New methods and observations in neurosonography

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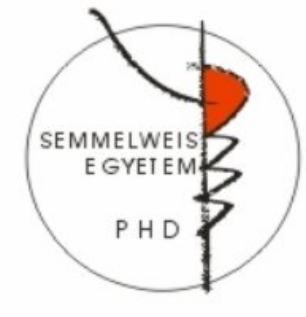

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1. Introduction

Intraventricular hemorrhages (IVH), periventricular leucomalatias (PVL), posthemorrhagic-, and postinfectious hydrocephali (PHH and PIH) are the most important diseases in neonatal neurology the, but their pathogeneses are not quite known. With my investigations, I aimed to learn more on the pathogenesis of these diseases and to deliver novel diagnostic methods, if possible.

My approach was neurosonography; there are essentially two main forms of neurosonography: the so called 2D imaging, and the Doppler flow velocity measurements.

The research I present in this thesis may be divided into two main areas based on the type of neurosonographic method used: cerebral blood flow measurements using Doppler techniques; and examinations of the spinal subarachnoidal (SSA) space in case of posthaemorrhagic and post-infectious hydrocephalus using the 2D method.

In my thesis, I will summarise the published original observations carried out by myself and my team and the new methods of examinations which we introduced, as first in our country, in some diseases of the central nervous system of neonates. These are the following:

1. The effect of dopamine on neonatal cerebral blood flow;
2. Changes of regional cerebral blood flow in the first 72 hours of life in neonates who suffered asphyxia;
3. Description of changes in echogenity in the subarachnoidal space of the spinal canal in PHH;
4. Description of changes observed by ultrasound in the spinal canal of neonatal-young infants with meningitis;
5. A controlled prospective study to look into the pathogenesis of PHH, based on changes in the spinal canal investigated by ultrasonography;

In addition to the abovementioned topics, I was the first in the country to introduce the method of intracranial compliance measurement used to differentiate

between slightly elevated intracranial pressure communicative hydrocephalus and ex vacuo hydrocephalus following generalised hypoxic-ischemic damage as the result of possible loss of cerebral tissue.

I use the same presentation frame for describing each topic:

a. Background
b. Aims
c. Methods and patients
d. Results
e. Conclusions

2.0 The examination of the CBF by Doppler sonography

2.1 Effect of low-dose dopamine (DA) infusion on cerebral blood flow

2.1.1 Background

Dopamine has been the drug of choice to combat hypotension in critically ill neonates. However, the pathogenesis of intraventricular hemorrhage (IVH) and periventricular leucomalatia (PVL) is almost certainly related to changes in CBF. Because autoregulation of CBF in preterm neonates is impaired, enhanced responsiveness of these infants to the pressor effects of DA may put them at risk for the development of IVH and/or PVL. The effect of the dopamine-induced homodynamic changes on CBF in the sick preterm infants has not been clarified previously. In addition, we have had the suspicion, that DA might have had a direct selective vasodilatory effect on the cerebral vasculature, too, which can also lead to IVH or PVL.

2.1.2 Aims

The aims of our study were:

1. To describe what is the effect of low-dose dopamine infusion on cerebral blood flow and autoregulation;
2. To check whether the pressor effects of DA put the newborns at risk for the development of IVH and/or PVL
3. Does the dopamine has a direct, selective vasodilatory effect on the cerebral vasculature?

2.1.3 Methods and patients

CBF has been measured in separate groups of 15 preterm and 15 term neonates. Clinical data is shown in Table 1. Only patients who met the following criteria were enrolled: (1) <24h of age; (2) hypotension (SBP <15 Hgmm below the predicted normal value); (3) adequate arterial pO_2; (4) no significant change in pH, pCO_2, pO_2, heart rate, and Hct during the study.

	Preterm infants	**Term infants**
N	15	15
Birth weight (g)	1434 ± 496	3067 ± 478
Gestational age (wk)	30,8 ± 3,4	39,1 ± 1,4
Diagnosis		
IRDS	11	
Sepsis/pneumonia	3	9
Presumed sepsis	1	5
Meconium Aspiration Syndrome		1
Baseline syst. BP (Hgmm)	30,5 ± 3,5	45,8 ± 5,8
Baseline diast. BP (Hgmm)	11,2 ± 3,2	25,13 ± 5,1
Heart rate	148 ± 12	141 ± 14
pH	7,35 ± 0,06	7,37 ± 0,08
pO_2 (Hgmm)	90 ± 5	89 ± 4
pCO_2 (Hgmm)	38 ± 6	40 ± 5
Hct	0,41 ± 0,7	0,39 ± 0,5

Table 1.

