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Meeting abstracts

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INTRODUCTION

S1 51st Annual Meeting of the Society for Research into Hydrocephalus and Spina Bifida

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The 51st Annual Meeting of the Society for Research into Hydrocephalus and Spina Bifida was held in the University of Heidelberg, Department of Neurosurgery at the invitation of Professor Andreas Unterberg and Dr. Alfred Aschoff. We are indebted to Alfred for his hard work in making the meeting such a success.

Scientific sessions were held in the impressive auditorium of the new *Kopfclinic* and the social program took place within the old city of Heidelberg. Home to the oldest university in Germany, Heidelberg was largely rebuilt in the 18th century. Delegates were able to enjoy the charms of this beautiful city, the more adventurous tackling the Philosopher's Walk (*Philosphenweg*) high above the banks of the Neckar River.

The Annual General Meeting and Reception were held at the university *Alte Aula*, (Old Assembly Hall) built between 1712 and 1718. The Society dinner was held in the magnificent setting of Heidelberg Castle, with the famous Heidelberg Tun (A wine barrel made in 1751, with a capacity of 220,000 liters) visible in one corner of the hall.

The Outing was a boat trip on the picturesque river Neckar, giving excellent views of Heidelberg and the surrounding countryside. The society's amateur photographers were given many excellent opportunities for landscape photography under rapidly changing skies. The evening was rounded off with a hearty stew and German beer in one of the many famous student haunts in the Old Town.

The scientific sessions as usual covered a wide range of topics on basic scientific research and clinical topics. Sessions were held on *Chronic Hydrocephalus, Spina Bifida, Bowel and Urodynamic Function, Hydrocephalus Pathology, Shunts, Psychosocial Issues and Hydrocephalus and CSF*. Our President, Ray Fitzgerald presented this year's Casey Holter Essay Prize to Dr. Helen Williams for her essay entitled 'An Essay Concerning the Pathogenesis of Hydrocephalus'. This essay will be expanded and published in *Cerebrospinal Fluid Research* in the near future.

The abstracts of all the presented papers are published in this supplement. It is the Society's policy to publish abstracts without editing. Any comments should be addressed directly to the authors.

The meeting closed with an invitation from Drs John Duncan, Conrad Johanson and Gerald Silverberg to the 52nd Annual Conference to take place in Providence, Rhode Island on 11–14th June 2008.

ORAL PRESENTATIONS

S2 VEGF-R2+ activation in the caudate: an adaptive angiogenic response to hypoxia in chronic hydrocephalus?

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S2

Background: Chronic hydrocephalus (hydrocephalus) is characterised by impaired gait, and associated with decreased cerebral blood flow and oxygen delivery. We investigated the role of chronic hypoxia in the caudate which is a known motor nucleus involved in gait control. Also, increased ICP and vascular compression as the result of enlarged ventricles may be directly responsible for the gait problems in hydrocephalus. VEGF, which is triggered by ischemic/hypoxic events causes associated adaptive angiogenesis and also plays a critical role in neuronal protection. Previously, using an experimental model of hydrocephalus, we have shown decreased cerebral blood flow, oxygen delivery and increased capillary density. Here we investigated whether neuronal and glial VEGF-R2 expression is associated with an adaptive angiogenesis in the caudate.

Materials and methods: We investigated the relationship between the duration and severity of hydrocephalus and the percentage expression of VEGFR2+ neurons, glia and blood vessels (BV) in the periventricular and deep layers of the caudate. Hydrocephalic animals were divided into Short Term (ST, n = 5) and Long Term (LT, n = 5) and compared with Surgical Controls (SC, n = 5). The density of blood vessels and

cellular VEGF-R2+ was estimated using stereological cell counting methods. Values were expressed as %VEGF-R2+ cells to the total number of cells in each region.

Results: Overall, there was approximately 300–400% increase in %VEGF-R2+ neurons, and approximately 10–15% increase in %VEGFR-R2 glia in the caudate of hydrocephalic animals compared to SC. Specifically, %VEGFR-R2+ neurons were significantly greater in LT (55–60%) than SC (10–25%). Similarly, %VEGF-R2+ glia were significantly higher in hydrocephalic animals (55–60%), then SC (15–25%). BV density was found to decrease in hydrocephalic animals than SC. Overall, we found that the BV density decreased 60% in the periventricular caudate and 20% in the deep caudate compared to SC. BV density was not significantly correlated with ICP or CSF ventricular volume. Finally, caudate volume was not significantly different in hydrocephalic animals compared to SC.

Conclusion: The 300–400% increase in %VEGF-R2+ neurons and glia in hydrocephalus indicates a stimulated VEGF response that may be related to hypoxia in the caudate. The observed increase in VEGF-R2+ was not associated with angiogenesis, however may play a role in neuroprotection. Modulation of VEGF receptors may be important in our understanding of the role of hypoxic in the pathophysiology of hydrocephalus and lead to adjunct treatments.

S3

Does NPH equal ischemia?

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Background: It has been postulated that NPH equals pressure- and distortion-induced ischemia. Such a postulate fails to take into consideration the high co-incidence of AD and cerebrovascular disease (CVD) with NPH; as well as the observation that ischemia persists despite resolution of the elevated CSFP and ventriculomegaly [1, 2]. We offer an alternate postulate, that NPH is a multifactorial disease and that defective metabolite clearance, e.g., amyloid-beta peptides (A β) and Tau protein, via the CSF and across the blood-brain barrier (BBB), play a significant role in the dementia and ischemia of NPH.

Materials and methods: Aged Sprague-Dawley rats (12 mos) had hydrocephalus induced by intracisternal kaolin injection [3]. Brains were harvested at two, six and 10 weeks post-induction, n = 4–6 for each experimental group. The brains were stained for A β , hyperphosphorylated Tau (hpTau), and the A β transporters LRP-1, Pgp and RAGE (receptor for advanced glycation end products) by immunohistochemistry (IHC). Three epitopes of hpTau were used: pT231, pS262 (intraneuronal) and AT100 (extraneuronal). Cerebral microvessel isolations (MVs) were performed and the extracted RNA and protein were assayed for the A β transport proteins. Western blots and ELISA were used to assay A β and Tau accumulation. Aged matched non-operated rats serves as controls.

Results: On IHC, A β accumulated in cortex and hippocampus with increasing hydrocephalus, particularly around microvessels and in and around neurons. HpTau, pT231, was seen in neurons in a typical AD pattern: loss of dendritic hpTau and accumulation and margination of hpTau granules in the cell soma. Extracellular hpTau, AT100, was also seen to accumulate around blood vessels. The A β transport proteins were significantly altered in the MVs compared to controls: LRP-1 and Pgp were down-regulated whereas RAGE was up-regulated.

Conclusion: These studies show that induction of hydrocephalus (increased resistance to CSF absorption and decreased CSF production and turnover) leads to defective CSF and BBB metabolite clearance, and to the accumulation of A β and hpTau, similar to what is seen in AD [4, 5]. The localization of A β , a known vasoconstrictor, and hpTau to cerebral blood vessels suggests that these toxins may play a role in the persistent ischemia and CVD seen in NPH. Hydrocephalus in aged animals, therefore, causes severe metabolic dysfunction, due to a progressive inability to clear metabolites, and is likely a major cause of the pathology in NPH.

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S4

Opposite changes in cerebellar vs. cortical blood brain barrier (BBB) expression in aged and hydrocephalic rats

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S4

Background: Little is known about the cerebellum in NPH. Studies show that neurotransmitter changes in the cerebellum

are opposite to the cortex [1, 2]. In Kaolin-induced hydrocephalus, increases of A-beta peptides at cortical and hippocampal microvessels were found [3]. Reciprocal changes in BBB receptors, LRP-1, which transports A-beta out of, and RAGE, which transports A-beta into the brain, indicated a defective clearance might be causal. We looked at LRP-1 and RAGE expression changes in the cerebellum vs. the cortex in hydrocephalic and aged rats.

Materials and methods: In Brown-Norway/Fisher (BN/F) rats, Western blots (WB) of the BBB transporters LRP-1 and RAGE were performed in the cortex, cerebellum and in microvessel preparations, N = 8 at ages 3 (young), 12 (mid-aged) and 36 months (senescent). In fifteen 12 months-old Sprague-Dawley (SD) rats with Kaolin-induced hydrocephalus, cortical and cerebellar cryosections were investigated by specific A-beta42, LRP-1 and RAGE antibody immunohistochemistry (ICH), performed 2, 6 and 10 weeks post induction.

Results: In the BN/F rats, cortical and hippocampal tissue and microvessel WB of LRP-1 at 12 and 36 months showed a loss at the LRP-1 kDa range, compared to 3 mos. rats. In the cerebellum, however, there was a 3-fold increase of positive WB staining at 36 mos compared to 3 mos. For the RAGE blot at 3 mos, the amount in cerebellum at about 42–45 kDa was greater than in the cortex. In the hydrocephalic rats, parenchymal as well as perivascular A-beta stained accumulations were observed in the cerebellar molecular layer, and significantly increased up to 10-weeks of hydrocephalus (Mann-Whitney-U). LRP-1 stained microvessel counts showed decreases ($n \times 40$ microscopic field) at 2, 6 and 10 weeks, however, to a lesser degree than observed in the cortex and the hippocampus (ANOVA, $p > 0.05$). Different from changes seen in the cortex, cerebellar RAGE microvessel staining was decreased at 10 weeks compared to the age-matched controls (ANOVA, $p < 0.01$), and correlation between the amount of stained amyloid and RAGE vessel count was negative (-0.469 , $p < 0.05$).

Conclusion: Qualitatively and quantitatively, the BBB receptor expression in the cerebellum appears to be opposite to that in the cortex in ageing rats. Different from cerebellar changes seen in the ageing rat model, and different from A-beta/BBB receptor relationships seen in the cortex, in hydrocephalus, the cerebellar LRP-1 vessel staining mirrored the cortical changes while the RAGE opposed them. The findings might indicate a role for “remote” mechanisms in the cerebellum in hydrocephalus.

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S5

Shunting in AD increases ventricular CSF protein levels

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S5

Background: Defects in CSF circulation may impair clearance of toxic metabolites (i.e. amyloid-beta peptides – A β), from the brain via interstitial fluid (ISF) and so contribute to pathology in Alzheimer’s disease (AD). On this view, constant drainage of CSF via a low-flow ventriculo-peritoneal shunt could facilitate clearance of toxic moieties from ISF and so slow disease progression. We tested this possibility in a prospective, randomized, double-blind controlled, multi-centre trial. We have reported elsewhere that patients with active shunts showed less cognitive decline than controls. Here, we analyse the effects of shunting on CSF protein concentrations in AD patients.

Materials and methods: The study group consisted of 164 patients with probable AD (NINDS-ADRDA criteria) with mild to severe dementia by Mattis Dementia Rating Scale (MDRS) (baseline MDRS scores of 54–137). We measured total protein concentration in ventricular CSF at shunt implantation (baseline time = 0), and 3, 6, and 9 months post-operatively, using each centre’s standard protocol. We analysed changes in protein levels using linear mixed effects models incorporating an exponential variance function to adjust for heteroscedasticity over time. The analyses excluded 25 observations for protein levels, over 70 mg/dl, below 10 mg/dl, missing baseline or 9 month data.

Results: 139 patients had protein data (overall mean 21.8 mg/dl). Protein levels for the control patients decreased by 0.37 mg/dl per month after operation ($t = -2.41$, 125 df, $p = 0.017$) but those in the actively shunted group increased by 0.40 mg/dl per month ($t = 2.16$, 111 df, $p = 0.033$). The contrast between the active shunt and control groups was highly significant ($t = 3.08$, 236 df, $p = 0.003$). The variability of protein levels increased over time in patients with active shunts, but not in controls (LR $\chi^2 = 7.7$, 1 df, $p = 0.006$).

Conclusion: AD patients with inactive control shunts showed reductions of both cognitive level and CSF protein concentrations. These results suggest the possibility of a progressive failure in mechanism(s) that transport proteins from the ISF to the CSF in AD. Conversely, active CSF shunting increased CSF protein levels in AD patients and helped maintain their cognitive

function. These results support the hypothesis that CSF shunting may ameliorate AD by facilitating clearance of toxic moieties from ISF to CSF. The increased variability in protein levels in patients with active shunts may result from the beneficial effects not occurring in some patients, and/or possibly from unwanted side effects in a few individuals.

S6

Ultrastructural study of the permeability of *in-vitro* and *ex-vivo* human models of human arachnoid granulation CSF outflow pathway

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S6

Background: In communicating hydrocephalus and also idiopathic intracranial hypertension, disturbed CSF dynamics may result from an increased resistance to CSF outflow at the arachnoid granulations (AGs). To better understand the mechanism of CSF egress, we modelled the outflow of CSF through human AGs using both cell culture (*in-vitro*) and whole tissue (*ex-vivo*) perfusion models. Ultrastructural studies were done using microparticles, ruthenium red, and TEM and to elucidate the mechanism of fluid flow.

Materials and methods: Human AG tissue was harvested within 24 h post-mortem and used to isolate AG cells for growth on filter inserts or fit into an Ussing perfusion chamber. Cell phenotype was identified in culture with immunocytochemical staining. Tissue was perfused at physiologic and increased pressure with serum-free media. Cells/tissue were perfused with fluorescent microparticles, or ruthenium red, and then fixed under experimental pressure. Fixed tissue was processed for TEM or cryo-sectioned and stained for visualization.

Results: *In-vitro* serum-free permeability results showed flow through the AG cells was uni-directional in the physiologic direction from the basal to apical (B→A) cell membrane. The average cellular hydraulic conductivity ($L_{p_{ave}}$) for AG cells perfused B→A was $93.05 \pm 10.69 \mu\text{L}/\text{min}/\text{mmHg}/\text{cm}^2$ ($n = 19$) with average perfusion pressure (ΔP_{ave}) across the cell layer of $2.92 \pm 0.08 \text{ mmHg}$ which was statistically higher ($p < 0.0001$) than $L_{p_{ave}}$ for cells perfused A→B (non-physiologic direction), $0 \mu\text{L}/\text{min}/\text{mmHg}/\text{cm}^2$ ($n = 5$) with ΔP_{ave} of 3.23 mmHg .

