Functional analysis of the neonatal brain

Zsófia Róna

PhD Summary

Clinical Medicine Doctoral School

Semmelweis University

Head of the Program and Supervisor: Zoltán Papp MD, DSc

Official reviewers: Ilona György MD, PhD

Miklós Szabó MD, PhD

Head of the Final Examination Committee: Fekete György MD,DSc.

Members of the Final Examination Committee: Lajos Kozák,PhD
Péter Mandl PhD
Mónika Popper PhD

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1. Introduction

Premature birth presents enormous complexities for all to consider, especially for expectant families. Survival rates of this population have dramatically increased in the last decades, although enthusiasm for this improvement is tempered by the long-term follow-up experience with these children. Follow-up examinations of surviving infants born before tfirsthe 27th week (post menstrual age) from different institutions and populations demonstrate outcomes that seem to be remarkably consistent. Approximately 25% of infants suffer severe neurologic damage, 25% moderate impairment, and 50% are judged to be mildly impaired or normal.

The improvement of continuous bedside monitoring for physiological and neurological variables and novel neuroimaging methods play an essential role in everyday neonatal practice and provides reliable information in the prognosis of neurodevelopmental outcome.

The author of this paper would like to present through her research different aspects of neonatal neurophysiological examinations and neuroimaging methods, in order to better understand the development of neonatal brain pathologies and their effect on neurodevelopmental outcome. Five studies have been included.

2. Aims

2.1. Hydrocephalus study

The first aim of the present prospective study was to evaluate the role of flash visual evoked potentials (fVEP) and amplitude integrated EEG (aEEG) in the monitoring of elevated intracranial pressure in congenital hydrocephalus and the development of PHVD in preterm infants and to define pattern changes with decompressing neurosurgical interventions. Secondly, we wanted to correlate our findings with the degree of ventricular dilatation and Doppler sonography. Thirdly, we wanted to compare late versus early intervention with the primary outcome, the need for long term ventriculoperitoneal shunt insertion and with the secondary outcome of follow-up neurocognitive examinations and motor development.

2.2. MR-compatible Incubator Study

Aim of our study was to assess our initial experience with an MRI-compatible incubator and analyse its impact on examination feasibility and further clinical management. So we first analyzed the use of MRI itself in unstable patients under intensive care management and secondly the usefulness of a special device (MRI-compatible incubator) making MRI examination in unstable patients more feasible. Because the main advantage of the MRI-compatible incubator is optimizing thermoregulation during the MRI, we separately analyzed the usefulness in patients weighing under 2000g.

2.3. Asphyxia Study

The aim of our retrospective study was to analyse early versus late MRI and aEEG data separately and correlate its effect on the prognostic outcome of children with HIE with two years of age. Secondary aim was to combine aEEG and MRI data in order to develop a more exact prognostic value for this patient population.

2.4. Mismatch Negativity Study

The aim of the prospective Miss-Match-Negativity (MMN) study was to test the maturation of phoneme and stress discrimination in case of natural speech in premature infants and healthy controls at 6 and 10 months of age. The main principle along which we planned our experiment is to investigate the typical stress information at the word level. Hence we used a complex pattern of acoustic cues while varying stress information using the miss match negativity paradigm of event related potentials. Our hypothesis was that we will find differences between the two age groups in case of both phoneme and stress detection, but preterm infants will show maturational lag only in case of stress processing.

2.5. Intraventricular Haemorrhage Study

The aim of this prospective study was to compare outcomes of preterm infants with different grades of IVH born below 32 weeks of gestational age (GA) with outcome of controls without IVH. Emphasis was on the comparison of the influence of low grade IVH on the neurodevelopmental outcome. Cranial ultrasound examinations were carried out on the 1st 3rd, 5th, 7th, and 10th day of life and then once a week until discharge.