Clinical data of patients enrolled in the study of CBF measurements

The calculated RI was used to assess changes in CBF during the study:

$$RI = \frac{ESBFV - EDBFV}{ESBFV} \ [\%],$$

where ESBFV is End Systolic Blood Flow Velocity; EDBFV is End diastolic Blood Flow Velocity.

Both ESBFV and EDBFV were measured in anterior cerebral artery (ACA) by Doppler method. Arterial blood gases and Hct values were obtained from indwelling arterial

catheters. Heart rate (Ht), blood pressure (BP), and pO_2 were monitored as part of routine clinical care. BP measurements were performed via oscillometry.

After determination of the control data (baseline Doppler measurements of CBF velocity, Ht, BP, and arterial blood gas) DA infusion was begun at 2 g/kg/min. All of the measurements were repeated at 20 min (DA2/20) and at 60 min (DA2/60) during the infusion of 2 g/kg/min DA. The dose of DA was then doubled, and all measurements repeated at 20 min (DA4/20) and 60 min (DA4/60) (Fig. 1.).

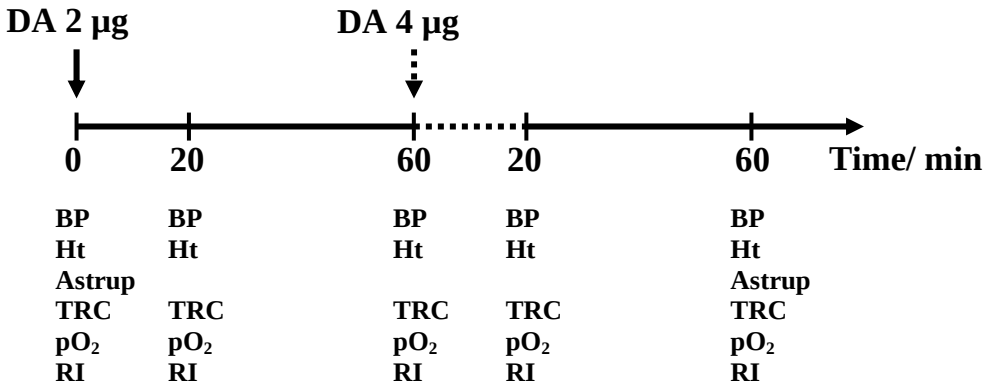


Figure. 1.Examination protocol

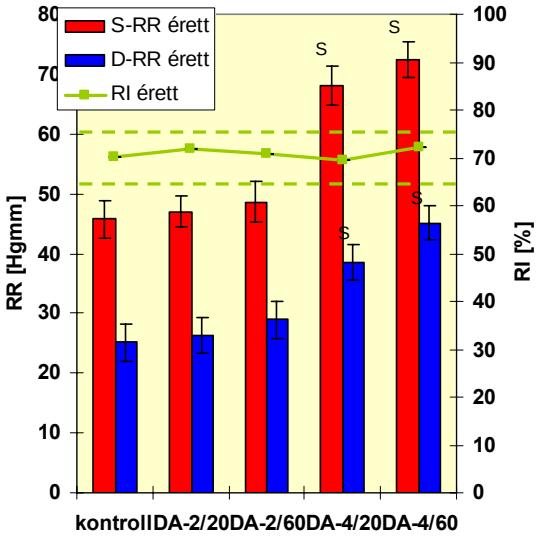
One-factor ANOVA were used for statistical analysis of the data and $p<0.05$ was considered significant.

2.1.4 Results

In the moderately hypotensive term neonates, the RI was in the normal range (65.75%) during the control period (Fig. 2a). Administration of 2 g/kg/min DA did not induce significant changes in BP or RI at either 20 or 60 min after the drug infusion. In contrast, 4 g/kg/min DA significantly increased BP in both the DA/20 and DA/60 periods ($p<0.05$), but the RI remained unchanged.