Ex-vivo serum-free perfusion experiments performed at 5 mmHg pressure B→A resulted in $L_{p_{ave}}$ of $7.5 \pm 2.2 \mu\text{L}/\text{min}/\text{mmHg}/\text{cm}^2$ ($n = 9$). The $L_{p_{ave}}$ of tissue perfused in the A→B direction was $0.06 \pm 0.01 \mu\text{L}/\text{min}/\text{mmHg}/\text{cm}^2$ ($n = 3$). The $L_{p_{ave}}$ at 15.9 mmHg in the B→A direction was $6.42 \pm 1.76 \mu\text{L}/\text{min}/\text{mmHg}/\text{cm}^2$ ($n = 9$), which was not statistically different from the $L_{p_{ave}}$ at the lower pressure.

Sections of arachnoid membrane with no visible granulations were perfused at physiologic pressure resulting in significant flow, suggesting the presence of microvilli in the membrane contributing to total CSF outflow. The CSF outflow area contributed by the microvilli must be considered in estimating total outflow capacity of the membrane.

Cells perfused physiologically showed extra-cellular cisternal spaces between overlapping AG cells suggesting a pathway for para-cellular fluid transport. Several vacuoles within the cytoplasm, which did not stain with ruthenium red, were shown and suggest a trans-cellular pathway for fluid flow.

Conclusion: AG perfusion results in both *in-vitro* and *ex-vivo* models showed that flow was uni-directional and physiologic. TEM showed large intra-cellular vacuoles and extra-cellular cisternal spaces which represent two distinct mechanisms by which AG cells move fluid: 1: Trans-cellular transport via intra-cellular vacuoles, 2: Para-cellular transport via extra-cellular cisterns, which were traced by microparticles. *Ex-vivo* perfusion results are being studied further to understand the complex relationship between flow through the visible AGs and microvilli.

S7

Hydrocephalus in primary craniosynostosis

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Background: Ventricular dilatation in the presence of primary craniosynostosis is a unique condition with respect to pathogenesis, clinical significance, and management. We report on our personal experience with this condition over a period of 20 years.

Materials and methods: In a series of 613 patients treated for craniosynostosis and subjected to at least one detailed evaluation by ultrasound, CT scanning or MRI we found 134 to be affected with various degrees of ventricular dilatation. 32 of them ultimately turned out to be shunt-dependent.

Results: Hydrostatic hydrocephalus was rarely observed in nonsyndromic craniosynostosis, and in these cases it was usually attributable to coincidental disorders including four cases of myelo-meningocele associated with coronal suture synostosis. Conversely, progressive hydrocephalus was a fairly common feature in syndromic craniosynostosis of the Crouzon or Pfeiffer type, whereas in the Apert syndrome the usual finding was that of non-progressive ventriculomegaly which, however, was also noted in some cases of Crouzon syndrome.

Conclusion: The pathogenesis of progressive hydrocephalus in Crouzon patients is a matter of still ongoing debate. A hypoplastic posterior fossa leading to crowding of its contents and extrusion of the cerebellar tonsils as well as venous outflow compromise are the main causative factors currently being discussed. The diagnosis of progressive hydrocephalus is hampered by the fact that intracranial hypertension may be attributed to both, CSF circulation disorder and premature sutural fusion. Moreover, in a synostotic skull accelerated head growth cannot be expected, classical clinical signs of intracranial hypertension may be absent, and ventricular dilatation may become evident only after decompressive cranial surgery. Therefore, careful surveillance of intracranial pressure and ventricular size in the pre- and postoperative period is a diagnostic mainstay in these cases. Ventriculo-peritoneal

shunting remains the most reliable mode of treatment although surgical expansion of the posterior fossa has been suggested as an alternative option.

S8

Reliability of the MRI diagnosis of the Chiari type2 malformation

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S8

Background: Every clinician familiar with spina bifida knows what Chiari type2 malformation (C2M) is about. However, as soon as it concerns a single patient, the discussion starts whether or not it is justified to make the diagnosis in that particular case. This complicates the insight in the epidemiology and pathogenesis, complicates the indication for (fetal) surgery and complicates inferences on the effect of treatment. This was reason for us to investigate the reliability of the diagnosis of C2M.

Materials and methods: We investigated the reliability of the diagnosis of C2M, by testing the inter observer correlation of 49 MRI criteria which in the literature are considered specific for C2M. With this aim two investigators reviewed MRIs of presumed C2M cases and healthy controls (n = 10). The images were blinded for demographic and clinical information, subsequently arranged by projection (sagittal, axial, coronal) and finally by individual. As a consequence, the connection between the different projections per individual was taken away. Yes/no criteria with more than 80% agreement were considered sufficiently reliable. For quantitative criteria a Spearman rho correlation coefficient of 0.9 was taken as boundary.

Results: Seven out of 29 yes/no criteria and seven out of twenty quantitative criteria fulfilled the requirements of reliability ($\geq 80\%$ agreement or Spearman rho ≥ 0.9). These criteria were: downward herniation of the vermis; herniation around the brain stem; narrowed 4th ventricle; mesencephalic beaking; flattening of the pons; kinking of the medulla; and qualitative measures as position of tonsil, vermis and 4th ventricle; tentorium length; pons thickness; and cerebellar width. The majority of these criteria were obtained from sagittal images (11/29 sagittal criteria); a few from the other images (1/7 coronal criteria; 2/14 axial criteria). Thirty-five criteria did not fulfil the requirements of reliability; some were virtually immeasurable.

Conclusion: A considerable number of criteria that are by tradition considered specific for C2M seem quite unreliable. Against this, a considerable set of criteria, in particular those in the sagittal projection, remains helpful for the diagnosis. Analysis of a larger sample is in progress with the aim to further substantiate the present findings and to make inferences on the specificity of the criteria for C2M.

S9

Pathogenesis of cerebral malformations in perinatal spina bifida aperta

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S9

Background: Spina bifida aperta (SBA) is associated with cerebral morbidity, such as hydrocephalus, Chiari II malformation and cortical dysplasia. Insight in the pathogenesis of these malformations is incomplete. In fetal SBA, such information may help to improve pre- and early postnatal treatment strategies. In perinatal SBA, we investigated the time of initiation of concurrent cerebral malformations.

Materials and methods: In 7 SBA fetuses and 1 neonate [16–40 (median 28) weeks gestational age (g.a.)], we cross-sectionally investigated the histology of the aqueduct [n = 5], cerebral convexity and parenchyma [n = 8] by haematoxylin-eosin and nestin staining. The meningocele was located at cervical [n = 1], thoracic [n = 3] and lumbar [n = 4] spinal level. Cerebral histology was intra-individually associated with fetal ultrasound parameters (ventricular size, head circumference and Chiari II malformation). The mean and median duration between fetal ultrasound and histological assessment were both 4 days.

Results: In SBA fetuses of all gestational ages, histological malformations at the aqueduct (hemosiderophages/gliosis [5/5] and forking/slit like deformities [5/5]) were present. In the two youngest fetuses (16 and 21 weeks g.a.), we observed peri-aqueductal ependymal denudation, progenitor cell loss and heterotopia. From the 2nd half of pregnancy onwards, Chiari II malformation concurred with ventriculomegaly [4/6] and successively, with macrocephaly from 37 weeks g.a. onwards [3/3]. In absence of arachnoidal fibrosis, delivery-related haemorrhages were present in all fetuses (at the fossa posterior and/or cerebrum in 6/7 and 5/7 fetuses, respectively). In the only patient that succumbed during the first week after birth (39 weeks g.a.), raised intracranial pressure concurred with arachnoidal fibrosis at the convexity.

Conclusion: In fetal SBA, the earliest peri-aqueductal alterations precede the development of hydrocephalus. During the 2nd half of pregnancy, ventriculomegaly appeared unrelated to CSF malabsorption. After birth, however, CSF malabsorption may increasingly contribute to the development of high-pressure hydrocephalus. These data may implicate that peri-aqueductal ependymal denudation and progenitor cell loss occur by a mechanism independent of high-pressure hydrocephalus or ventricular distention.

S10**Cystatin C: a potentially useful marker for identifying individuals with spina bifida and early renal insufficiency**Eric Levey¹, Susan Demetrides¹
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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S10

Background: Individuals with spina bifida (SB) are at risk for deterioration of their upper urinary tracts due to neurogenic bladder and subsequent progressive chronic renal insufficiency (CRI). Serum creatinine (SCr) is the most widely used marker to assess renal function and to estimate glomerular filtration rate (GFR), although it has significant limitations. SCr is dependent on age, height, gender and muscle mass and has been shown to be an unreliable marker of renal function in SB. Cystatin C (CyC) is a cysteine proteinase inhibitor of low molecular weight, produced at a constant rate by all nucleated cells, freely filtered at the glomerulus, and not secreted or reabsorbed at the renal tubule. CyC is independent of age, height, and gender and is believed to be independent of muscle mass. Over the past several years, serum CyC has been shown to be a better marker of renal function and GFR than SCr (using the Schwartz formula) in children. One study by Pham-Huy in 2003 showed that CyC was much better correlated with GFR than SCr in children with SB.

Materials and methods: We made arrangements with the Johns Hopkins Hospital Department of Laboratory Medicine to make Cystatin C available as a clinical laboratory test and began recommending yearly Cystatin C and serum electrolytes as part of routine care for patients in the SB Center at Kennedy Krieger Institute in July 2006.

Results: To date, CyC has been measured in 34 patients, mean age of 18.2 years, and range 1 to 47. None of these patients were previously diagnosed with CRI. For 33 of the patients with SB, the CyC measurements were within the previously established normal range for children and adults of 0.5 – 1.0 mg/L. These 33 SB patients had a mean CyC of 0.75 mg/L, range 0.56 to 0.94, and standard deviation of 0.10, fitting a very typical normal distribution. The 47 year old had an elevated CyC of 1.91 mg/dL, suggesting CR. Review of her history showed several episodes of acute renal failure in the past as well as chronic metabolic acidosis and other clinical evidence of CRI, although her measured serum creatinine was normal at 1.0 mg/dL. Of the 33 patients, 19 (58%) had SCr measured below normal while CyC was always within the normal range. One patient had CyC measured twice, 6 months apart, and values were consistent 0.81 initially and then 0.85.

Conclusion: Cystatin C shows promise as a simple blood test that can be used to screen individuals with SB for early development of chronic renal insufficiency and for estimating GFR.

S11**Muscle echogenicity is increased in fetuses with spina bifida aperta**Renate J Verbeek¹, Johannes H vd Hoeven²,
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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S11

Background: In spina bifida aperta (SBA), movements caudal to the meningomyelocele (MMC) are present in utero, but they disappear shortly after birth. Insight in onset and progression of movement loss is therapeutically relevant. Determination of muscle echogenicity (or density (MD)) is used to estimate onset and progression of various neuromuscular disorders in children. In prenatal SBA, we hypothesized that MD assessment could indicate onset and progression of muscle damage in relation to movement loss. Objective: To estimate onset and progression of muscle changes in fetal SBA by MD assessment.

Materials and methods: MD (muscle/bone pixel-density) was obtained in calibrated images (by standardized ultrasound methods). In SBA (n = 6; GA 22–37 wks) and control fetuses (n = 11; GA 17–36 wks), we assessed MD in gluteus/gastrocnemius (L5-S1), tibialis ant. (L4-5), quadriceps (L2-4), and biceps/triceps (C5-8) muscles. MMCs were at Th12 (n = 1), L4-5 (n = 1) or L5-S1 (n = 4) level. In SBA fetuses, MD was compared between muscles from myotomes caudal and cranial to the MMC. Additionally, MD was compared between SBA fetuses and aged matched controls (n = 6 and median GA 33 wks in both groups), and between pre- and postnatal SBA (<1 week after birth). In succumbed fetuses, MD values were related to histological observations in affected muscles (3 SBA fetuses).

Results: During MD assessment, movements caudal to the MMC were present in all SBA fetuses. MD values correlated with gestational age, both in controls and in SBA myotomes cranial to the MMC (r = 0.44, p < 0.01; r = 0.50, p < 0.05; resp.). In contrast, MD values in SBA myotomes caudal to the MMC did not correlate with gestational age (r = 0.26, p = 0.13), and were significantly higher than cranial to the MMC (median +19%, p < 0.01) and controls (+45–60%, p < 0.01). Longitudinal pre- and postnatal MD values caudal to the MMC did not significantly differ (mean 14%). MD values in SBA myotomes caudal to the MMC corresponded with histological assessment (extent of atrophic/hypertrophic muscle fibres).

Conclusion: Despite persisting leg movements in fetal SBA, MD in myotomes caudal to the MMC is increased prenatally. Early postnatal disappearance of leg movements is unrelated to an additional increase in perinatal MD. Present data support the concept that permanent movement loss is related to acute spinal damage rather than to intrinsic muscle impairment.

S12**Complete tendon transfer and inverse lambrinudi arthrodesis. A new developed operative treatment for paralytic pes calcaneus in spina bifida**

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S12

Background: Paralytic pes calcaneus, which is commonly seen in spina bifida continues to be one of the most difficult deformities to treat.

The purpose of this study is to report on a new developed operative procedure to dynamically correct pes calcaneus and to report on its midterm follow-up.

Materials and methods: Eleven consecutive patients (16 feet) with paralytic pes calcaneus were evaluated between 1999 and 2005. Preoperative functional statuses as well as preoperative radiographic parameters were compared with postoperative results. A retrospective review evaluated pain, independence, function, motion and pre- and postoperative complications.

Results: Ten out of eleven patients reported good to excellent results. All patients gained independent activity and walked without assistive devices. Six out of eleven patients still required bracing but more minimally than their preoperative condition. The strength of the plantarflexors increased from an average of 1 out of 5 preoperatively to 4 out of 5 postoperatively, according to the Medical Research Council (MRC) scale for grading muscle power. Pain and function utilizing the AOFAS hind foot score improved from an average of 34 to 82. Range of follow-up was an average of 23 months.