3. Methods

3.1. Neurophysiological Methods

3.1.1. **Conventional EEG with video**

Conventional EEG is today´s gold standard for neurophysiologic diagnosis in all age groups. Nevertheless it is not suitable for continuous recording since producing large data volumes which cannot be assessed directly at the bedside. In an effort to solve this problem, various methods of reducing and compressing the EEG signal have been developed, the amplitude-integrated EEG (aEEG), being one of them. The electroencephalogram (EEG or conventional EEG) is a signal recorded from scalp electrodes and derived from the electrical activity of cortical neurons. The EEG signal represents the synchronous activity of neurons arranged at right angles to the surface, mainly the pyramidal neurons. The EEG changes through the neonatal period and childhood, thus it is essential to compare EEG measurements with normal values at the same maturational stage. EEG should be interpreted for background pattern, reaction to external stimuli, level of consciousness and for presenting pathological phenomena. Video recordings are essential in the differential diagnosis of neonatal seizures.

3.1.2. **Amplitude Integrated EEG**

The aEEG was recorded as a single-channel EEG from biparietal surface disk electrodes using a cerebral function monitor (Olympic Cerebral Function Monitor 6000). In brief, the obtained signal is filtered, rectified, smoothed and amplitude-integrated before it is written out at slow speed (6 cm/h) at the bedside. (Maynard et al. 1979 Hellström-Westas et al. 2006)

3.1.3. **Flash Visual Evoked Potentials**

Visual Evoked potentials can be evoked by brief changes either in luminance (fVEP: flash visual evoked potentials) or in the contrast (pattern VEP, pVEP) within the visual field. As there is no need for fixation to evoke the fVEP and luminance changes are detected through the closed eyelids as well, it is an optimal method to use in the non-cooperative neonatal population.

3.1.4. **Event related Potentials and Miss Match Negativity**

Event related potential (ERP) is a response to a stimulus, where from many trials the results are averaged together, causing random brain activity to be averaged out and the relevant

waveform to remain. Currently, ERP is one of the most widely used methods in cognitive neuroscience research to study the physiological correlates of sensory, perceptual and cognitive activity associated with processing information. Mismatch negativity (MMN) is an event-related potential (ERP) component that provides a good measure of auditory perception and function and is typically observed between 100 and 250 ms (Näätänen, 2007). MMN is generated by the automatic response of the brain to a mismatch in auditory stimulation.

3.2. Imaging Methods

3.2.1. **Magnetic Resonance Imaging**

Preterm infants are at high risk of developing brain injury. Neuroimaging does not only play an important role in prognosticating later neurological problems, but provides also essential information and support for the neonatologist in clinical decision-making in critically ill neonates. MR imaging of the premature infant has been proved to be superior to the widely used serial ultrasonographic examinations. (de Vries 1998), MRI has enabled a non-invasive high resolution evaluation of the developing brain, where several studies have shown delayed grey-white matter differentiation, and diffuse white matter signal intensities after premature birth. (Woodward et al 2006)

3.2.2. **Cranial Ultrasound**

Sonography is the method of choice for prenatal and postnatal malformation screening at the bedside. Blood velocities of cerebral arteries are especially usefull in hypoxic ischemic encephalopathy. Makiko 2012 Serial cranial sonographic examinations are part of the daily routine on the neonatal ward for the detection of common brain pathologies such as intracranial bleedings, PVL, PHVD and Neonatal encephalopathy. IVH is classified according to Papile. (1978) PHVD is classified according to the ventricular index of Levene and recently an additional anterior horn width (AHW) and thalamo-occipital distance (TOD) helps better evaluation (Brouwer et al. 2012)

4. Results

4.1. Hydrocephalus Study

The study population included 20 infants. In the PHVD group statistically significant differences prior to and after neurosurgical intervention were found for fVEP latencies, ventricular width in mm, aEEG score and occurrence of SWC (p=0.02). The congenital hydrocephalus group showed a tendency towards normalisation of fVEP wave latencies and aEEG activity, although only 33% actually reached normal values in comparison with 58-82% in the PHVD group. Neurosurgical intervention was conducted significantly earlier in the congenital hydrocephalus group, at the 13th day of life instead of the 24th day of life.