In the hypotensive premature infants, the RI was also in the normal range (65-75%) during the control period (Fig. 2b). Administration of 2 g/kg/min DA increased the BP, but this effect did not reach significance. At 20 min after the initiation of higher doses (DA 4/20) RI

significantly decreased and BP increased in both the DA/20 and DA/60 periods ($p<0.05$). Despite the sustained significant elevation in the BP, however, RI returned to normal at DA4/60.



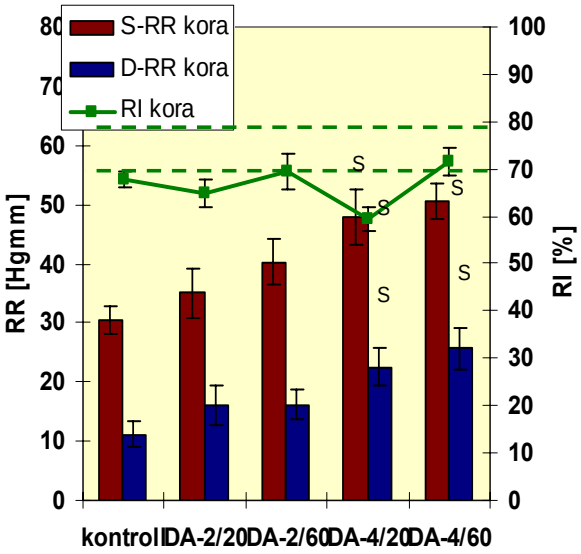


Figure 2a **Figure 2b**

Systolic BP (S-RR) and diastolic BP (D-RR) and RI in 15 term (Fig. 2a) and in 15 preterm (Fig. 2b) infants before (control) and during 2 (DA-2) and 4 (DA-4) g/kg/min dopamine therapy. Measurements were performed at 20 and 60min on DA-2 (DA-2/20 and DA-2/60, respectively) as well as on DA-4 (DA-4/20 and DA-4/60, respectively).The dashed lines represents normal range for RI. 'S' denotes significant changes compared to baseline values

2.1.5 Conclusions

The correlation of RI to CBF which was measured using the Xe 133 clearence technique is only 0.56, but in a self-controlled study (no significant changes in Ht, Hct, pH, pCO_2 and pO_2) is considered as a reliable indicator of CBF.

Our observations: (1) 2 g/kg/min DA cannot produce significant changes in BP or in CBF either in the ternm or the preterm infants; (2) 4 g/kg/min DA produced significant increase of the BP in both groups; (3) term neonates have an intact and effective autoregulation of CBF; (4) preterm infants have slow, but not totally ineffective autoregulation of CBF: the pressor effects of DA may put them at risk for the development of IVH and/or PVL; (5) 4 g/kg/min DA can cause severe disturbance in the otherwise intact autoregulation of term infants.

2.2 Changes of regional cerebral blood flow (rCBF) during the first 72 hours of life in asphyxiated term newborns

2.2.1 Background

The incidence of the postasphyxia syndrome (PAS) is 2-4 in 1000 term newborns. The patomechanism includes disturbances in metabolism, the extracellular accumulation of excitatory aminoacids (mainly glutamate), production of free oxygen radicals (FOR), and the accumulation of intracellurar Ca. These factors, either alone or in combination, can induce changes in rCBF. A shift in rCBF can alone be the determining factor in the development of the syndrome. Obviously, if we were able to better describe the changes in rCBF we would be closer to a better understanding of the pathophysiology of PAS and to a better treatment regime, as well.

Based on the Doppler method, Taylor in the early 1990's devised the Time Average Peak Flow Velocity (TAPFV) measure, being the integral of the area under the Doppler peak flow velocity curve, which is highly correlated (r=0.82) to the results obtained by the Xe133 clearance technique.

The definitive diagnosis of postasphyxia syndrome is difficult; the clinical picture is mostly undistinctive. Moreover, in the acute phase neither 2D ultrasonography, nor RI is appropriate for the diagnosis of asphyxia. In this stadium computed tomography (CT) is inapt, as well, only MRI (T2, diffusion weighted with ADC, and MR spectroscopy sequences) has the proper sensitivity and specificity, but the realization of the study is fairly difficult in, gravely affected infants. Nevertheless, the therapeutic window is very short. It further hinders the diagnosis that it is impossible to delineate, based on the clinical picture, acute intrapartum asphyxia from subacute hypoxic ischemic encephalopathy developed in the last intrauterine days, thus being inaccessible for therapeutic appraches.