Conclusion: The new developed technique consisting of a complete tendon transfer and an inverse Lambrinudi provides an excellent functional result without the residual complications associated with ankle-arthrodesis.

S13**Current prevalence of latex sensitization in children with spina bifida with use of latex precautions**Eric Levey¹, Susan Demetrides¹, Robert Hamilton² and N Franklin Adkinson²

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S13

Background: Children with spina bifida (SB) historically were found to have high rates (up to 50%) of latex sensitization and allergy believed due to repeated high-risk exposures including surgeries and catheterization. Latex allergy can in some cases be life-threatening and certainly impacts quality of life. Since the association between SB and latex has been substantiated, most SB Centers have begun using latex avoidance measures with presumed lower rates of sensitization. Objective: The purpose of this study is to evaluate the prevalence of latex

sensitization and allergy in a population of children with spina bifida that was born after the institution of latex avoidance measures, and to assess associated risk factors for latex sensitization.

Materials and methods: Individuals with spina bifida, age 0 to 18 years, are being recruited from a regional SB Center during routine clinic appointments. Study participants complete a latex allergy questionnaire regarding demographics, history of allergy, number of surgeries, and use of CIC. A blood sample is obtained for measurement of latex-specific IgE, total IgE, and two multi-allergen screens, one detects IgE antibody to 15 common aeroallergens (Phadiatop) and the other, IgE to the 5 foods (milk, egg, soy, wheat, and peanut) that cause most food sensitivities in children (FX5).

Results: N = 35, mean age 7.8 years, range 0.3 to 17 years. Of the 35 patients tested, 5 (14%) tested positive for latex-specific IgE. One child was 6.5 years old and had her initial surgery in United Arab Emirates without latex precautions. The other 4 children who were sensitized to latex were 10 years of age or older. All 5 latex IgE positive individuals had total IgE levels that were significantly elevated (>200 U/mL). There was no statistically significant relationship between positive Phadiatop or FX5 and positive latex IgE. Positive latex IgE was statistically associated with black race (p = 0.006) but was not associated with gender, number of surgeries, CIC, or history of atopy or food allergy.

Conclusion: The prevalence of latex sensitization has decreased substantially with the use of latex avoidance measures. None of the 19 children under 10 years of age who were born in the U.S. had detectable latex-specific IgE. The relationship between race and latex sensitization needs to be explored further. The study may be underpowered to detect an actual relationship between latex sensitivity and some risk factors. We are continuing to recruit study participants.

S14**Early start to therapy preserves kidney function in spina bifida patients**

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S14

Background: Renal scarring and renal failure remain a life-threatening problem in children born with spinal dysraphism; in the literature it is reported that more than 20% of these children die within the first year of life due to renal problems. We show that optimal treatment of the neurogenic bladder from birth onwards can preserve kidney function in most spina bifida patients.

Materials and methods: We reviewed data on all newborns with spinal dysraphism admitted to our hospital between January 1988 and June 2001. We looked at their situation at admission and at follow-up, when treatment was started and the type of treatment (antimuscarinic agents, continuous intermittent catheterisation (CIC), antibiotic prophylaxis), as well as renal function (ultrasound, DMSA scan, serum creatinin, creatinin clearance: Schwartz formula) and bladder function (urodynamic studies). Cases were followed for a maximum of 13 years.

Results: Data from 144 children out of a cohort of 176, could be evaluated by the end of the study: 5 patients had pre-existing renal abnormalities; 69 patients had an overactive sphincter 27 of the 144 patients had reflux and 6 had renal scarring. None of these patients are currently developing end-stage renal disease. 5 of the 6 patients with renal scarring were started on therapy with intermittent catheterisation and antimuscarinic therapy. 63 out of 82 children with spina bifida were dry at school age (6 years).

Conclusion: Early start to therapy helps enormously in safeguarding renal function for children born with spinal dysraphism.

S15

Does long term intravesical oxybutynin treatment of hyperreflexic neurogenic bladder result in bladder auto-augmentation?

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S15

Background: The main goal of the treatment of neurogenic bladder is to promote continence and protect the upper urinary tract from deterioration. Conversion of a hyperreflexic detrusor to a lower pressure detrusor could be reached by the use of anticholinergic medication and clean intermittent catheterization (CIC). Important alternative to reduce side effects and lower the detrusor pressure is the intravesical administration of oxybutynin. The presented study investigated the urodynamic effects of the long-term administration of intravesical oxybutynin in hyperreflexic neurogenic bladder to evaluate the property of bladder auto-augmentation.

Materials and methods: The study included two groups of patients with hyperreflexic neurogenic bladder. Group I was treated with CIC and oral anticholinergic medication, group II with CIC and intravesical oxybutynin instillation. Urodynamic assessment was performed before treatment and every following year.

Results: Group I included 9 patients (mean 17.6 years), group II 12 patients (15.8 years). The bladder compliance of 3/9 patients of group I increased to normal values with age (>10 ml/cmH₂O). 6/9 patients of group I responded partially with an increase of bladder compliance. The overall bladder capacity increased from 177 ml +/- 104 ml up to 367 ml +/- 123 ml in group I. 2/12 patients of group II stopped the treatment due to side effects. 7/10 patients of group II increased their bladder compliance up to three times with age and reached normal values. The bladder capacity (group II) increased from 148 +/- 61 ml up to 351 +/- 105 ml. 3/10 patients of group II responded only partially with a moderate increase of bladder compliance (2/10) or no improvement (1/10).

Conclusion: Oral anticholinergic medication and intravesical oxybutynin are effective to increase bladder capacity. Furthermore intravesical oxybutynin also increases bladder compliance. This leads to diminished bladder pathophysiology. Intravesical oxybutynin instillation enables sufficient bladder auto-augmentation in selected patients with neurogenic hyperreflexic bladder.

S16

“Whose bowel is it anyway?” A case study illustrating the practical difficulties resulting from a childhood procedure that impinges upon an adult with spina bifida attempting to live independently

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S16

Background: John is 23 years old, has spina bifida, shunted hydrocephalus and left hemiparesis. John had caecostomy with insertion of a gastrostomy button 10 years ago for the purpose of antegrade colonic enema (ACE) bowel management. The bowel washouts caused severe abdominal discomfort and were ineffective. The button was therefore replaced by a jejunostomy feeding tube, which delivered the fluid into the mid transverse colon making him continent with a regime of washouts every third day. After attending college for several years, John moved to live alone in a flat, away from his very supportive parents. John's physical disabilities prevented him from completely managing his bowel irrigation independently. Community nurses have insufficient resources to assist John without detracting from his limited social life. Care staff are willing but not allowed to assist.

Materials and methods: Interviews with John and his parents: Telephone interviews with community nurses and social care agencies.

Results: Following lengthy discussion between all parties, a satisfactory solution was reached. John changed the method of funding his social care in order to create a contract with his social carers allowing him greater flexibility to meet his needs. The procedure was reduced to its component parts. John performed the elements of which he was physically capable, leaving his social carers to undertake the remainder. District nurses undertook risk assessments to ensure that the procedure was carried out with no breach to John's safety and wellbeing.

Conclusion: Childhood procedures may have implications for management in adulthood and in the ever-changing health and social care climate consideration must be given to the long-term needs and abilities of the client.

S17

Auto-augmentation: ought it to be done?

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S17

Background: Neuropathic bladder secondary to spina bifida may result in serious kidney damage and socially-disabling urinary incontinence. Failure to respond to clean intermittent catheterisation and anti-cholinergic medication may necessitate bladder augmentation, a major operation with significant risks, including the possibility of malignant transformation of the augment.

The development of auto-augmentation (detrusorotomy or detrusorrectomy) as an alternative procedure, where the hypertrophic detrusor muscle is split and separated from the intact mucosa of the bladder, promised avoidance of many of the consequences of traditional augmentation. However, the literature remains unclear as to whether auto-augmentation is effective in such patients, or a sub-group thereof, or has a role in delaying the need for a more complicated procedure until later in life, when the potential for stunting of growth may be less important.

Materials and methods: The records of all children undergoing auto-augmentation from 1996 to 2006 in a regional specialist paediatric surgical unit were analysed. Comparisons were made between the pre- and post-operative status for the following endpoints: continence, nephropathy, and video-urodynamic parameters (bladder capacity, maximal detrusor pressure [MDP], and vesico-ureteric reflux [VUR]).

Results: Comparative data were available for six girls and five boys aged between 5 and 14 (mean = 10.3) years at the time of detrusorotomy, in two cases accompanied by colposuspension. Follow-up period was between 1.3 and 6.8 (mean = 3.5) years post-operatively. Spina bifida was the underlying condition in all but one of the children, all of whom had small, poorly compliant bladders with upper tract deterioration and/or failed maximal medical therapy.

Five of the 11 patients had an increase in bladder capacity (mean increase = 40%), as a function of the predicted capacity for age. Three had an improvement in MDP (13 – 69% reduction). Two of the three patients with pre-operative VUR had resolution following surgery. None of the four patients with no pre-operative VUR developed it post-operatively. Four were unable to be assessed due to incomplete urodynamic data.

There was no deterioration on DMSA or renal ultrasound scan in 10 patients. One patient suffered progressive renal scarring between the two DMSA scans, but there were 20 months between the pre-operative DMSA and surgery, during which time this scarring may have occurred. Five patients had a subjective improvement in continence. To our knowledge, no patient has had further surgery to date.

Conclusion: Our study suggests that auto-augmentation was beneficial in terms of improved urodynamic parameters in five out of eleven children, in the medium term at least, and does not cause deterioration in VUR. However, pre- and intra-operative predictors of success remain elusive. We suggest the continued inclusion of auto-augmentation in the surgical armamentarium for neuropathic bladder, but continued follow-up is required post-operatively.

S18

Bowel and bladder continence among children with spina bifida: a retrospective study

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S18

Background: Spina bifida (SB) remains a common birth defect in the United States, affecting approximately one in three thousand live births. Bowel and bladder continence has a significant impact on quality of life in individuals with spina bifida. Objectives: To describe (1) the range of continence outcomes for children with spina bifida receiving usual care from an established multidisciplinary SB clinic and (2) the physiologic, medical, individual, family and environmental factors that contribute to bowel and bladder continence in children with SB.

Materials and methods: Records of patients evaluated during the last 3 years at a regional SB center were reviewed. Inclusion criteria included: age 5 through 18 years, SB diagnosis and no history of bladder or cloacal extrophy or sacral agenesis/caudal regression. Medical records of 96 eligible patients, from a total of 116 screened, were abstracted. Sample mean age was 11.5 years. Fifty-one (53%) were males and 45 (47%) were females. The majority (85%) had myelomeningocele and 79% had hydrocephalus.

Results: The majority of children (76/95) utilized clean intermittent catheterization (CIC) for bladder emptying. Of the remaining children, 9 were continent with spontaneous voiding, 5 used timed toileting, and 5 voided into a diaper. The vast majority of children using CIC reported some leaking (73%). Most children who had urine leakage also had bowel incontinence (74%). There was a positive relationship between having a recent urinary tract infection (UTI) and leaking between CIC/voids ($\Phi = 0.41$, $p < 0.01$). Other treatments for urinary incontinence included anticholinergic medications (46%), urologic surgery (31%) and behavioral approaches. Bowel management included oral medications, suppositories, antegrade and retrograde enemas, and assisted evacuation. Bowel surgery was done in 29%. The top barriers to adherence to toileting routines for the child were: initiation, anxiety, organization, and memory. For adults/caregivers barriers to adherence included lack of provision of positive reinforcement, lack of understanding of developmentally appropriate supervision, and lack of medication/routine organization.

Conclusion: The majority of children with SB still have some bowel and bladder incontinence despite medical intervention. This research demonstrated the prevalence of incontinence in this population and formed the basis for our current prospective randomized controlled study to assess whether a behavioural intervention can improve compliance, decrease medical complications, and improve health-related quality of life in children with SB.

S19

Outcome on renal function in children with neurogenic bladder dysfunction of a standardised follow-up programme

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S19

Background: Renal damage still constitutes a major reason for morbidity and mortality in persons with Spina Bifida [1].

Clean intermittent catheterisation is the cornerstone in treatment of neurogenic bladder dysfunction often combined with anticholinergics [2]. Multiple techniques of renal protective surgery have been developed but have also significant risks of both short- and long-term side effects. In Sweden national guidelines for follow-up of children with Spina Bifida have been developed [3], now under revision.

Materials and methods: Records and cystometries of 40 consecutive children with spina bifida, and 1 child with sacral agenesis were reviewed. The children, 19 girls and 22 boys, were born 1993 unto 2003 and were followed in our department with repeated urodynamics and other evaluations according to the guidelines. Thirty had ventriculoperitoneal shunts and all but one neurogenic bladder dysfunction. Clean intermittent catheterisation (CIC), was used by 38/41. Most children were followed from birth giving a mean follow-up time of 9 years. Children who twice had resting pressure >30 cm H₂O at maximum CIC or voided volume were regarded as a high pressure group.

Results: All children had a normal total renal function but 4 of the 41 had a detectable renal damage by renal scintigraphy (MAG3 or DMSA). In two of these children the damage was already existent before entering the standardised follow-up programme (at age 2 respectively 3 years) and had shown no further deterioration since. Two of the children had a borderline GFR on Cr-EDTA-clearance, but in the normal range, while the remaining had normal laboratory results. At the end of the study 23 children were receiving anticholinergic treatment, all but three intravesically, and only three children used prophylactic antibiotics. None of the children had been through any renal protective surgery. Of seven children in the high pressure group four had renal damage, while none in the low pressure group (significant $p < 0.05$). It is noticeable that these four children had all a complicated social situation. Urinary tract infections were significantly more frequent in the high pressure group and in the children with renal damage ($p < 0.05$).

Conclusion: A pro-active follow-up programme with early conservative treatment showed a high rate of success in preventing renal damage. This was reached without any renal protective surgery. Those with high resting pressures had significantly more renal damages and urinary tract infections.

