for post-haemorrhagic hydrocephalus

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**Background:** Early results of an international RCT comparing drainage, irrigation & fibrinolytic therapy (DRIFT) for prematurity-associated post-ventricular dilatation (PHVD), with standard treatment suggested no benefit in terms of avoidance of shunt dependency. There was also an increased rate of secondary bleeds in those having DRIFT. The longer-term benefits or otherwise of DRIFT treatment were unknown.

**Materials and methods:** We randomly allocated 77 preterm infants with PHVD to either DRIFT or standard treatment (i.e. tapping off cerebrospinal fluid to control excessive ventricular expansion). Severe disability was assessed at 2 years corrected age.

**Results:** Of 39 infants assigned to DRIFT, 21 (54%) died or were severely disabled versus 27 of 38 (71%) in the standard group (adjusted odds ratio 0.25 [95% confidence interval: 0.08–0.82]). Among the survivors, 11 of 35 (31%) in the DRIFT group had severe cognitive disability versus 19 of 32 (59%) in the standard group (adjusted odds ratio: 0.17 [95% confidence interval: 0.05–0.57]). Median Mental Development Index was 68 with DRIFT and 30 with standard care.

**Conclusions:** Despite inducing an increased rate of secondary intraventricular bleeding, DRIFT reduced severe cognitive disability in survivors and overall rates of death or severe disability. A modification of DRIFT involving simple ventricular lavage and fibrinolytic therapy (limited to unblocking clogged-up drainage catheters) will now be employed in clinical practice at our unit.
Clinical symptoms greatly improved after treatment with a fragmented sleep. Computerized tomography showed no change in ventricular size in either case.

Results: Both patients were started on nighttime noninvasive ventilation (NIPPV) with rapid resolution of symptoms.

Conclusions: Children with meningo(myelo)coele, particularly those who appear to have had resolution of infantile bulbar dysfunction, may present later in life with severely disordered sleep ventilation, and warrant careful lifelong followup, with a low threshold for polysomnography and institution of ventilatory support.

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Temporary tracheostomy required as an infant may be a risk factor for future centrally mediated disordered sleep ventilation

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Background: Children with spina bifida experience lifelong complex medical issues. The problems of locomotion, and neuropenic bowel and bladder are well appreciated, and the necessity of shunting obstructive hydrocephalus is equally well known. There are however, serious, less common problems associated with control of ventilation. Most common is vocal cord dysfunction, with unilateral or bilateral vocal cord paralyses, and as a consequence, upper airway obstruction. Rarer still, are patients with life threatening breath holding spells, central apnea, or mixed central and obstructive apnea. In many cases, surgical decompression of the posterior fossa can result in return of vocal cord function, and relief of obstructive apnea. In a few cases tracheostomy is required. With a Chiari II malformation, the upper medulla, where the nuclei of cranial nerves IX and X lie close to the rostral tracts of the respiratory centre, may have an abnormal and tenuous blood supply. The medulla may be compromised by bony pressure or by compromise of the blood supply (herniation or chronic arachnoiditis).

Materials and methods: The Spinal Cord Program at British Columbia's Children's Hospital has cared for 956 patients since 1982. Over the same period, the Home Tracheostomy Care/ Home Ventilation Program has cared for 346 children, eight with spinal dysraphism. Two girls with meningo(myelo)coele and Arnold Chiari type II malformations, who had required tracheostomies as infants, presented as adolescents with symptoms suggestive of disordered sleep ventilation. Both had required a tracheostomy despite timely posterior fossa decompression, but over time (years), gag and vocal cord function returned, and they were successfully decannulated. Patient 1, with a lumbosacral meningo(myelo)coele was referred to the Home Ventilation Program at fourteen years of age when her mother, a registered nurse reported erratic breathing at night, with weight loss, and deteriorating school performance. Patient 2, with a lumbum meningo(myelo)coele presented at fifteen years of age complaining of daytime somnolence, but denied morning headaches. In both cases polysomnography showed a similar, chaotic pattern of respiration with frequent arousals and severely fragmented sleep. Computerized Tomography showed no change in ventricular size in either case.

Results: Both patients were started on nighttime noninvasive ventilation (NIPPV) with rapid resolution of symptoms.

Conclusions: Children with meningo(myelo)coele, particularly those who appear to have had resolution of infantile bulbar dysfunction, may present later in life with severely disordered sleep ventilation, and warrant careful lifelong followup, with a low threshold for polysomnography and institution of ventilatory support.
Conclusions: Children with meningomyelocoele/ Arnold Chiari malformation, with shunt dysfunction can present with disordered sleep ventilation in the absence of either the classical symptoms of shunt dysfunction or central hypoventilation. When the clinical course of an illness in a shunt dependent child takes an unexpected turn, evaluation of shunt function is indicated.