2.2.2 Aims

1. To measure changes in RCBF using a new Doppler method (TAPFV) in healthy and asphyxiated term infants using a much longer follow-up regime (first 72 hours of life) than published previously with a much higher precision (measurements taken in every 6 hours in 3 main cerebral arteries) to investigate the pathophysiology and pathogenesis of asphyxia;

2. To investigate whether TAPFV measurements provide an appropriate tool to diagnose asphyxia, and whether the method has any prognostic and therapy guiding value.

2.2.3 Methods and patients

The details of the infants included in this study can be appreciated in Table 2.

		Control	Asphyxia
N		18	25
Apgar	1 min	10	0-1
	5 min	10	< 4
Neurological symptoms		-	Coma - comatosus Areflexia - hyporeflexia Decreased muscle tone
Anamnesis		negative	positive

Table 2.

During the first 72 hours of life I measured the TAPFV in every 6 hours in the arteria cerebri anterior (ACA) and in the right and left arteria cerebri media (ACM). In the same time arteric pH, pCO2, pO2, systemic blood pressure, pulse rate was estimated. Hemoglobin and hematocrit was measured once every day.

Infants in the control group, in general, had mild disturbances in their respiratory functions (e.g. wet lung, possible sepsis, etc.) without any abnormality in the abovementioned parameters.

2.2.4 Results

A slow linear increase of TAPFV can be seen in the control group both in the ACA and in the bilateral ACMs. The TAPFV was always significantly higher in ACMs than in the ACA, and the flow in the bilateral ACMs was roughly the same. (Fig 4a).

The TAPFV was higher both in the ACA and in the MCAs in the asphyxiated group compared to the controls (Fig 4b). In 2 cases, despite of the clear-cut clinical symptoms and the neurological deficit developed in the first year, I found only mildly elevated CBF. In other 3 cases the TAPFV was extremely low.

There was no significant difference in the blood pressures values of the control and the asphyxiated group.