4.2. MR-compatible Incubator Study

A total of 129 infants underwent magnetic resonance neuro-imaging during our three year study period. The mean imaging time decreased with 4 minutes; 34,43 min without and 30,29 min with the INC during the two periods. During the MR imaging a mean of 1 additional sequence was performed in the INC group. There was a significant increase in the number of infants under 2000g examined, while the number of critically ill infants and ventilated infants increased with 18-16% respectively using the MR-Compatible Incubator. Due to infant instability and insufficient sedation 10% of MR examinations were terminated incompletely or interrupted and started again without the INC, while all planned protocols were finished with the INC. More than 50% of all cases was management change initiated after MRI, or the clinical diagnosis changed or further specified.

4.3. Asphyxia Study

A total of 44 infants fitted the inclusion criteria. We have found a significant positive correlation between neurodevelopmental outcome at two years of age and both MRI and aEEG scores. The aEEG had a better prognostic value when the measurement was within two days after birth, while in contrast late MRI (after the first week) showed stronger correlations with good neurodevelopmental outcome. The positive predictive value of the MRI score was 88% while the negative predictive value was 83%.The aEEG had a positive predictive value of 92% und negative predictive value war 89% in our study cohort. The presence of seizure

activity at all times had a strong correlation but no significance with unfavourable neurodevelopmental outcome.

4.4. Mismatch Negativity Study

The data of 37 infants were analysed. Summarizing the results obtained in the phoneme deviant condition we can say that in respect to the question of maturation there are only age related differences in case of the first time window. Two MMN components were present to the phoneme deviant in all the four groups. We could find differences only in case of the first component by age: younger infants had bigger MMN to the phoneme deviant than the older infants. No differences were found between the preterm and full-term groups.

In case of the stress deviant condition all the infants detected the presence of stress (S+) in the middle of the acoustic stimuli, synchronized to the extra stress cue on the second syllable. When the two time windows were analysed separately, in the first time window (300-350ms) we did not find a significant main effect of condition. In the second time window (500-550ms) a significant main effect of status was found. Preterm infants had smaller positive mismatch responses than those of the full-term group.

4.5. Intraventricular Haemorrghage Study

151 infants 37/151 (24,6%) developed an IVH grade I, 84/151 (55,6%) an IVH grade II, 18/151 (11,9%) an IVH grade III and 12/151 (7,9%) an IVH grade IV. Group I. had 121 patients with low grade IVH and Group II. had 30 patients with high grade IVH. that premature infants with IVH were smaller and younger, than the healthy control patients and had significantly more morbidities, such as CLD, RDS, PDA, ROP and of course PHH. Delivery was more often vaginal in the IVH group suggesting severe threatening premature birth, where there was less time for an elective cesarian section, although the rate of cesarian section was very high in the whole group of patients under 32 weeks of gestation with 85,3%.

Predicted probabilities for impaired outcome in dependence on GA and IVH show that the interaction between gestational age and IVH was significant (p 0.01). This effect is even more significant in mild IVH grades (I and II) compared to severe grades of IVH (grades III and IV). It is also very important to notice that this premature group has impaired cognitive and motor outcomes, such as 10%CP and 17% abnormal Bayley Scales at three years of age even with no IVH. This could be due to accompanying pathologies such as ROP.

5. Conclusions

The above described studies present a variety of examples for the vulnerability of the premature/term infants' nervous system. Despite joint efforts of neonatologists, obstetritians and radiologists, neurodevelopmental impairment of premature infants remains a serious problem. Neurophysiological methods became standard procedures in everyday decision making. The amplitude integrated EEG plays an essential role in continuous seizure detection, basic screening for adequate maturation and in prognosticating neurodevelopmental outcome in different pathologies, especially in neonatal encephalopathy. Flash visual evoked potentials (VEPs) have great additional value in defining severity of hydrocephalus and its impact on brain function.

The strength of the **Hydrocephalus study** is to show how accurately neurophysiological methods define brain disfunction before and after the neurosurgical intervention to decrease elevated intracranial pressures. Flash visual evoked potentials and amplitude integrated EEG changes paralelly with intracranial pressure elevation and normalisation. Reconvalescence of wave latencies of fVEP and aEEG patterns are observed and in most cases normalisation can be accurately followed. The degree of ventricular dilatation on cranial sonography has not shown significant correlation with the delay of fVEP latencies and aEEG patterns. This underlines the fact, that cranial ultrasound is just a morphologic/imaging method of the central nervous system and does not provide sufficient information about the extent of constraint on brain function.