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S20

Independence in the toilet activity in children with myelomeningocele

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Background: Most children with myelomeningocele (MMC) have neurogenic bladder dysfunction, with often lifelong needs of treatment making many of them dependent into adulthood. The aim of the present study was to identify and describe deficits in motor respectively executive functions, and time-concept perception hindering independence in the toilet situation for children with MMC treated with clean intermittent catheterisation (CIC) and secondarily to describe their own opinions on how their toilet activity works.

Materials and methods: In a hospital setting 22 children (11 girls) with MMC and neurogenic bladder dysfunction, 6 – 19 years old (md 13.1 ys) were observed in a toilet visit when performing CIC. Before visiting the toilet the children were asked to rate, using the Canadian Occupational Performance Measurement (COPM), how well they experienced their toilet activity performance and the satisfaction the way they managed it. After the toilet visit a semi-structured interview and an assessment of the time-concept perception (Ka-Tid [1]) were performed.

Results: Twelve children rated their toilet activity performance as maximally good, as well as the satisfaction the way they managed it. Only five rated themselves as median or below. In contrast the observation showed that just five children were independent and 17 children showed varying motor and/or executive limitations for independence in the toilet activity.

Concerning the time-concept test only two children scored top scores on all items, indicating impaired perception of time since the instrument was developed for children 6–10 years (md 6.1 ys). A significant correlation (Rho 0,675, $p = 0,001$) was found between the degree of independence in the toilet situation and time-concept perception.

Conclusion: It seems as the children have an unrealistic apprehension of their abilities but how to become independent when not realizing you are dependent? It is important to identify time-concept impairment, in order to offer children means of training and/or compensation with technical aids. To increase the children's awareness of their abilities and limitations in toilet activities, the adoption of a client centred framework is recommended.

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S21

Simple clinical and bedside urodynamic evaluation is sufficient for successful management decisions in spina bifida patients with urinary incontinence and the machine urodynamics are not necessary

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S21

Background: Our experience with evaluation of spina bifida with urinary incontinence has evolved through three phases. In

the first phase, before the year 2000 we were doing only machine urodynamics. In the second phase with machine urodynamics from (2000 to 2003), we took study to compare the observations and results of simple clinical bedside evaluation (SCBE) in taking management decisions in patients with spina bifida and urinary incontinence. In the third phase, from 2004 onwards, we have stopped doing machine urodynamics completely in evaluation of patients and now do only SCBE. We believe that SCBE is sufficient to take management decisions in such patients. In this paper we will present data of 10 patients of spina bifida whose management decisions were made using SCBE.

Materials and methods: In the past three years ten patients of spina bifida (age limit 1.5–16 yrs) were treated for their urinary incontinence. All of them were evaluated by SCBE (resting pressure, random residual volume, leak point pressure, bladder capacity, MCU, USG). Based on the results of these tests, management strategies were decided. The case histories, treatments given and outcome (after six months to one year follow up) of these ten patients will be presented and discussed.

Results: These ten patients have shown significant clinical improvement in continence, which was further ascertained by improvement in findings by SCBE.

Conclusion: Thus, we strongly believe that SCBE is sufficient for successful management decisions in urinary incontinence and cumbersome and expensive machine urodynamics are unnecessary and need not be performed as routine in these cases.

S22

Hyperdynamic pulsatile flow and ventricular dilation in experimental communicating hydrocephalus

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Background: In communicating hydrocephalus (CH), where either there is no obvious physical blockage within the subarachnoid space, or the obstruction can be variable in location, explanations for the symptoms and clear-cut effective treatments have been elusive. A few investigators have begun to stress the importance of pulsatile vascular and CSF dynamics. While it is known that pulsatile flow through the cerebral aqueduct is often significantly elevated in hydrocephalus, a clear link between abnormal pulsations and ventriculomegaly has been yet to be established. The purpose of this study was to characterize the temporal changes in intracranial pulsatility in a novel model of CH.

Materials and methods: Kaolin (25%) was injected into the basal cisterns (n = 8) after anterior exposure of the CI-clivus

interval. On days 1, 2, 8, 15, and 31, animals were scanned on a 9.4 Tesla magnet. Ventricular volume was based on CSF-bright 3D-TrueFISP images and aqueductal flow was assessed using a gradient echo phase contrast sequence.

Results: Animals developed ventricular dilation and increased aqueductal pulsations according to two very distinct patterns. Group 1 animals (n = 4) developed severe ventriculomegaly, which progressed steadily for most of the time period investigated. Aqueductal pulsations were also significantly elevated and increased with time in correlation with ventricular volume (R² = 0.75, p < 0.0001). Ventricular volumes and pulsations increased to approximately 10 and 30 times normal, respectively. Group 2 animals (n = 2) developed mild ventriculomegaly, which changed very little after Day 1. Aqueductal pulsations were increased on Day 1 and remained so until Day 15, whereupon they returned to control levels and remained low. Ventricular volumes in this group increased to approximately 3 times normal and pulsations increased to approximately 6 times normal (before decreasing on Day 15). In both groups, ventricular volume and aqueductal pulsations were found to be elevated even on Day 1 post CH-induction.

Conclusion: These preliminary results suggest that basal cistern-induced CH is associated with an immediate change in ventricular CSF pulsatility. While the severely hydrocephalic animals demonstrate a clear connection between ventricular dilation and ventricular pulsations, the mildly hydrocephalic animals seem to indicate that this relationship is not strictly held. In fact, the late drop in pulsatility may be indicative of a compensatory mechanism, which may help to control progressive ventriculomegaly.

S23

Mechanism of obliteration of Sylvius aqueduct in the H-Tx rat

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Background: There is strong evidence associating a dysfunction of the subcommissural organ (SCO) with the pathogenesis of fetal onset hydrocephalus. In the HTx rat, obliteration of Sylvius (SA) and dilatation of the lateral ventricles start to occur at around E18. This rat animal model of fetal onset hydrocephalus has been the subject of numerous investigations. However, the mechanism and sequence of neuropathological events leading to SA obliteration are not known. The aim of the present investigation is to clarify the role actually played by the SCO in the obliteration of SA.

Materials and methods: The brain of normal and hydrocephalic E15, E16, E17, E18, E19, E20, E21, PNI, PN3, PN5, PN7 and PN10 H-Tx rats was processed for: (1) immunocytochemistry using antibodies against (i) the secretory proteins of the SCO (AFRU), (ii) nestin and (iii) ciliated ependyma; (2) *Limax flavus* agglutinin (LFA; affinity = sialic acid) binding; (3) transmission and scanning electron microscopy.

Results: Up to E18, all embryos from the same litter have a patent SA. However, some of these embryos, most likely corresponding to the mutants that will develop hydrocephalus, displayed an abnormal SCO. The cephalic third and the caudal

third of the SCO were strongly immunoreactive with AFRU, anti-nestin and strongly bound LFA. The middle third of the SCO did not react with AFRU and anti-nestin and LFA binding was weak.

At E18 the middle, non-secretory, third of the SCO progressively fused with the opposing region of the ventral wall of SA, resulting in the SA obliteration detected from E19 on.

Conclusion: 1. In the rostro-caudal axis, the SCO is formed by three distinct zones whose differentiation would be controlled by different genes. 2. A malformation of one of these zones precedes the obliteration of SA. 3. Such a malformation is the primary cause of SA obliteration.

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S24

Anti-Reissner's fibre and anti-p73 co-expression in the subcommissural organ of the mice and rats with spontaneous hydrocephalus

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Background: Reissner's fibre (RF) is formed by the polymerisation of the glycoprotein secreted by the subcommissural organ (SCO). The SCO also secretes soluble glycoprotein into the cerebrospinal fluid (CSF), variations in the RF and SCO have been reported in hydrocephalus. The protein p73 belongs to the tumor suppressor factor family, which also includes p53 and p63. The p73 has several isoforms: the transactivating (TA) isoform that induces apoptosis through p53 target genes and the N-terminal truncated (Δ N) isoform whose levels are dramatically decreased when there is sympathetic neuron apoptosis. Thereafter, p73 isoform equilibrium is involved in neuronal survival and death. In the present work, we analyze the variations of RF and p73 co-expression in the CSF and SCO of the spontaneously hydrocephalus mouse and rat.

Materials and methods: Brains from mice and rats with spontaneous hydrocephalus of 5 and 12 months of age respectively were used. Control mice and control rats (CoR) of the same ages were also used. The paraffin section containing the SCO was immunohistochemically processed with anti-TAp73, anti- Δ Np73 anti-Reissner fibre (AFRU). p73 and AFRU band were also detected in the CSF by western blot.

Results: The different parts of the subcommissural organ ependymal and hypendymal cells showed AFRU immunoreactive material (ir) which was altered in the mice and rats with spontaneous hydrocephalus. The anti-TAp73 was present in the apical part of the SCO ependymal cells, while the hypendymal cell did not show Tap73-ir, the hydrocephalic animals also showed Tap73-ir but with an important variation in its expression when compared with the control. However, the

Δ Np73 was expressed in the cellular nucleus but was scarcely present in the SCO of both rat and mouse groups. The choroideus plexus and other brain structures showed both the isoforms of p73 immunoreactive material with some differences when the mouse and rat groups were compared. This result could mean that the glycoprotein of Reissner's fibre and the Tap73 are interconnected in the functions of the SCO in this kind of animal, which produce alterations in the subcommissural organ secretions. Protein bands were found in the CSF of the hydrocephalic rats that were scarcely present or almost undetectable in the CSF of the control rats.

Conclusion: Hydrocephalus produces alterations in the secretions of the SCO of the mouse and rat and Tap73 protein could play a role in the normal function of the SCO, since TAp73 is interconnected with glycoprotein secreted by the SCO. The alteration of this interconnection produces changes in the secretions of the circumventricular structures and consequently variations of some of the proteins in the CSF.

S25

Lack of formation of Reissner fiber leads to hydrocephalus

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Background: The subcommissural organ (SCO) differentiates early in ontogeny and remains fully active during the entire life span. It secretes glycoproteins into the cerebrospinal fluid (CSF) flowing through the Sylvius aqueduct (SA); these proteins either assemble to form Reissner fiber (RF), or remain soluble in the CSF and circulate throughout the CSF compartments. Overholser *et al.* (1954) have demonstrated that offspring littered by rats maintained on a diet deficient in folic acid and/or Vitamin B12 lack a SCO and develop hydrocephalus. This led them to propose that a dysfunction of the SCO during development leads to stenosis of the SA and hydrocephalus. We have investigated several animal models in which the SCO would play a role in the pathogenesis of hydrocephalus. We have now performed a comparative analysis of the changes occurring in the SCO-RF complex of these animal models, with the aim to find a landmark common to all hydrocephalic animals that might help to unfold the mechanism of SCO-dependant hydrocephalus.

Materials and methods: A comparative study of the SCO-RF complex and SA of five animal models characterized by a dysfunction of the SCO and development of hydrocephalus was carried out. Conventional light and electron microscopy and immunocytochemistry were applied.

Results: Model I. Immunological blockage of RF formation by maternal transfer of antibodies against RF-glycoproteins: undamaged and secretory active SCO, missing RF, stenosed

SA and moderate hydrocephalus. Model 2. *hyh* mice with a point mutation of α SNAP gene: undamaged and secretory active SCO, missing RF, obliterated SA and severe hydrocephalus. Model 3. HTx rat: subcommissural portion (two distal thirds) of SCO missing, supracommissural portion (rostral third) of SCO secretory active, RF absent, obliterated SA and severe hydrocephalus. Model 4. Transgenic mice deficient in transcription factor RFX4-v3: subcommissural portion of SCO missing, supracommissural portion of SCO secretory active, RF absent, patent SA and moderate to severe hydrocephalus. Model 5. *fyn* knockout mice: subcommissural portion of SCO missing, supracommissural portion of SCO secretory active, RF absent, SA with an abnormal shape and severe hydrocephalus.

Conclusion: 1. The SCO is formed by two zones: the subcommissural and the supracommissural portions. 2. Differentiation of both zones would be controlled by different genes. 3. The subcommissural portion of the SCO is essential for RF formation. Mutant and transgenic animals lacking this portion, although still have a secretory active supracommissural portion, do not form a RF. 4. The only common feature to all animal models is the absence of RF. 5. RF-glycoproteins appear to be essential for a normal flow of CSF throughout SA. 6. Absence of RF could cause SA obliteration or a turbulent CSF flow through SA what, in turn, would lead to hydrocephalus. Supported by Fondecyt 1030265 (Chile), the Intramural Program of the NIH, NIEHS (USA), and MEXT (Japan).

S26

p73 isoforms expression in the cerebrospinal fluid and circumventricular organs of BPH mice and SHR rats

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Background: It has been reported that the blood pressure high (BPH) mouse shows an increase in blood pressure and alterations in the brain catecholaminergic system as well as normal ventricular size. However, spontaneously hypertensive rats (SHR) show ventricular dilation, changes in CSF proteins and variations in the brain angiotensin-vasopressin system. The subcommissural organ (SCO), the organum vasculosum of the lamina terminalis (OVLT), the subfornical organ (SFO) and the area postrema (AP) are circumventricular organs (CVO) located in the third and fourth ventricle which are rich in neuropeptides such as angiotensin II and catecholamines. Variations in the SCO have been reported in hydrocephalus and hypertension. The SFO has connections with the brain regions involved in the central regulation of blood pressure and cardiovascular function. The p73 isoforms function as essential pro-survival molecules in both the CNS and PNS and are important not just during the period of developmental death but also for the maintenance of at least some populations of adult neurons. In the absence of

p73, ventricular enlargement occurs as neurons degenerate and tissue mass decreases, a phenomenon also observed in the degenerating human brain. The purpose of the present work is to study the TAp73 and Δ Np73 expression in neuroepithelial structures such as: the CVO and their variations in ventricular dilatation and arterial hypertension.