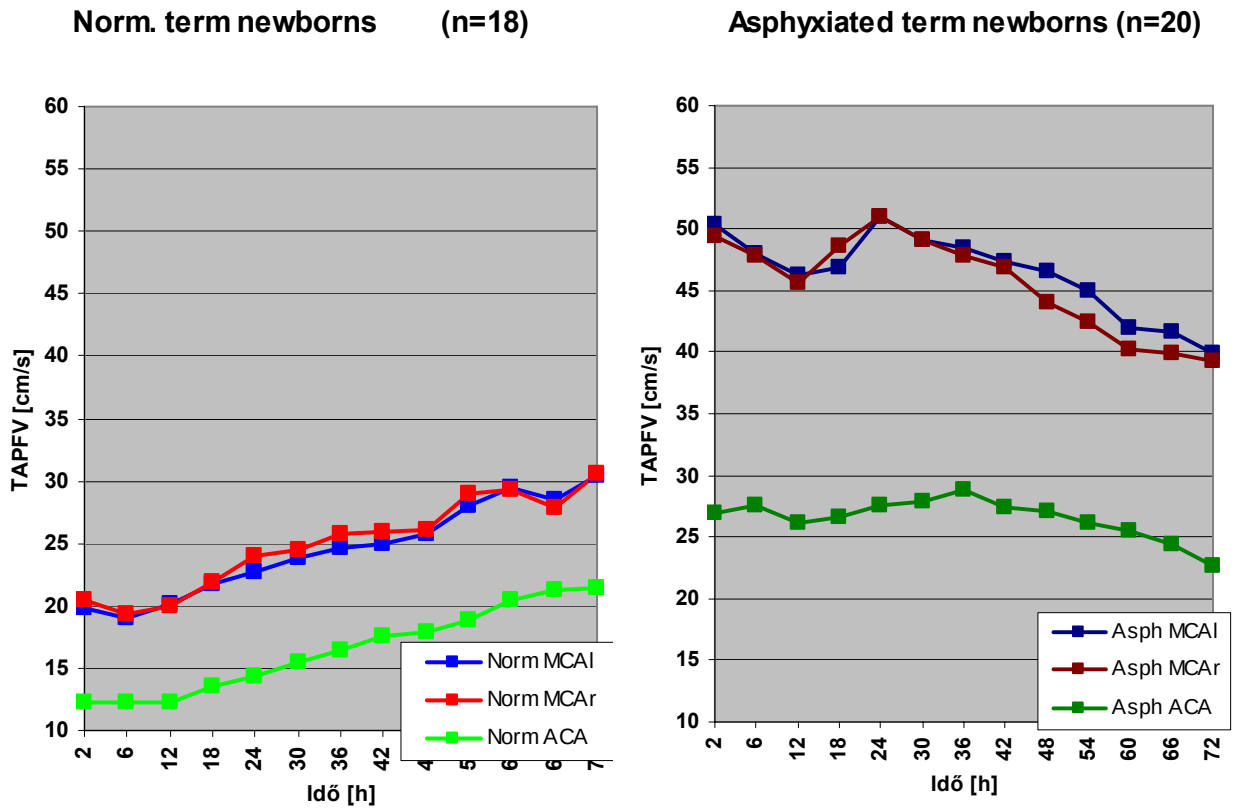


Figure 4.Cahnges in TAPFV(CBF) during the first 72 hours of life in mature, healthy (a) and asphyxiated (b) infants in ACA and the two ACMs

The long term outcome can be appreciated in Fig 5.

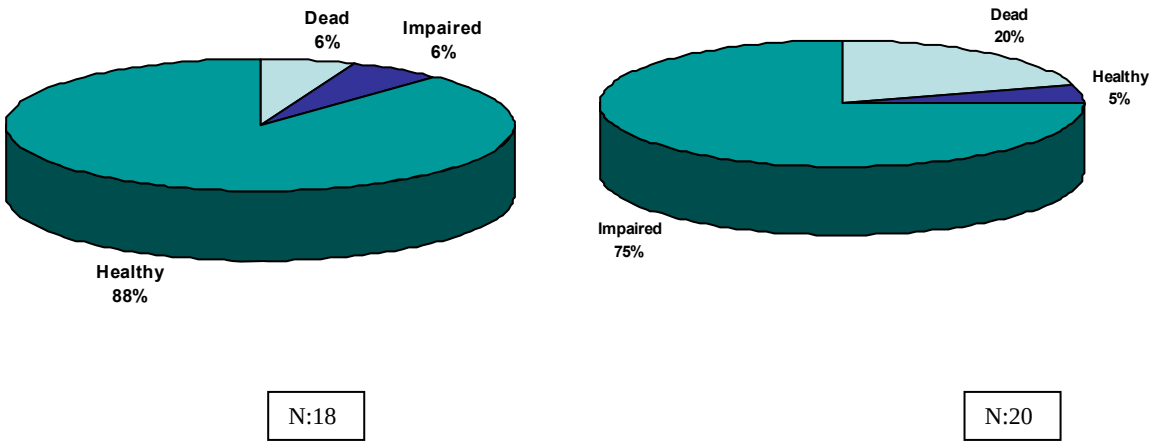


Figure 5. Long term follow-up of the control (a) and the asphyxiated (b) group

2.2.5 Conclusions

We managed to implement a new clinical approach – a TAPFV Doppler spectrum analysis with the constant monitoring of physiological parameters determining the CBF — which is capable of a much better estimation of CBF than other previous Doppler methods. Using our method, we were able to investigate rCBF in mature infants with higher precision than it was possible with previous methods, moreover, our relatively long protocol provided an opportunity to investigate the long term dynamics of cerebral blood flow.

I conclude that postasphyxia syndrome has most likely a diverse pathogenesis and thus a diverse pattern of progression. Diffuse hyperaemia is the characteristic phenomenon in high proportion of the severe cases, however in the gravest patients a prominent decrease of CBF is observed. Hyperaemia is present for a longer period then we previously thought.

It is impossible to delineate the acute (intrapartum) and subacute (intrauterine) – asphyxia based on the clinical symptoms. Thus, we can assume that the 2 infants having normal CBF despite the clear clinical symptoms were indeed suffering from subacute asphyxia so the measured cerebral blood flow represent the decay phase of the luxury perfusion. This observation might help discriminating between acute and subacute asphyxia.

TAPFV can be of high importance both as a diagnostic and a prognostic factor, multiple TAPFV measurements can even be used for guiding the therapy.