S53 Health Sciences Online: an extraordinary opportunity for the democratization of health sciences knowledge

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Background: According to the World Health Organization, health care requires more innovative, trans-disciplinary and less-expensive training methods to increase local education and service opportunities. We are addressing this issue through Health Sciences Online (HSO) - a virtual learning centre for comprehensive health professional education. HSO is a portal that provides access to a collection of top-quality courses and references in medicine, public health, nursing, dentistry and other health sciences disciplines. These materials are donated, hosted and maintained by distinguished content partners so anyone, anywhere in the world can access a free, current, world-class education through the portal.

Materials and methods: HSO includes more than 50,000 learning objects from already-existing reliable resource collections, and we are still growing. Material regarding hydrocephalus and spina bifida is available, provided by medical specialty societies, accredited continuing education organizations, governments and universities (including the Centre for Genetics Education, the Canadian Paediatric Society, and the University of Pittsburgh School of Medicine).

Results: As our next phase, we’re beginning work with colleagues all over the world in creating what we hope to be the largest, most accessible, and one of the best health sciences universities – all done with distance HSO-based didactics, local hands-on mentoring, and peer-to-peer distance feedback. We plan to train many thousands of trainees at a time, particularly in developing countries, with the students remaining in their home environments (and thereby building capacity, instead of encouraging brain drain). Examples of certificates currently under development are in 1) Exercise and Health, in partnership with CDC, the American College of Sports Medicine, the Fundacion Fe Santa Fe Bogota Active Living Program, and the Pedagogical University of Colombia, 2) Perinatal Care, in collaboration with WHO, and piloting in Africa and South East Asia, 3) Emerging Infectious Diseases, with WHO, and piloting in a rural community in Panama, 4) Dermatology for Primary Care Providers, in collaboration with NATO and Armenia’s Yerevan State Medical University and 5) Addiction Medicine for Medical Students and Residents, in collaboration with the Betty Ford Institute and the Annenberg Physician Training Program in Addiction Medicine.

Conclusions: HSO is an extraordinary resource for medical professionals around the world, and we hope to utilize this conference to teach others about its origins, uses and goals.

S54 Patients with spina bifida and bladder cancer. Our experience

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Background: Patients with neurogenic bladder dysfunction due to spina bifida have been reported to be at increased risk for bladder cancer. The publications suggest that intermittent or permanent catheterization, bacteriuria, bladder calculi and bladder augmentation are a significant risk factor. We reviewed our experience with treating patients with spina bifida and bladder cancer.

Materials and methods: Patients with spina bifida treated for bladder cancer between 1990 and 2010 were identified. Patient demographics, mode of bladder management, risk factors and presenting symptoms were recorded along with therapy, pathological findings and outcome. A review of all known published studies was made.

Results: We found four patients with a mean age of 37.25 years old, one man and three women. Any patient had undergone bladder augmentation. Three patients used as mode of bladder management intermittent catheterization or permanent urethral catheter, and the male had used collector and had been diagnosed of repetitive bladder calculi. Abdominal pain was the first presenting symptom in two patients, hematuria in another one and the last one was diagnosed because of an ureteral obstruction. All of them had previous history of recurrent urinary tract infections. 75% patients had locally advanced stage (T3 or greater) or lymph node metastases at the time of diagnosis. Two patients had died at the time of the study.

Conclusions: Bladder cancer should be considered on in this patient population, even in young adult women. Therefore a complete screening would be beneficial for earlier detection and improved outcomes in every spina bifida patient with hematuria or chronic infection.

S55 Shunting in chronic hydrocephalus induces VEGFR-2 and blood vessel density changes in the caudate nucleus

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Background: Chronic hydrocephalus (CH), which is characterized by increased cerebrospinal (CSF) fluid volume with or without increased intracranial pressure (ICP), is often associated with decreased cerebral blood flow and oxygen delivery. While CSF shunting can improve neurological symptoms, the cause of these symptoms in hydrocephalus and the mechanism of shunt reversal remain unclear. We have previously observed a decreased cerebral blood flow in CH which was associated with a stimulation of Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) expression and changes in vascular density. In this study we investigated the effect of shunting on neuronal and glial VEGFR-2 expression and blood vessel densities (BVd) in the caudate nucleus.

Materials and methods: Fourteen (n=14) young adult canines were divided into three groups: CH-Shunted (CH-S, shunted at 12 weeks, n=4); CH-Untreated hydrocephalic (CHU, 12-16 weeks, n=5); and Surgical Controls (SC, 12-16 weeks, n=5). The experimental model of CH was previously developed and investigated in our lab. The density of blood vessels and VEGFR-2 positive neurons and glia was estimated using stereological counting methods and expressed as a percent (% of total cells.