Materials and methods: Brains from one year-old BPH mice, blood pressure normal mice (BPN), control Wistar-Kyoto rats (WKY) and spontaneously hydrocephalus rats (SHR) were used. The paraffin sections containing the SCO, OVLT and SFO were immunohistochemically processed with anti-p73 isoforms (TAp73 and Δ Np73). P73 bands were identified in the CSF by western blot.

Results: The BPH mouse shows a slight dilation in the lateral ventricle while the SHR presents a greater increase in ventricle size compared to normal sized WKY rats. The TA p73 expression was higher in the SFO of the hypertensive rats than in the WKY rats. Although TA p73 was positively expressed in the SCO and OVLT of the WKY rats, this expression was scarce in this organ of the SHR rats; in the control mouse the reaction was more intensive in the AP. The Δ Np73 isoform was scarce or almost undetectable.

Conclusion: The Δ Np73 is essential for survival of peripheral sympathetic neurons. Δ Np73beta may have distinct functions under certain cellular circumstances. The present results and the fact that the Δ Np73 is essential for the survival of sympathetic neurons, could indicate that p73 is an essential survival protein in CNS catecholaminergic neurons in centres involved in cardiovascular regulation.

S27

Postnatal ependymogenesis occurring in wild-type *hyh* mice increases significantly in hydrocephalic *hyh* mice

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Background: The *hyh* (hydrocephalus with hop gait) mouse carries a point mutation in alpha-SNAP protein and develops inherited hydrocephalus. Mutant mice are born with moderate hydrocephalus and a patent Sylvius aqueduct (SA). During the first postnatal week, SA obliterates and a severe hydrocephalus characterized by an enormous expansion of the dorsal third ventricle and of the collicular recess of the SA, develops. Interestingly, neither of these dilated cavities present spontaneous ventriculostomies. The aim of the present investigation was to elucidate some of the cellular phenomena occurring at the ventricular walls that allow such enormous ventricular dilatations.

Materials and methods: Brains of wild type (non-hydrocephalic) and mutant (hydrocephalic) *hyh* mice were studied by light and transmission electron microscopy at various age intervals (PN-1 to PN-120). Proliferative activity, especially at the ventricular walls, was studied by PCNA (proliferative cell nuclear antigen) immunocytochemistry, and 5'-Bromo-2'-deoxyUridine (BrdU) labelling.

BrdU protocols included pulse and cumulative labelling of postnatal animals, combined with short and long survival periods after the labelling.

Results: In wild-type mice no BrdU-labelled or PCNA-positive cells were observed in the ependyma of the ventral walls of SA and third ventricle. However, proliferative cells were found in two discrete ependymal regions of the dorsal walls of the third ventricle (3Vd) and the SA (SAd). Here, proliferative activity continued at least during three weeks after birth. The localization, cytology and immunocytochemical properties indicate that both regions originate ependymal cells. Interestingly, in mutant (hydrocephalic) *hyh* mice, postnatal ependymogenesis occurring in 3Vd and SAd increased several fold.

Conclusion: 1. In non-hydrocephalic animals all ependymal cells lining the floor of the aqueduct are born during the fetal life; however, in the dorsal wall of the aqueduct and the roof of the third ventricle ependymogenesis continues during postnatal life. 2. In mutant mice, the hydrocephalic process triggers a dramatic increase of proliferative activity in these two ventricular regions letting them to expand without any disruption and, probably, allowing a longer survival. 3. In the cerebral aqueduct of hydrocephalic mice there are various ependymal lineages: one of them detaches, other proliferates while another neither detaches nor proliferates. Since all these ependymal populations are exposed to the same pressure and composition of the CSF, their differential response to the hydrocephalic status can best be explained by their distinct genetic programme. Supported by Fondecyt 1030265-Chile to EMR, CONICYT and DID-UACH D-2005-12 to LFB, FIS PI030756 and FIS PI060423 to JMPF.

S28

Antibiotics for eradication of propionibacterium acnes biofilms

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Background: *Propionibacterium acnes* is a member of the normal flora of the skin, but it has been implicated in infections in cerebrospinal fluid shunts and spinal instrumentation e.g. for scoliosis. Though *P. acnes* are fully susceptible to a range of common antibiotics, treatment of infections is very difficult. Recently we demonstrated that *P. acnes* can develop biofilms in such infections and this explains the poor treatment responses and frequent relapses. We have now explored the use of three antibiotics to eradicate *P. acnes* biofilms on biomaterials. Penicillin is often used but more advanced antibiotics have been suggested to improve the outcome. Linezolid penetrates tissues (including the blood – CSF barrier) and is active against *P. acnes*, and could be expected to eradicate it from shunts and from spinal hardware. However, the performance of such antibiotics is often improved by the addition of rifampicin, which penetrates equally well. We therefore investigated the activity of these antimicrobials in eradication of *P. acnes* biofilms and on relapse rates, in an *in vitro* system.

Materials and methods: Sterile titanium discs were coated with human plasma conditioning film and exposed to *P. acnes*, after which they were incubated anaerobically for biofilms to

form. The series of discs with biofilms were then exposed to penicillin, linezolid and linezolid + rifampicin for either 7 or 14 days. Further discs were exposed then left for 9 days with no antibiotic to detect “relapse”. Presence of bacteria was detected after sonication by chemiluminescence and culture.

Results: Penicillin eradicated *P. acnes* from all samples after both 7 and 14 days; 30% relapsed after 7 days but none after 14 days treatment. Linezolid eradicated only 30% after 7 days but 100% after 14 days; all relapsed after 7 days and 77% after 14 days. Linezolid + rifampicin eradicated 50% after 7 days and 100% after 14 days; 23% relapsed after 7 days but none after 14 days.

Conclusion: Despite apparent eradication the relapse rates were disappointing. Penicillin appears to be the agent of choice, for 14 days, for *P. acnes* infection of spinal hardware but in view of its poor penetration into the CSF a combination of linezolid and rifampicin might be suitable for shunt infections. Linezolid alone gave poor results.

S29

Conservative management of cerebrospinal fluid shunt infections

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Background: Brown *et al.* [1] published a favourable experience with treatment of *Staphylococcus coagulase negative* (SCoN) caused cerebrospinal fluid shunt (CSF) infections without surgery using Rifampin (Rif). We have presented our management of CSF shunt infections, in part indicating surgery is not needed for some cases. This paper is to further describe our experience over the last 45 years.

Materials and methods: We describe a retrospective review of prospectively collected data stored in two computer databases for 3,889 shunt related operations involving 1,226 patients. Infections were defined as positive cultures of the CSF or the shunt. Antibiotic levels in the CSF and Minimal Bacteriocidal (MBC) levels are expressed in ug/ml. Operative procedures as part of the treatment were complete shunt removal, ventriculostomy, antibiotics (abx) until CSF was sterile, then replacement of the shunt (CSR+V+abx+R), externalization of the distal limb + abx + replacement + (Ex+abx+R) and other procedures. Analysis was by transfer to Excel files, Fisher Exact and Student t-test. A cure was defined as 16 months without recurrent infection or a new infection with another organism.

Results: 195 infections (5.0% of shunt procedures) involved 176 patients (15.9%) of which 62 were due to SCoN organisms (32%), 122 that were insensitive (61%), including 41 due to *Staphylococcus aureus* (21%), 13 (7%) due to Enterococcus, 15 *E. coli* (8%), and 14 due to other sensitive organisms (concentration of CSF antibiotic ≥ 10 mcg/dl) including *Streptococcus pneumoniae* (5; 1:245) and *Hemophilus influenzae* (9; 1:136). 28 of S Co N were treated medically of which

22 (79%) were cured. The proportion of cures was not different compared to CSR+V+abx+R 38 of 42 (90%), Fisher Exact $P = 0.5$, but better when compared to Ex+abx+R = 6/12 (50%), $P = 0.01$. Severity of infection, as measured by white blood cell count in the CSF, was the same for the medically treated (Mean 217, Range 0–939) and those with surgery (Mean = 368, Range 1–1380), t -test $P = 0.3$. When polymorphonuclear cells alone were evaluated, the similarity remained, $P = 0.48$.

Conclusion: 1) Rifampin and another antibiotic, to prevent resistance, can cure some S Co N shunt infections. 2) Patients with CSF shunts should be immunized against *H. influenzae* and *S. pneumoniae*, 7 valent under 2 years of age with addition of 23 valent agent for older and after age 2 years.

Reference

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S30

Are adjustable valves effective? Data from the UK Shunt Registry

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Background: Adjustable (often-called programmable) 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 as a simple procedure. The proportion of these valves used in the UK and Ireland has increased from 4.9% in 2000 to 22.4% in 2006. 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 nearly 30,000 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 either a Medtronic Strata Valve or Codman Hakim Programmable Valve was used. Of these 1,389 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 patient age, diagnosis and revision status but using Medtronic or Codman fixed-pressure valves. Matches were found for 943 procedures.

Results: The one-year cumulative valve revision rate for the two adjustable valves was 4.8% as compared to 7.3% in conventional, non-adjustable valves. A logrank test suggests that adjustable valves perform significantly better ($P < 0.05$) for the first 98 weeks of use. After that point, there is no significant difference in the curves for the two types of valve.

Conclusion: Our data suggest that adjustable valves may be effective in overcoming short-term problems due to incorrect pressure selection. However the long-term problems associated

with valve implantation still apply. Patient selection is probably the crucial factor in the effectiveness of adjustable valves.

S31

Limits and options for electronic devices for the treatment of hydrocephalus

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S31

Background: The available shunt-systems for the treatment of hydrocephalus are exclusively based on simple mechanical principles. In comparison to pacemakers or other sophisticated medical devices, shunt-technology is said to be “old-fashioned” and the introduction of electronic intelligent systems should be a second remarkable breakthrough after the introduction of the first shunts in the beginning of the fifties. The decisive question is how far an electronically controlled device can present new possibilities for the treatment without a significant increase of new risks. Which concept promises significant improvements?

Materials and methods: All available shunt-systems operate depending on the pressure difference between the ventricular system and the abdominal cavity or the atrium of the heart. The used mechanical principles react to changes of this differential pressure. The goal is to re-establish physiological pressure values in the ventricular system of the patient. The obvious solution to control the intra-ventricular pressure (IVP) electronically is the opening and closing of the device depending on the actual measured IVP. But this simple approach leads to severe unsolved technical problems like long-term drift and general accuracy. It is a matter of controversy whether a shunt-system should re-establish a certain IVP, a certain ventricular size or possibly a certain condition of the brain tissue. However, the main purpose of drainage is the withdrawal of CSF from the ventricular system. The amount might depend on changing individual conditions or on age, on the height of the patient or on the kind of hydrocephalus. The introduction of an electronically controlled programmable switch presents new perspectives for the diagnosis, the general understanding and the therapy of hydrocephalus. The switch works without a pressure transducer. The device is programmed by a physician, who determines at what time during the day or the night the shunt without a valve is open or closed. The shunt can be closed at any time non-invasively or it can be programmed to be always open. The telemetric programming allows any kind of individual adaptation. Because a battery is needed, the size of the device has to be similar to pacemakers. Therefore, it is recommended to implant the switch in the chest of the patient.

Results and conclusion: The concept of an electronically controlled switch broadens the possibilities of the treatment of hydrocephalus. This clear advantage might be counterbalanced by the drawbacks like the big housing needed or the new risks introduced by the electronic components. The first implantations of the new device are scheduled to be performed in the beginning of 2006. If the clinical results confirm the benefits of the concept the electronic switch will be an option especially for adult patients with NPH.

S32**Changing definition of non-responsiveness to shunting – the influence of valve-adjustability**

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Background: The published data of clinical results in larger series of shunted hydrocephalus reveal a remarkable broad spectrum, ranging from 31% to over 90% in the relatively well-outlined subgroup of NPH. This discrepancy in clinical results, which also exists in other aetiologies, is not only due to different inclusion criteria, variability of pressure-settings or length of follow-up. In addition there exists a controversy concerning the group of “non-responders” up to now. By our experience with a new adjustable valve we would like to elucidate the changing definition of this entity.

Materials and methods: The investigation of non-responsiveness following shunting was conducted by comparing our experience in valves with fixed opening-pressure and the evaluation of the results after implantation of the adjustable gravitation-assisted valve (proGAV) from February 2004 to September 2006 in 82 patients of different etiologies. We focused on complications, differentiating those related to the valve-function from those not dependent on the device, and on indications to change the opening pressure. Finally we concentrated on the radiological outcome and the clinical results including the possibilities for improvement by readjustments.

Results: In 54 patients we did not see an indication to change the initial pressure setting and the clinical results were satisfying in 49. The first group of “non-responders” are those with a reduction of ventricular size but no clinical improvement. But an only minimal or even no reduction of ventricular size can be accompanied by a positive clinical “response”. The combination of unsatisfying clinical outcome and unchanged ventricles necessitates ruling out shunt-insufficiency before adding this cohort to the group of non-responders. In 18 cases with the “complication” of functional underdrainage we saw an indication to lower the opening pressure. 7 patients suffering overdrainage related complications could be treated successfully by elevating the pressure setting.

Conclusion: In the “stone-age” of shunt-therapy too many patients were classified as belonging to the non-responders only because of surgical mistakes, infectious or mechanical complications. Only those patients should be subsumed under the category of “non-responders”, who, after exclusion of shunt-insufficiency and relevant accompanying illnesses, do not improve clinically after exchange of valves with fixed opening pressure or following adequate alteration of pressure-setting in programmable devices. In cases with severe intra-operative or postoperative complications the term “non-responder” should be avoided. The results of the proGAV-series support our opinion that the majority of re-operations can be avoided and the number of responders to shunting can be increased.

S33**23 hydrocephalus valves tested over 367–514 days**

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Background: Hydrocephalus valves are potentially life-long implants. In spite of this fact a minority only of the 1400 published in vitro tests had a duration of more than 3 months, maximally 1 year. In addition, in literature tests of susceptibility on external pressures and valve body deformation, elevated CSF protein, simulated gas-sterilizations, pumping volumes and pressures, temperature variations, reflux, syphoning, in adjustable valves the reaction on electromagnetic fields, decentration during adjustment, possibility of emergent adjustment without special apparatus are sporadically available only.