The simultaneous use of multiple diagnostic tools, – such as TAPFV measurements, amplitude-integrated EEG, and MRI examination methods developed in the last few years, – can help to discriminate the different forms and phases of PAS, thus, providing a better outcome for therapy.

Moreover, it would be important to clarify the possible pathogenetic implications of an increased CBF. This could lead to a TAPFV guided therapeutic approach with a targeted optimal CBF.

3 Changes in echogenicity of the spinal subarachnoid spaces in PHH and PIH

3.1Background

Subarachnoid hemorrhage in the spinal canal can be found in 35-60% of deceased neonates. Both the source and pathophysiologic relevance of these findings are challenged and their existence in vivo could not be proven by radiological methods.

This has prompted me to initiate a series of comprehensive examinations to explore the changes of the subarachnoid space in the spine, in addition to routine cranial ultrasound.

Preliminary results of this survey have shown that changes of echogenicity in the spinal subarachnoid (SSA) space can be observed primarily in post-PHH, but to some extent in PIH.

3.2 The first observations of changes in echogenicity of the spinal subarachnoid space in PHH

3.2.1 Background

The first unambiguous changes were observed in a neonate delivered during the 29th gestational week. The patient has had IRDS and subsequent tension pneumothorax on the 3rd day. Repeated cranial ultrasonography on day 4 has shown stage IV IVH. The next step was an ultrasound scan of the complete spine (cervico-thoraco-lumbo-sacral segments), assuming that there were visible changes in echogenecity of SSA space.

3.2.2 Methods

Ultrasonography of the spine was performed with ATL 9 HDI ultrasound system, using a 5-10 MHz wide spectrum linear transducer in the axial and sagittal planes with the patient in prone position.

3.2.3 Results

The posterior subarachnoid space of the spine had markedly increased echogenity to the level of the L I. vertebra in both axial and sagittal planes. The anterior subarachnoid space had the usual, fluid-like, completely echo-free picture.

We were unsure whether we found the subarachnoid haemorrhage causing the CSF flow disturbances we have been looking for. Since we have not found any related publication in the literature we intended to confirm our ultrasound findings with MR imaging. Unfortunately, at the level of technical development of the time (1995), we were unable to obtain appropriately detailed MR imaging. It is still worth mentioning that due to the small dimensions (approximately 1 mm thick abnormality) and the artefacts caused by the vertebrae, MR imaging is still unable to visualize these changes. This was the first time, that it has become evident, that the resolution of the ultrasound – for superficial lesions – supersedes that of the CT and the MR.

Repeated spinal ultrasound examinations have shown slow improvement, and the discrepancy between the ventricular and lumbar puncture samples has gradually faded away.

At the age of 6 weeks VP shunt operation was performed on the preterm neonate. A repeat spinal ultrasound examination did not show any abnormality at the age of 3 months.

We have come to the conclusion that, as a result of the circulation of cerebrospinal fluid in the spinal column, and the continuous supine position of neonates blood entering the CSF from the stage IV IVH and cellular elements from the haemorrhagic necrosis have subsequently been deposited in the dorsal region of the spinal subarachnoid space, thus forming a barrier. We termed this deposited material as „debris" to allow it to be introduced in international literature. It has been suggested, that this "debris" may have a role in the development and progression of PHH. Furthermore, the possible role of "derbis" in the discrepancy between ventricular and lumbar CSF (pressure, chemical and cellular content, microbiological results) has also been raised, which suggests, that when therapeutic decisions (such as shunt operations) are being made, the presence of "debris" should be considered. We assume ultrasonography of the spine may be of great benefit in such cases.

3.3 The first observations of changes in echogenicity of the spinal subarachnoid space in PIH

3.3.1 Background

Following the first positive result in case of PHH, we have extended our spinal ultrasound examinations to include the meningitis cases.

3.3.2 Methods

All of the patients with suspicion of meningitis have had spinal sonography, too. The technique of the ultrasound examination of the spine was the same as in case of IVH and PHH and we used the same equipment, as well.

3.3.3 Results

The first positive result was observed in a preterm neonate born on the 32nd gestational week. The patient has become lethargic, vomited and developed pyrexia on the 6th day. Lumbar puncture has shown CSF protein level of 12 g/l, glucose level of 0.1 mmol/l, and white cell count of 6000. Bacteriology cultures have confirmed Group B Streptococcus, and as cranial ultrasound has excluded haemorrhage, the diagnosis of meningitis has been made. We performed the first spinal ultrasound examination and found the subarachnoid space surrounding the spinal cord to be increased in echogenicity.