Results: Untreated hydrocephalic animals had approximately 2-3 times the amount of %VEGFR-2 neurons compared to controls. Shunted animals had a significantly lower %VEGFR-2 neuronal expression (32%) compared to CH-U (50%) (p≤0.01). BVd was significantly lower in CH-U (826 BV/mm3) and was lowest in CH-S (675 BV/mm3) compared to SC (1012 BV/mm3; p≤0.05). %VEGFR-2 glial expression was not significantly different among the three groups. No correlation was found between %VEGFR-2, BVd and ventricular volume (Vv); however, 2/4 animals showed a decrease in Vv following shunting which was associated with improved BVd. Similarly, 2/4 animals showed improved oxygenation following shunting which was associated with improved BVd.

Conclusions: In the caudate, CSF shunting appears to significantly reverse VEGFR-2 neuronal activation and CH-induced changes in blood
vessel density. This is consistent with the hypothesis that hydrocephalus is associated with chronic hypoxia/ischemia which is resolved by CSF removal. Shunting does not seem to have any effect on VEGF-2 gial expression which might suggest that other factors may be involved in gial activation. Control of VEGF system activation through agonists or antagonists may ultimately provide a means of reducing brain injury and improving function.

S56
Defects in cell-cell junctions lead to neuroepithelial/ependymal denudation in the telencephalon of human hydrocephalic foetuses
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Background: In human foetal hydrocephalus and spina bifida aperta (SBA), the pathogenesis of abnormal cortical development is poorly understood. Previous reports have shown that neuroepithelial/ependymal denudation is involved in the neuropathogenesis of human foetal hydrocephalus and SBA. Interestingly, loss of the neuroepithelium/ependyma (denudation) at the Sylvian aqueduct is preceded by defective expression of adherent and gap junction proteins. In human foetal hydrocephalus, we aimed to investigate whether abnormal cortical development is similarly associated with intercellular ependymal defects at the telencephalic (sub)ventricular zones.

Materials and methods: Human foetal hydrocephalic and SBA foetuses were characterized according to their underlying pathogenesis (SBA [n=5, 21-40 weeks GA] and hydrocephalic foetuses with other congenital brain abnormalities [n=8, 12-40 weeks GA]) and studied by immunocytochemistry using antibodies against junction proteins (N-cadherin and connexin-43). Cilia (IIIIV-tubulin) and neuron/neuronal precursor (IIIItubulin) markers were also used.

Results and conclusions: In human foetal hydrocephalic foetuses, we observed telencephalic subventricular zones with already denuded areas together with areas that were likely to undergo ependymal denudation (as shown by altered lining of neuroepithelial/ependymal cells). These areas were associated with abnormal expression of N-cadherin, formation of rosettes and periventricular heterotopias. In human foetal hydrocephalus, these findings support the concept that defective ependymal cell-cell junction proteins are related with abnormal neurogenesis and migration.

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S57
The disruption of the ventricular (VZ) and subventricular (SVZ) zones of the ganglionic eminences in hydrocephalic hyh mice is associated to abnormalities in the cortical GABAergic neurons
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Background: The structure of the cerebral cortex results from the orderly migration of two major types of neurons, the glutamatergic projection neurons and the GABAergic interneurons. Most GABAergic neurons originate from the ganglionic eminences. They first migrate tangentially toward the pallium and then migrate radially through the developing brain cortex. The disruption of the VZ and SVZ of the pallium and subpallium has been shown to occur at key developmental periods in the hydrocephalic mutant mouse hyh. The aim of the present investigation was to study whether such a disruption of the VZ and SVZ results in abnormalities of the GABAergic neurons populating the brain cortex.

Materials and methods: The brain of non-hydrocephalic and hydrocephalic hyh mice at postnatal day 7 (n=20) were processed for immunocytochemistry and immunofluorescence using antibodies against GABA and the marker of neuronal nuclei NeuN. Sections processed for double immunofluorescence were inspected with an epifluorescence microscope provided with the multidimensional acquisition software AxioVision Rel. Single and overlay images were used for quantitative analyses of the whole populations of cortical neurons (NeuN-reactive) and that of GABAergic neurons. Absolute and relative cell density and intracortical distribution were recorded for the GABAergic neurons.

Results and conclusions: The mutant hyh mice were characterized by (i) a marked reduction in the width of the cerebral cortex; (ii) a reduction in the total number of GABAergic neurons; (iii) a reduction in the relative number of GABAergic neurons with respect to the total population of neurons (GABA/NeuN); (iv) an abnormal distribution of GABAergic neurons in the cortex layers, with a significant reduction in layers II and III and an increase in layer IV and V. The hyh mutation is associated with: (i) a decreased number of GABAergic neurons migrating from the ganglionic eminences; (ii) abnormal migration of GABAergic neurons through the developing brain cortex; (iii) in hyh mice disruption of the VZ and SVZ is associated to the onset of hydrocephalus and abnormal corticogenesis.

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