Materials and methods: 22 new valves (10 designs, 6 manufacturers) and one specimen explanted after 34 years revision-free function were tested non-stop over 367–513 days with a test-battery of maximum 20 subtests for the open-minded criteria.

Results: 15/23 showed mean deviations of >20%, max. 240% related to the specifications. Only 10 have been drift free over the complete period. 17 over-, 2 underdrained; 2 worked physiologically. All specimens were reflux-resistant, all except 5 temperature-stable. 10 showed deviations (max. 53%) by flexion. External diffuse pressure produced variations of 13–82%, directed pressure max. -37%. 18/23 changed their properties after 50× pumping up to 34%. After gas sterilization with 65°C (1 h) 5 specimens only were stable; 5 increased, 8 decreased in resistance; protein let to occlusions of 2 and an increased resistance (max. 52%) of 15 specimens. Medos were adjustable to 21 mm distance; however, a decentration of 2 mm or rotation of 5 degrees can lead to failures. Catheters ruptured between 1.2–4.1 kg.

Conclusion: In spite of the fact that 6/10 valves were designed in the last decade, multiple significant safety or accuracy failures were documented.

S34**Latex sensitisation in hydrocephalic patients with and without spina bifida**

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S34

Background: Natural rubber latex (NRL) sensitisation, often with serious symptoms of latex allergy, is a widespread problem of patients with spina bifida. With genetic factors not being well characterized till now, repeated surgeries beginning soon after birth are the best-known risk factor. Operations of the shunting devices mainly contribute to the number of surgeries in spina bifida patients. There has been much less investigation into the prevalence of NRL-sensitisation of hydrocephalic patients with spina bifida.

Table I (abstract S34)

| Group | Patients n | NRL sensitized | NRL allergic | Number of surgeries, mean/maximum |
|-------------------------|------------|------------------------|--------------|-----------------------------------|
| Spina bifida/no shunt | 49 | 11/22.4%* ¹ | 4/8.2% n.s. | 2.6/9* ¹ |
| Spina bifida/with shunt | 123 | 63/51% | 17/13.8% | 7.0/30 |
| Shunt/no Spina bif. | 34 | 6/17.7%* ¹ | 2/5.8% n.s. | 5.7/12 n.s. |

*¹ Chi square test; p = 0.01; n.s. = not significant

Materials and methods: In this study the risk of NRL-sensitisation of hydrocephalic patients with and without spina bifida is compared to give recommendations for NRL-prophylaxis. The sera of a group of spina bifida patients without (n = 49) or with shunted hydrocephalus (n = 123) and a group of 34 hydrocephalic patients without spina bifida were tested for specific IgE antibodies against NRL by ImmunoCAP system. The number of surgeries and symptoms of NRL allergy were taken from the medical history and a questionnaire.

Results: See Table I.

In all groups the prevalence of sensitisation against NRL increased with the number of surgeries.

Conclusion: Due to repeated surgeries a remarkable sensitization against NRL proteins in patients with shunted hydrocephalus without spina bifida has to be considered. The risk increases with the number of surgeries like in spina bifida patients and other congenital malformations. These patients should be tested for specific IgE by blood or skin test before surgeries, to establish prophylactic measures, especially a latex-free operating theatre.

S35

Gravitational valves. Personal 27 year experience in 420 patients

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S35

Background: The first gravitational valve, the Cordis-Hakim-Lumbar (CHL) was patented in 1975. In 1980 the author assisted two implantations in LP-shunts, but similar to all contemporary neurosurgeons he does not recognise the technical breakthrough. In spite of a brilliant concept the CHL flopped, probably due to the exclusive design for the rare lumbar shunts (transversal connectors) and a round valve body with a strong tendency to rotate in the lumbar fat and resulting dysfunctions. Fred Jackson, the initiator of the first large series in the USA died by an air crash in 1980; his encouraging results were never published. In 1989 the CHL was tested with excellent results by Richard and us. As the first we proposed the combination with adjustable valves on 91 and implanted a modified CHL with a Medos-P in 83. We conceived longitudinal valve bodies, which stimulated the development of Cordis GCA and Miethke Shunt

Assistant (94). Independently the Chhabra Z-Flow, the Sophysa AS and the Affeld-valve, a precursor of the Miethke Dual-Switch, were developed.

Materials and methods: Retrospective study on 420 patients treated with Cordis Hakim-Lumbar or -GCA, Miethke ShuntAssistant, -DualSwitch, -Paedi/GAV and ProGAV. Follow-up since 1984.

Results: The overdrainage was reduced: Only 5/420 patients required surgery due to subdurals (1.2%); 6 other mild hygromas disappeared conservatively. Of 11 chronic hematomas, five were caused by significant head traumata, two by incorrect (diagonal) valve placement, one by inadequate pressure selection and one by pneumatocephalus. We counted only two valve related "real failures" with consecutive cSDHs. Of 110 NPH-patients two only (1.8%) presented hygromas. The quote of infections, catheter problems and valve dysfunctions met standard experiences.

Conclusion: Gravitational valves have largely solved the problems of overdrainage. However, residual problems such as the adaptation on the growth of children or high abdominal counter pressure in adipous patients with resulting underdrainage require further improvements, especially adjustable g-valves. The current state-of-the-art is the crossover of adjustable and gravitational valves.

S36

Interaction between hydrocephalus shunt and pressure waves

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Background: The majority of contemporary hydrocephalus valves are designed to introduce a low resistance to flow into the cerebrospinal fluid (CSF) drainage pathway. This, according to mathematical models, and clinical observations may influence the magnitude of ICP waveform. On the other hand, exaggerated waves of ICP may influence drainage through the shunt. We attempted to review these phenomena systematically both in clinical practice and laboratory.

Materials and methods: From our database of nearly 1600 pressure recordings (both infusion tests and overnight ICP monitoring) in patients routinely diagnosed for hydrocephalus we selected 35 patients in whom CSF infusion study was repeated before and after shunting. The relationship

between pulse amplitude and mean ICP was compared between patients with functioning (121) and blocked shunt (127). We discussed recordings from three patients with unusually strong respiratory wave. In laboratory we studied six constructions of medium-pressure valves. Valves have been mounted in the testing rig, perfused with deionised water with a rate of 0.3 ml/min and proximal pulsating pressure of different amplitude (from 2 mm Hg to 30 mm Hg peak to peak) and frequency (70 cycles/min to 10 cycles/min) were superimposed.

Results: Although, in NPH, mean ICP not always decreases after shunting, baseline pulse amplitude of ICP significantly decreased from median (range): 2.5 (0.2; 5.9) mm Hg to 1.4 (0.3; 4.1) mm Hg; $p < 0.0051$. In three patients with functioning shunts and high amplitude of respiratory pattern, baseline pressure was negative (from -2 to -7 mm Hg). The relationship between pulse amplitude and ICP was stronger in patients with blocked shunts ($R = 0.48$; $p < 0.03$; slope 0.14) than in patients with properly functioning shunt ($R = 0.057$; $p = 0.765$). In the laboratory, the mean operating pressure decreased in all valves when simulated amplitude of respiratory and heart pulsations increased. The rate of this decrease was dependent on type of the valve (variable from 2.5 to 5 mm Hg per increase in peak-to-peak amplitude by 10 mm Hg). The decrease was not related to the frequency of the wave.

Conclusion: The shunt's operating pressure, which determines the mean ICP in shunted patients may be influenced by the dynamics of a patient's ICP waveform. Shunt, in turn, has an ability to reduce dynamics in pressure waves. Decrease in pulse amplitude of ICP pulse waveform may be a marker of proper shunt drainage.

S37

Early puberty in boys with myelomeningocele.

Risk factors for early puberty

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Background: Children with myelomeningocele (MMC) run an increased risk of developing early or precocious puberty (E/PP). In a previous study on girls with MMC we found increased intracranial pressure during the perinatal period to be strongly associated with E/PP. We also found the incidence of E/PP among girls to be as high as at least 52%. In a number of studies PP in boys also has been reported, but most studies have been based on selected groups of children. The aims of the present study was to investigate the incidence of E/PP in boys with MMC treated at a regional habilitation centre, and to identify possible risk factors associated with the development of early or precocious puberty. In addition we analyzed the clinical course of pubertal development.

Materials and methods: The study population comprised all boys born between 1970 and 1992 admitted to the Folke Bernadottehemmet at least at one occasion ($n = 59$). The medical records were examined and those who had reached 10.2 years ($n = 47$) were evaluated regarding pubertal status,

growth charts, perinatal problems and medical problems and problems regarding other areas of function.

Results: Of the 47 boys who had reached the age of 10.2 years or above, 43 boys were possible to evaluate regarding onset of puberty. Nine of these boys had had an early puberty and one a precocious puberty. Thus the incidence of E/PP in this group is at least 21% (10/47). The boys with E/PP had significantly higher incidence of both increased intracranial pressure during the perinatal period and early and severe symptoms of brainstem dysfunction. In 18 boys, sufficient data for complete analysis of both growth spurt and Tanner stages were obtained. Analysis showed that in 14 boys out of 18 the growth spurt was the first sign of puberty.

Conclusion: We found an increased incidence of E/PP in the boys with MMC. Early puberty was significantly associated with high intracranial pressure during perinatal period. In addition, we found that pubertal development seemed to be accelerated in many boys with an early growth spurt.

S38

Neurological bypass for sensory innervation of the penis in patients with spina bifida

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Background: Most male patients with spina bifida eventually have normal sexual desires. During puberty they begin to realize that they can achieve erection and sexual intercourse but without any sensation in the penis. We hypothesized that restored sensation in the penis would greatly contribute to their quality of life and sexual health. In this prospective study we investigated the outcome of a new operative neurological bypass procedure in patients with spina bifida.

Materials and methods: In 15 patients, 12–34 years old, with lumbosacral spinal lesions, the sensory ilioinguinal nerve (L1) was cut distal in the groin and joined by microneurorrhaphy to the divided ipsilateral dorsal nerve of the penis (S2-4) at the base of the penis. All patients underwent preoperative and postoperative neurological and psychological evaluations.

Results: By 15 months postoperatively 12 patients had achieved excellent sensation on the operated side of the glans penis. 6 patients experienced a "groin feeling" in the penis. However 6 patients reported a true "glans feeling". They were all positive about the results and the penis had become more integrated into the body image. The sensations were not (yet) erotic in 7/12 patients. Most patients report amelioration of their sexual relation/sexual activity. No adverse effects were seen.

Conclusion: The newly designed neurological bypass procedure in patients with spina bifida resulted in excellent sensibility in the glans penis. The new sensation appeared to contribute to the quality of the patient sexuality and sexual functioning as well as to the feeling of being a more normal and complete individual who is more conscious of the penis. This new operation might become standard treatment in patients with spina bifida in the future.

S39**Psychosocial adaptation and cognitive functioning in young male adults with myelomeningocele**

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Background: Myelomeningocele (MMC) is a multifaceted condition with complex neurological and neuropsychological sequelae mainly due to the MMC itself, hydrocephalus and Arnold-Chiari malformation (ACM). Quality of life and social functioning are known to be impaired in this patient group. Little is known about how clinical history, neurological findings and cognitive functioning influence psychosocial adaptation for young male adults. The aim of this pilot study is to investigate the relationship between these factors and psychosocial functioning. It is hypothesised that cognitive functions, especially executive functions, are of major importance for psychosocial adaptation.

Materials and methods: 6 young male adults between 24 and 35 years of age were recruited from TRS National Resource Centre for Rare Disorders. The study group was selected by using the following inclusion criteria: (1) interruptions in the course of education, (2) unemployment, (3) lack of social relations, and (4) social isolation. The study group underwent a systematic clinical history, a neurological investigation and a neuropsychological assessment. The assessment test battery consisted of Wechsler Abbreviated Scale of Intelligence (WASI), the Grooved Pegboard, the Stroop Test from the Delis-Kaplan Executive Functioning System (D-KEFS), letter-number sequencing from Wechsler Adult Intelligence Scale III (WAIS-III), and the Trail making Test. In addition, the Symptom Checklist 90-R (SCL-90) was used.

Results: All the patients were severely disabled by paresis in the lower limbs, multiple shunt-revisions, ACM, tethered cord, orthopedic surgeries, at least one type of stomy, and reduced sexual function. The results showed in particular deficits in the executive functions, visual-spatial function, and visuo-motor processing. Furthermore, all the patients achieved better results on the verbal subtests than the performance tests. SCL-90 revealed minor psychological problems and symptoms of psychopathology.

Conclusion: The neuropsychological assessment supported the hypothesis that the visual-spatial function and the executive functions were most impaired. This indicates that these functions may be especially important for psychosocial adaptation. We recommend a multimodal examination integrating neuropsychological assessment in the follow up of the MMC patients.

S40**Global assessment of function in adolescents with myelomeningocele**

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Background: In a previous study we found that the majority of 9-year-old children with myelomeningocele (MMC) had

multiple problems, regarding many areas of function in school. The purpose of the present study was to investigate the same group of children with myelomeningocele during adolescence regarding the occurrence and nature of any clinical problem requiring specific help or strategy. We also analyzed risk factors associated with severe problems in function.

Materials and methods: Our study included 18 patients (10 boys and 8 females) with MMC admitted to our centre from 2001 to 2004. The ages varied between 13 and 19 years and the median age was 15 years. Seven children were ambulant and 11 were non-ambulant. All children had hydrocephalus and 14 of these had a shunt inserted. All children had some degree of impaired urinary bladder function. Six children had shown signs of brainstem dysfunction early in life. All adolescents were assessed by structured methods, during a two-week period, by a team constituted of paediatric neurologist, physiotherapist, occupational therapist, neuropsychologist and a teacher.

Results: The group of adolescents had a mean number of six medical problems that required continuous treatment and supervision. A complex medical situation, (seven or more medical problems), were strongly associated with both early signs of brainstem dysfunction and multiple shunt revisions. The neuropsychological tests showed that cognitive functioning in most of the adolescents were in the lower normal range ($n = 13$) or below the normal range ($n = 3$). All adolescents had some impairment in specific cognitive functioning (slow processing, planning difficulties, decreased spatial ability), requiring specific help and support at school. Ten adolescents had severe cognitive impairments, leading to dependence on others in daily life. Severe cognitive impairments were also seen in ambulant children without shunt.