3.3.4 Conclusion

After reviewing the literature, I have concluded that these kind of changes in the spinal subarachnoid space have not yet been reported in either PHH or PIH.

The observed increase in echogenicity in SSA space can be explained by the raised protein and cellular content of the CSF, which is, in part, a result of the arachnoiditis, but in PHH the cellular particles carried by CSF flow (blood, necrotic tissue, etc.) could also have relevance.

These changes are of the following possible clinical relevance: (1) they may have a role in the development of CSF flow disturbances; (2) they could explain the discrepancy often observed between the biological and chemical constitution of CSF from ventricular and lumbar punctures; (3) they offer a simple diagnostic tool, which may help in the daily routine to support the validity of the lumbar puncture, or aid in deciding whether lumbar puncture is at all worth pursuing.

3.4 A controlled, prospective study to examined the pathogenesis of PHH, based on the changes in the spinal canal visible by ultrasonography;

3.4.1 Aims

The following study next was a prospective and controlled study, aimed to evaluate the frequency and the clinical significance of the echogenecity in the spinal subarachnoid space (SSA) at risk for progressive ventricular dilatation (PVD).

3.4.2 Methods

Spinal sonography was performed on 15 neonates with severe IVH (n=10) or bacterial meningitis (n=5). Spinal sonography also was performed on 16 control neonates. Images were analyzed for the presence and location of echogenecity within the thoracolumbar SSA. Lumbar punctures were performed on all 31 neonates, and CSF was analyzed for cell count and protein content. Ten of 15 neonates required ventricular drainage prociders.

3.4.3 Results

PVD occurred in11 of 15 neonates with IVH or meningitis. Echogenic debris was present in the thoracolumbar SSA on spinal sonography in every neonate with PVD compared with none of the 16 control neonates ($p < 0{,}0001$ by chi-square analysis). In addition, the 11

neonates with echogenic SSA space had significantly higher protein and RBC contents in the lumbar CSF (p<0, 04).

3.4.4 Conclusion

1. I could find echogenic SSA space after IVH III.-IV. (ca. 70-80%) and after meningitis. ***2.*** Echogenic SSA space could explain the discrepancy which is often observed between the biological and chemical constitution of CSF from ventricular and lumbar punctures and it has strong influence on the choice of the following diagnostic and therapeutic activity. ***3.*** This change after the IVH - presumably – has a "filter" function, but in case of the meningitis, it has an "obstruction" result. ***4.*** This change can play a role in the development of the PHH or PIH, because in the patients with echogenic SSA space, I could find 90% PVD after the bleeding or meningitis, and in contrast, the patients without echogenic SSA space, I could find PVD. ***5.*** Further studies are required to determine the role of the increased echogenecity of the SSA space in the development of PHH or PIH.

3.5 Changes of the spinal subarachnoidal space echogenicity in the time

3.5.1 Introducion

Because of the last question, I have decided to make a new study where I can follow the spread of blood from IVH until the SSA space and a follow up until the PVD will disappear or the shunt surgery becomes essential.

3.5.2 Aims

The aim of the next study was to study

1. the frequency and
2. rate of the spread of blood into the SSA space and
3. to evaluate the relationship of this finding and PHH.

3.5.3 Methods and patients

9 consecutive premature infants with major IVH (gr. 3 or 4), and 10 premature babies with minor IVH (gr.1) or no evidence of IVH (control group) were identified and underwent serial cranial and spinal sonography at the time of initial diagnosis, 12-24h after the IVH and weekly thereafter for at least 9 weeks. Sagittal and axial scans of the thoracolumbar spine were obtained and evaluated for the presence of echogenecity in the dorsal SSA space.

3.5.4 Results

The SSA space was echofree (normal) in all cases at time of initial sonography. Within 24 h, all babies with major IVH developed increased echogenicity of the cervical and thoracic SSA space. Echogenicity of the SSA space decreased gradually over several weeks. Although transient ventricular dilatation was present in every patients, only one patient had rapidly PVD requiring shunt placement. Transient cyst of the cervicothoracis SSA space were identified in two patients 6-7 weeks after the IVH. The SSA space remained echofree in all control patients.