Neuroimaging proved to be part of the everyday practice of NICUs. The increasing number of MRI studies provide information regarding the pathophysiology of different perinatal problems such as birth asphyxia or white matter injuries and play a major role in understanding normal brain development. Our **MR-compatible Incubator Study** has shown, that MR imaging with the use of the INC is a safe and clinically informative examination even in the most unstable, critically ill premature infant. A separate analyses has shown, that patients under 2000 gram profited mostly from this imaging device. The MR Imaging has added reliable and important diagnostic information in more than 50% of all cases and management changes were initiated also in more than half of the study population. The safety of the imaging process increased, as there was no need terminate the imaging process due to instability or increase sedatives using the INC.

We were able to reproduce international results in our **Asphyxia study**, that early aEEG examination has a better correlation with neurodevelopmental outcome in patients with hypoxic-ischeamic encephalopathy, than late examination after the 1st week of life. We could also demonstrate that late MR Imaging was to early examination, regarding outcome prognosis. Both methods showed high sensitivity and specificity for adverse outcome. The combination of the two methods provides neonatologists with a reliable tool in clinical decision making and parent councelling, although the process of withdrawal of care in severe cases of birth asphyxia still remains a complex question that has to be answered individually for every patient. Additional sequences to routine MR protocols in neonatal encephalopathy, such as proton spectroscopy should be added, as they improve the sensitivity and specificity of early MR Imaging.

In the **Mismatch Negativity Study** we were able to demonstrate that speech maturation can be assessed with event related potentials and the MMN component in infants in the first year of life. There was only an age dependent maturation in the phoneme deviant condition (banán-panán), which demostrates that there is no difference in the detection voiceless and voice (zöngés-zöngétlen) phonemes. In contrast we found differences in speech perception between term and premature infants at 6 and 10 months of age regarding stress word detection. Premature infants had smaller MMN responses detecting atypical stress at the second syllable at both age groups, which suggests a developmental lag in language processing in premature infants. Furthermore, we can conclude that infants start to use stress information in differentiating words already at six months of age.

As the most common cause of hydrocephalus is caused by IVH in premature infants, it is extremely important to understand the extent of neurodevelopmental deficit in all grades of this pathology. The **Intraventricular Haemorrhage study** points out, that even in low grade IVH there is a significant risk for abnormal neurodevelopmental outcome, especially in extremely premature infants and the severity of IVH correlates with adverse neurodevelopmental outcome. We could also prove that gestational age is an independent variable in patients with IVH for neurodevelopmental outcome, as extreme premature infants under 28 weeks of gestation showed a worse outcome in all IVH groups when compared to other preterm populations.

Minimal intraventricular bleedings leed to a maturational deficit due to the proinflamatory response and the sensitivity of olidendrocytes and subplate neurons. Cranial ultrasound has its

limitations defining the extent and severity of IVH, this is why it is so important that MR imaging techniques and the MR compatible incubator is avaible for this extremely sensitive and unstable population. Brain development can be followed by aEEG maturation, where sleep-wake cycling and background pattern are good indicators of normal neurodevelopmental outcome and intact brain function. Specific areas such as linguistic development can be studied with event related potentials, such as miss match negativity, where prosodic information and speech processing are essential components in normal speech maturation. The extent of developmental deficit in premature infants can be studied with standardised psychological tests, but evoked potentials and event related potentials provide reliable information in all pediatric age groups.

Neuroimaging proved to be part of the everyday practice of NICUs. The increasing number of MRI studies provide information regarding the pathophysiology of different perinatal problems such as birth asphyxia or white matter injuries and play a major role in understanding normal brain development. The combination of imaging and neurophysiological methods is not only essential in everyday clinical decision making, such as neurosurgical intervention with PHVD, but also provide reliable prognostic information for neonatologists and parents as it is described in the asphyxie study.

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6. Bibliography of the candidate's publications

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