Conclusion: In the present study we found that all adolescents with myelomeningocele had multiple medical and cognitive problems requiring specific help or strategies in daily life. Adolescents with early signs of brainstem dysfunction were at special risk of developing severe problems. Global assessments of function of all adolescents with myelomeningocele make it possible to develop individual treatment programs.

S41**Continence and dryness in spina bifida patients at school age**

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S41

Background: To analyse urinary continence and urodynamics in spina bifida aperta (SBA) and occulta (SBO) patients at school age.

Materials and methods: Our policy in SB patients is to offer dryness before school age. Out of 176 patients 141 were evaluated at school age: 106 with SB aperta and 35 with SB occulta.

All patients were treated with clean intermittent catheterisation (CIC), antimuscarinic agents, and antibiotic chemoprophylaxis from birth onwards in order to prevent obstructive uropathy and to preserve renal function. To secure low intra-vesical pressure, antimuscarinic agents were administered (oxybutynin,

sometimes replaced by tolterodine if necessary). If conservative management failed a sling and (auto) augmentation was offered. Our definition of 'continent' is when a patient can retain urine and can void normally. Our definition of 'dry' is when a patient is on catheterisation without requiring pads.

Results: SBO patients: 51% were continent, 29% were dry on CIC.

SBA patients: 8% were continent, 46% were dry on CIC. 45% of (partially) incontinent children would need a continence improving operation in the future.

Conclusion: SBO patients have, compared to patients with SBA, a better chance for continence and normal voiding. With adequate therapy most of the patients can be dry at school age. The majority of incontinence at school age is caused by parental refusal of surgical intervention. A minority of incontinence is caused by surgical failure.

S42

Shunting in AD slows progression of the dementia

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S42

Background: The pathogenesis of Alzheimer's disease (AD) may involve impaired clearance of toxic metabolites, e.g. amyloid-beta peptides (A β), from the brain via interstitial fluid (ISF) and cerebrospinal fluid (CSF) circulation, and the blood-brain barrier (BBB). If so, then increasing ISF and CSF circulation may improve CSF A β clearance and may slow the progression of AD. We tested this hypothesis in a prospective, randomized, double-blind, placebo-controlled trial of low-flow CSF shunting. Our previously reported analysis using the Generalised Estimating Equations showed no effect of CSF shunting. The present report provides post hoc analyses using linear mixed-effects models fit by maximum likelihood.

Materials and methods: The study group consisted of 164 people with mild to severe AD (baseline Mattis Dementia Rating Scale – MDRS-scores 54–137). We administered the MDRS prior to shunt implantation surgery (baseline, time = 0) and 3, 6, 9, and 12 months post-operatively. We also administered the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) at baseline and 9 months. Linear mixed-effects models fit by maximum likelihood compared the rates of decline for the two groups over the period of 3 to 12 months for the MDRS and 0 to 9 months for the ADCS-ADL. In the MDRS model we co-varied the baseline scores and incorporated random effects and variance functions to adjust for heteroscedasticity when estimating rates of decline.

Results: Rates of decline for both measures were less in the actively shunted AD group. The MDRS rate of decline was 0.54 ± 0.25 /month less than the control group ($p = 0.031$). The ADCS-ADL rate of decline was 0.66 ± 0.33 /month less than the control group ($p = 0.042$). Variability in the MDRS rate of decline in the active shunt group increased with time, compared to controls ($p < 0.001$).

Conclusion: CSF shunting reduced rates of cognitive and functional decline in patients with mild to severe AD. This supports the hypothesis that impaired CSF clearance of toxic moieties may contribute to the pathogenesis of AD. Mixed effects models of cognitive decline may be more efficient than marginal models, such as the Generalised Estimating Equations. The increased variability in cognitive scores in the group with active shunts may result from the beneficial effects not occurring in some patients, and/or possibly from unwanted side effects in a few individuals. Overall, however, CSF shunting in mild to severe AD was beneficial.

S43

Lymphatic cerebrospinal fluid absorption is impaired in a kaolin-induced hydrocephalus model in the rat

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Background: It has been assumed that the pathogenesis of hydrocephalus includes a cerebrospinal fluid (CSF) absorption deficit. Since a significant portion of CSF absorption occurs into extracranial lymphatic vessels located in the olfactory turbinates, the purpose of this study was to determine if CSF absorption was compromised at this location in a kaolin-induced hydrocephalus model in rats.

Materials and methods: Kaolin ($n = 10$) or saline as control ($n = 9$) was introduced into the basal cisterns of Sprague Dawley rats and the development of hydrocephalus was assessed using MRI. The degree of ventriculomegaly was calculated for each animal as the Evans ratio. Human serum albumin (¹²⁵I-HSA) was injected into the lateral ventricles. The enrichment of ¹²⁵I-HSA in the olfactory turbinates at 30 minutes post injection provided an estimate of CSF transport through the cribriform plate into the nasal lymphatic vessels.

Results: Injection of kaolin produced hydrocephalus in the majority of animals. The average Evans ratio in the kaolin group (0.48 ± 0.02) was significantly greater than that in the saline injected animals (0.35 ± 0.01 ; $p = 0.0042$). The CSF tracer enrichment in the olfactory turbinates (expressed as percent injected/gm tissue) in the kaolin rats averaged 0.99 ± 0.39 and was significantly lower than that measured in the saline controls (5.86 ± 0.32 ; $p = 0.0019$). A plot of the Evans ratio versus lymphatic transport revealed a significant negative correlation ($p = 0.0002$) with the largest degree of ventriculomegaly associated with the lowest levels of lymphatic CSF uptake.

Conclusion: We conclude that lymphatic CSF absorption pathways are compromised in a kaolin hydrocephalus model suggesting an important role for extracranial lymphatic vessels in this CSF disorder.

S44

The role of vitamin A and its CSF metabolites in supporting a novel mechanism of idiopathic intracranial hypertension

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Background: Elevated levels of retinoic acid (RA) may cause dynamic vitamin A metabolic and genetic transcriptional changes that will lead to decreased cellular viability, proliferation, cellular remodeling, adhesion changes and a resultant decrease in permeability, which contributes to elevated CSFP. RA and subsequent formation of retinyl esters, which act as surfactants may cause a toxic response in the arachnoid membrane leading to elevated CSFP.

Transthyretin (TTR) is a transport protein in blood and brain for BOTH vitamin A and RBP. TTR is also a critical transport protein for thyroxine, which is important in controlling metabolism and linked to obesity. The vitamin A transduction pathway links RBP, cellular retinoic acid binding protein (CRABP), TTR, retinol and RA.

Adipocytes are involved in retinoid metabolism and storage. (Okuno *et al*, 1995) This study even suggested that cellular retinol-binding protein (CRBP) gene expression is regulated dynamically in adipocytes by retinol uptake, intracellular transport and metabolism, which may be significant for the typical IIH patient (BMI > 30). The increased levels of adipocytes in these patients, which can dynamically regulate vitamin A metabolism by altering gene expression, are extremely important when trying to understand the etiology of this disease.

Methods: We prospectively obtained CSF and serum samples from 6 patients and 6 controls for analysis of RA, retinol, Retinol Binding Protein (RBP), and Transthyretin (TTR). Opening CSF pressures (OP) and BMI were obtained.

Results: No statistical differences were found between the mean ages or the BMI for these two groups. Patient OP obtained by radiologically-guided LP were statistically higher, mean 35.3 cm H₂O, vs 19.1 in Controls ($p < 0.0005$). Patient OP ranged from 25–48 and 8–23 among Controls. Patient means for both CSF total RA and CSF 13-cis retinoic acid were statistically higher ($p < 0.05$). Serum TTR/RBP approached significance ($p < 0.07$).

Conclusion: The results from this well-controlled clinical study which examined the CSF and serum of patients matched for BMI with and without IIH demonstrate significant elevations in CSF total RA and 13-cis-RA in IIH patients. There is also a trend toward significance for increased serum TTR/RBP in these patients. These data support our hypothesis for a significant role of vitamin A and its metabolites in the pathogenesis of IIH via directly altered metabolism and transcriptional regulatory changes in the arachnoid cells.

S45

Enhanced expression of the LRP-1 transporter at the blood-CSF interface in chronic hydrocephalus

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Background: Reduced CSF formation in chronic hydrocephalus (NPH) prompts the question of how the expression of choroid epithelial transporters is altered when flow is disrupted. In the Kaolin model of communicating hydrocephalus, we previously demonstrated that choroid plexus chloride transport (proportional to CSF production) is significantly decreased [1]. To investigate the expression of other choroidal transporters that effect CSF homeostasis, we have now analyzed the time course of LRP-1 expression in the plexus at various stages of hydrocephalus. LRP-1 is a transporter that mediates efflux of A-Beta peptide from the CSF. We postulate that LRP-1 in choroid plexus has a key absorptive role that stabilizes A-Beta in the CNS.

Materials and methods: In 15 Sprague-Dawley (SD) rats at 12 mo of age, we injected Kaolin into the cisterna magna to induce an NPH-like hydrocephalus. Animals were analyzed at 2, 6 and 10 weeks post-induction. Ventriculomegaly was confirmed by 4.7 Tesla MRI. Choroidal tissues were removed from the lateral ventricles and immunostained with antibody against LRP-1 or analyzed by quantitative (q) PCR to determine LRP-1 transcript levels. 4–5 rats were analyzed at each stage.

Results: Compared to controls, there was enhanced immunostaining of LRP-1 in the choroidal epithelium at 2 wk and 6 wk post-induction. At 10 wk, LRP-1 staining was even greater than at 2 and 6 wk, being especially marked at the apical (CSF-facing) pole of the epithelium. Apically-located LRP-1 can actively remove A-Beta from the CSF [2]. The immuno-histochemistry findings were corroborated by qPCR. Thus, LRP-1 transcript in choroid plexus, compared to control, was augmented even at 2 wk. Upregulated LRP-1 mRNA in the plexus was sustained at 6 and 10 wk. For comparison, we analyzed LRP-1 mRNA in human choroid plexus from patients with Alzheimer's disease (AD), a condition in which NPH often coexists. LRP-1 expression was also maintained in AD choroid plexus (i.e., the blood-CSF interface), unlike the cortical microvessels in AD, which lose LRP-1 [3].

Conclusion: When comparing NPH and AD with aging responses, there are contrasting differences in the expression patterns of LRP-1 at the blood-CSF vs. blood-brain interfaces. The ability of choroid plexus to sustain, and even increase, LRP-1 expression in chronic hydrocephalus suggests that the blood-CSF transport interface may help to cover deficient LRP-1 expression in cerebral capillaries in aging, NPH and AD.

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S46

Prospective evaluation of selected cytokines for hydrocephalus surgery

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Cerebrospinal Fluid Research 2007, 4(Suppl 1):S46

Background: The aim of the study was the evaluation of different cytokines in children with hydrocephalus (HC) of different genesis. Increasing ICP should lead to changes in cytokine levels in CSF and serum, respectively. We expected knowledge about the cellular pathology in HC children, but also findings improving diagnostics as well as early detection of higher risk for shunt blockage.

Materials and methods: From 2003 to 2006 47 children with HC receiving surgery for shunting and shunt revision were selected for cytokine analysis in CSF and serum. Interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), insulin-like growth factor I (IGF-I), leptin and fibroblast growth factor (FGF) were detected in CSF and serum samples by commercially available ELISA kits (R&D).

Results: All selected cytokines could be detected in the serum as well as in the CSF of all children. In comparison to children with HC caused from other geneses, children with posthaemorrhagic HC were characterised by significantly higher IL-6 levels in CSF. There was no correlation between ICP at time of operation and the level of cytokines in CSF and serum. In children with enhanced serum levels of FGF and IGF-I, a revision of the shunting system due to blockage was necessary within 18 months. In contrast to shunt revisions due to mechanical problems (dislocation, disconnection), shunt dysfunction due to obstruction was characterised by significantly higher levels of VEGF and leptin in CSF.

Conclusion: The initial assumption that cytokine levels in HC depend on the ICP was not confirmed. Depending on the clinical course we have found differentiated cytokine levels. The determined cytokines probably reflect complex cellular regulatory processes within the ventricular fluid that are grossly unknown. Our results have to be verified in a prospective clinical trial to determine the predictive value of cytokines for possible shunt complications.

S47

GLP-I secreting encapsulated human mesenchymal stem cells for neuroprotection

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Background: Neuroprotective treatment for the prevention of secondary injury to head injury still lacks clinical utility. In our experimental study of controlled cortical impact (CCI) in rats, we investigate, whether transplantation of GLP-I-transfected stem cells encapsulated in alginate may prevent cellular responses after trauma

Materials and methods: CCI was applied to 50 male adult Sprague-Dawley rats. Trauma groups consisted of trauma only, animals treated with GLP-I-transfected human mesenchymal stem cells (GLP-I hMSC) encapsulated in alginate beads, with non-transfected encapsulated human mesenchymal stem cells (hMSC) and sham-treated with alginate capsules only (ALG). Seven healthy and untreated animals served as age-matched controls. Alginate beads were stereotactically implanted into the right lateral ventricle before CCI. 14 days post-injury, GLP-I-concentrations in the CSF were measured and brains were histologically and immunohistochemically assessed using specific antibodies against NeuN, GFAP, MAP2 and GLP-I.

Results: Anti-NeuN immunostaining showed a significant decrease of vital neurons in the dentate gyrus in the trauma animals as well as in the groups treated with non-transfected hMSC and with alginate capsules only. Both, GFAP and MAP2-immunohistochemistry, assessed in the area of contusion, mirrored the Anti-NeuN results showing less pronounced cellular reactive changes in the GLP-I treated animals. Stem cells in the intraventricular compartment seem vital as well as positive staining of the GLP-I peptide at the trauma site was observed.