3.5.5 Conclusions

Spread of the blood from ventricular system into the SSA space after IVH is common and can be seen within 24h of initial IVH. SSA blood is associated with posthemorrhagic PVD and transient SSA cyst formation.

3.5.6 Discussion

That was the first publication of the visualization of the spread of blood from the ventricular system into the subarachnoid space following IVH. In more than half of the cases within 12 hours, I was able to detect the blood in the SSA space. I carried out 7-9 week long follow up of the increased echogenecity of the SSA space. My results suggest, that there is a strong correlation between the echogenecity of the SSA space and post-hemorrhagic ventricular dilatation.

4.0 Introduced of the Intracranial Compliance

4.1 Introducion

The differential diagnosis between brain atrophy and the slightly increased ICP at communicative hydrocephalus is could be quite difficult. The clinical picture and the conventional radiology often can not help. There are several limitations to use RI alone in the evaluation of infants with increased ICP.

4.2 Method

Doppler US examination is performed by means of the transtemporal approach. The middle cerebral artery is identified at color Doppler scanning, and the angle-corrected Doppler spectra from the middle cerebral artery were obtained at baseline US scanning while no pressure was exerted over the fontanelle, and during the simultaneous compression with ophtalmodinamometer of the anterior fontanelle with 50, 100, and 150 gr/cm2 of pressure.

4.3 Results

Increased fontenelle pressure resulted en very little changes in middle cerebral artery RI in healthy premature and term infants (p>0,4 ANOVA). In contrast, infants with abnormal cranial compliance showed significant increases in RI with every incremental increase in anterior fontanelle compression (p< 0,004 with ANOVA) (Fig.6).

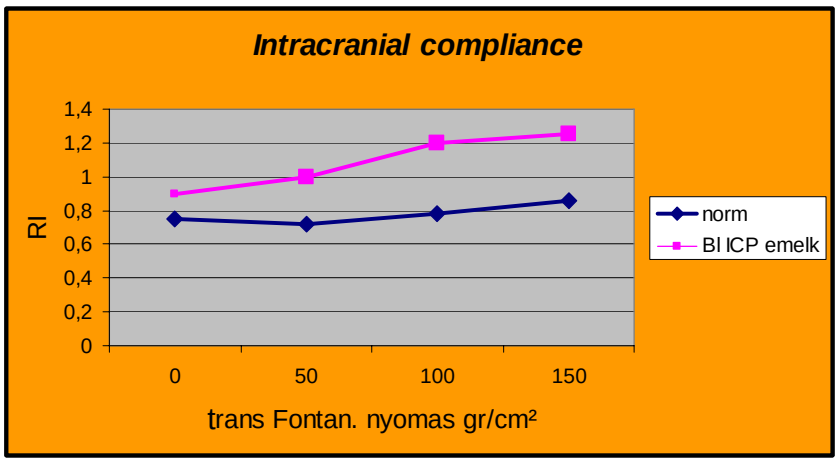


Fig.6

Change in middle cerebral artery RI versus fontanelle pressure

"BI ICP" = Progressive Ventricular Dilatation in a full term infant with increased ICP.

"norm"= healthy control subjects

4.4 Discussion

According to the Monro-Kellie hypothesis, the volume of brain, spinal fluid, blood, and other intracranial components is constant. Initially, a change in intracranial volume (ICV) is offset with volume shifts in other components such that ICP remains essentially unchanged. As the capacity to shift volume is surpassed, further increases in ICV result in elevation of ICP. This volume-pressure relationship can be described with a compliance curve with a long, flat initial portion, in which little ICP increase occurs with increasing ICV, and a steep portion in which small volume increments result in progressively larger elevations in ICP. During graded fontanelle compression in normal infants, cerebrospinal fluid or blood can be readily

displaced to compensate for the small increase in volume delivered by the ophtamodynamometer, which results in no increase in ICP. In infants with abnormal ICC, however, the increase in ICV with graded fontanelle compression is translated into a transient increase in ICP and a concomitant decrease in cerebral perfusion pressure. As a result, the MCA RI progressively increases.

4.5 Conclusion

This method may demonstrate changes in intracranial compliance prior to measurements of RI alone, and when the other radiological methods (US, MRI) are not enough informative.