Conclusion: Our immunohistological findings on treatment with GLP-I-transfected human mesenchymal stem cells in rats resulted in less histological sequels after controlled cortical impact trauma. This may break into new concepts for local neuroprotective therapy in traumatic brain injury as well as for other neurodegenerative diseases of the central nervous system, e.g. chronic hydrocephalus.

S48

High pressure hydrocephalus in neonates is associated with increased CSF concentrations of interleukin-18 and interferon gamma

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Background: High pressure hydrocephalus (HC) is associated with micro-glial activation and subsequent white matter damage. In addition to high pressure and ischemia, chronic inflammation may be pathophysiologically involved. In a rat model for HC (HTx rat, based on aqueduct stenosis), anti-inflammatory treatment reduces micro-glial scarring (Miller, 2006 CSFR). In human HC, immuno-regulatory processes involved in white matter damage are still largely undefined. Under various pathological conditions, increased CSF interleukin-18 (IL-18; expressed in micro-glial cells) and interferon gamma (IFNg; expressed in natural killer cells affecting oligodendrocytes) concentrations relate with white matter damage. We hypothesize that CSF IL-18 and IFNg concentrations are increased in neonatal high pressure HC, irrespective of underlying etiology.

Materials and methods: In 45 neonates with congenital high pressure HC (n = 30) CSF IL-18 and IFNg concentrations were determined (ELISA). HC neonates were grouped according to aetiology. Group 1: HC in spina bifida aperta (n = 20), group 2: triventricular non-hemorrhagic HC (n = 4), group 3: post hemorrhagic HC after fetal intracerebral hemorrhage (n = 6). Low risk neonates who underwent lumbar puncture for exclusion of meningitis (and appeared negative) served as controls (n = 15).

Results: In the three groups of HC neonates, IL-18 concentrations were significantly higher than in controls [medians and range; controls: 12.5 (12.5–158) pg/ml; group 1: 80 (23–232) pg/ml; group 2: 66 (55–226) pg/ml; group 3: 223 (103–406) pg/ml (each group vs. controls, p < 0.01; group 3 vs. group 1, p < 0.01)]. Similarly, IFNg concentrations were significantly higher in CSF of the 3 HC groups [controls: 8 (8–22) pg/mL; group 1: 35 (12–139) pg/ml; group 2: 22 (15–28) pg/mL; group 3: 22 (17–56) pg/mL (each group vs. controls, p < 0.01; between the groups, NS).

Conclusion: Irrespective of underlying aetiology, neonatal high pressure HC is associated with increased CSF IL-18 and IFNg concentrations. The increased CSF concentrations reflect their pathophysiological involvement in inflammatory white matter damage. We hypothesize that early anti-inflammatory treatment could ameliorate cerebral white matter damage in human neonatal HC.

POSTER PRESENTATIONS

S49

Vertical extension device for automatic adjustment of EVD-drip chambers or ICP-transducers

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Background: The external ventricular drainage (EVD) is a standard tool for ICP-monitoring and treatment of pathologic ICPs in neurosurgical ICUs. In a typical ICU-patient the position of the head is being changed at least 100 times per day. In order to achieve appropriate ICP-measurements and to avoid unwanted complications such as aneurysm bleeding or upward herniation due to rapid over drainage accurate positioning of the ICP-transducer and of the height of the drip-chamber is necessary. Therefore a mechanical device is required to constantly readapt the position of the drip chamber and the ICP-transducer to changes of the position of the head.

Materials and methods: A mechanical device was created to maintain the relative position of the outflow level and the ICP-transducer to the patient's head despite changes to the vertical position of the head using a vertical extension system. A chord is fixed to the patient's bed lateral to the head of the patient and is guided vertically up to enter a hollow stand that is inverse L-shaped and mounted to the patient's bed. Inside the stand the chord is guided further sliding on two rolls. In the vertical part of the stand the chord is fixed to a counterweight of 600 to 1000 g allowing mobility of the chord and still keeping the chord stretched despite changes to the vertical position of the patient's head. ICP-transducer or drip chamber can be easily attached to the free vertical part of the chord.

Results: Due to the vertical extension device constant readjustment could reduce positioning errors to ± 2 –3 cm minimizing hydrostatic measurement errors and preventing unwanted over drainage. Thus, occurrence of complications such as aneurysm bleeding, subdural hematoma/hygroma or even upward herniation could be significantly reduced.

Conclusion: We present an easily by oneself to manufacture, low-cost device to reliably avoid over drainage and erroneous ICP-readings.

S50

Independence and perceived quality of life in young adults with myelomeningocele. Function, needs and recommendations for what to do

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Background: Adults with myelomeningocele (MMC) mainly have the same type of problems, as do children with MMC,

implying a chronic disability and need for medical care and rehabilitation services throughout their lives. The aim of this study was to investigate function and needs in relation to independence and perceived health-related quality of life in young adults with MMC. We also propose recommendations for what to do to promote independence and quality of life.

Materials and methods: The population consisted of fourteen adults with MMC (md = 20 years). Six of them have been investigated till now. Two were community ambulators and four wheelchair users. The participants were investigated regarding medical needs, neuropsychological function, motor function, communication and learning skills. Independence and perceived quality of life were estimated from structured interviews (FIM, HRQOL and SF-36). The study was performed at Folke Bernadottehemmet, the regional rehabilitation unit of the Uppsala University Hospital.

Results: The results from six investigations are presented here. All six participants had shunt-treated hydrocephalus, bladder and bowel dysfunction and at least four medical problems each (mean = 8.3). One person was severely and one slightly mentally retarded. All had problem with executive functions, visuospatial function, memory and self-awareness. Some of them had problem with reading comprehension in spite of good understanding of single words and good spelling skills. Muscle strength of shoulders and hands was generally below average and motor performance was slow. The inability to initiate and organise activities seemed to be a clear hindrance for independence. The lowest independence was classified in the fields of memory and problem solving, toileting and bladder and bowel continence. Health-related quality of life was classified as rather positive despite the fact that the participants reported pain and low vitality. Recommendations: A first step was to increase individual awareness of specific difficulties. Our method was then to: • inform and teach about executive impairment • make the environment obvious by clear structure, sequencing strategies, a lot of preparation and feedback • have fixed routines and time/activity schedules • use clear, concrete verbal language and related questions to support communication • use visual support in school education and learning.

Conclusion: Medical and executive problems are common in young adults with MMC and together with low self-awareness they constitute a clear hindrance in daily life. Strategies to facilitate daily activities are available and should be applied so that independence and health-related quality of life is promoted.

S51

Anterior encephalocele: staged reconstruction

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Background: Encephaloceles are congenital herniation of cerebral tissue through the skull. It occurs in the midline sagittal axis from the occiput to the nasofrontal region. Anterior encephalocele comprises 15–20% of the cranial encephaloceles. They can be classified as Naso-frontal, naso-ethmoidal and naso-orbital or combination of these. It is rare in western countries, but seen frequently in oriental countries. In Assam, a north-

eastern state in India, anterior encephaloceles are seen commonly among the manual labours employed in the tea Industries.

Materials and methods: 28 patients (mean age: 38 months, range – 1 month to 12 years) with fronto-nasal swelling treated at Assam Medical College & Hospital, Dibrugarh, India between 1999 and 2007 are presented. 16 patients have undergone repair. Procedures adopted were VP shunt in patients with hydrocephalus followed by intracranial repair (bifrontal craniotomy + division of encephalocele + repair) and lastly extracranial repair with correction of hypertelorism. Patients without hydrocephalus were treated in 2 stages. In 4 patients all the procedures were done in one stage. Patients were followed up for periodic evaluation of physical and neuro-psychological status.

Results: Two patients with frontal dermoid cyst were excluded from our study. 16 patients had naso-frontal, 9 had naso-fronto-ethmoidal and 3 patients had naso-orbital encephaloceles. 12 patients had associated hydrocephalus. A total of 29 operative procedures were done: VP shunt (12 patients), external repair (8 patients), transcranial repair (12 patients), combined trans- & extracranial repair was done in 4 patients. 2 patients developed CSF fistula during post-operative period. One of them died. 1 patient had wound infection. Mean follow up was 38 months (1 month – 92 months). MPQ in operated patients were between 80–90%.

Conclusion: Anterior encephaloceles are rare in western countries and other states of India, but it is more commonly seen among the ethnic tea garden workers in Assam. Their unique life style, social customs, dietary habits and prevalent consanguineous marriage may provide some clue as to the etiological factors of this condition.

S52

Long-term experiences (max. 22 years) with 38 antisiphon devices

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Background: In 1973 Portnoy and Schulte developed the antisiphon-device for prevention of over drainage, a supplementary valve with a variable resistance depending on body verticalization respect. The variable suction of the water column in distal catheter. Clones were the SCD (Medtronic) and SLD (Radionics). All were assembled to other DP-valves or integrated in bodies combined with conventional valves (Delta, Novus). Unfortunately many cases with enigmatic hydraulic problems, especially under-drainage, but also over drainage were observed. In 1989 we identified the cause, the excessive susceptibility on external pressure, e.g. scars. For the compensation of these disturbing influences some users combined the antisiphons with adjustable Sophy- or Medos-valves. Unfortunately evaluations of these combinations, which anticipated the later Strata-valve, were not published. Generally long-term results of antisiphons are rarities.

Materials and methods: We evaluated retrospectively 38 patients with antisiphons 4–22 years after implantation, of them 18 with adjustable valves. 5 had telemetric ICP sensors.

Results: 12/38 antisiphons are still implanted (survival 32%), each 3 with good, fair, insufficient and poor condition. 20 patients were converted to gravitational, four to adjustable and one to a simple DP valve. Two became shunt free. The quote of sufficient results in long-term counted 7.9% (3/38).

Discussion: 34 years after introduction of antisiphons exist only two prospective randomized series with cumulative 430 Delta/Strata-patients (Drake 98, Kestle 05); both showed no differences compared to conventional valves in short term. Generally we found surprisingly few studies, approx. 50% with standard and 50% with inferior results (Miyake 99), but only mini-samples with superior data in short follow-up (Kondageski 07). 8 independent laboratory studies confirmed the excessive susceptibility on external pressure, which plausibly explains the clinical problems.

Conclusion: In short term, antisiphons show mostly no difference to other valves, sometimes they are inferior. In the course of time the specific problems increase and lead to a poor survival- and success-quote. Adjustable valves may damp, but are unable to compensate this effect.

S53

Controversies about adjustable shunts

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Background: The development of valves for the optimal treatment of patients with hydrocephalus is an ongoing challenge for decades. Over drainage and reliable long-term performance has been the focus for the different engineering teams. The so called Anti-Siphon-Device, flow reducing devices like the Orbis-Sigma-Valve or the Siphon-Guard and Gravitational shunts are still competing in respect to superior long term survival. On the other hand the requirement of non-invasive readjustment depending on the clinical aspects of the individual patient has led to several new developments. Whether or not adjustable valve could lower the likelihood of revisions could up to now not be shown in clinical trials. What are the options for a combination of adjustability on the one hand and over drainage avoiding devices on the other?

Materials and methods: All available shunts can be divided in two groups: traditional differential pressure valves and devices to avoid complications followed by over drainage. The only type of valve, which can be non-invasively readjusted, is the differential pressure valve. However, these devices do not take into account posture depending aspects in the shunt systems, which obviously are the reason for over drainage related complications. The systematic analysis of all available shunt-technology demonstrates the important range of therapeutic options, which have not been realized yet. Adjustable Anti-Siphon-Devices, adjustable flow-reducing devices or gravitational shunts are not on the market. Taking into account well known drawbacks of available adjustable DP-valves these devices promise to introduce further improvement for the treatment of

hydrocephalus. This can be supported by analytical and experimental investigations.

Results and conclusion: The adjustability of Anti-Siphon-Devices seems to be impossible: neither the adjustment of the influence of the subcutaneous pressure nor the adjustment of the height of implantation can be realized. The adjustment of flow-reducing devices is theoretical possible. However, technically this approach is an enormous challenge. The realisation of an independent readjustment for the lying and the upright position of the patient is unrealistic. However, the adjustment of the posture activated gravitational part is possible and promises another step into the direction of further improvement.

S54

Analysis of 120 cases of treatment of spina bifida and neural damage through complete release of pressure of sacrum nerve

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Background: Since this method was first used to cure Patient Y, a patient suffered from congenital spina bifida with complication of fecal and urinary incontinence on 23rd of November, 1998, a total number of 120 cases of patients have been treated by the same method and satisfactory results have been obtained.

Materials and methods: 1) Patients lie on left side; 2) Epidural anesthesia or general anesthesia; 3) A longitudinal incision is cut along the middle of sacrum and lower lumbar; 4) Dissect out the sacral nerve, release the conglutination and enlarge the neural hole; 5) Cut from the bottom of the dural cyst the adhesion with sacrum vertebrae and release the dural cyst.

Results: Assessment aspects: 1) restoration of urinary function; 2) restoration of bowel function; 3) restoration of function of lower limbs; 4) restoration of sexual function (restoration of emmenia for female patients); Assessment criteria: Excellent: attain of fecal and urinary function; restoration of lower limbs sensation, distinct improvement of muscle force and restoration of sexual function; Good: one of the fecal or urinary function is restored; restoration of lower limbs and sexual function; Fair: restore sensation of fecal and urinary activities but couldn't control; lower limbs function restored badly. Poor: no respects restored Assessment of result: Excellent and good 86%, Fair 12%, Poor 1.2%, Death: 1 case.

Conclusion: Because of sacrum spina bifida, the sacrum nerve is not protected by the spinal bone. During the growth period, the spinal cyst and sacrum nerve are getting tethered with sacrum, resulting damage to the nerves. With develop of age, the spinal is growing and the damages to nerves become worse. The operation is to release the adhesion between sacrum nerve and sacrum, restore the nerve path and blood circulation to the nerve. Therefore many patients restored their nerve function. The younger the patient is, the better is the result of the operation. The advantages of the operation are:- 1). It targets to cure the cause of the neural damage; 2). Though the operation method is very completed, it is safe and has no harm to the nerve.