

## NEONATAL NEUROLOGY

### FP100

#### ROTAVIRUS INFECTION CAN CAUSE SEIZURES ACCOMPANIED BY DIFFUSE CEREBRAL WHITE MATTER INJURY IN FULL-TERM NEWBORNS

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**Aim:** Some viruses can cause neonatal seizures accompanied by diffuse cerebral white matter injury.<sup>1-3</sup> The purpose of this study is to identify the viral causes of seizures and diffuse cerebral white matter lesions in full-term newborns, and describe the clinical characteristics.

**Methods:** Twenty-two full-term newborns with seizures accompanied by bilateral diffuse cerebral white matter lesions on diffusion-weighted imaging (DWI) of brain MRI were admitted to our hospital between 2011 and 2012. We retrospectively review the records of 15 of these patients who tested positive for parechovirus, enterovirus, or rotavirus using real-time reverse transcription polymerase chain reaction. Specimens for examination were the stool in 15 patients, serum in 12 patients, and cerebrospinal fluid (CSF) in 11 patients.

**Results:** Rotavirus was detected in all 15 stool specimens, but not in the serum and CSF. Parechovirus and enterovirus were not identified in any specimens. The rotavirus genotype identified in the stool was G4P6 in each of the 15 patients, who were all healthy prior to seizure onset. Their 1- and 5-min Apgar scores ranged between 7 and 9. The patients' age at seizure onset was 4.4±0.7 days (range, 3–6 days). In the three-month follow-up brain MRIs, 8 of 13 patients showed no specific abnormalities. The other 5 patients, however, demonstrated cystic changes or atrophic changes in the cerebral white matter.

**Conclusions:** Rotavirus infection should be considered in newborns with seizures accompanied by diffuse cerebral white matter lesions on DWI, particularly around 5 days of life.

### FP101

#### BURDEN OF NEUROLOGIC DISEASE IN A PERUVIAN NEONATAL INTENSIVE CARE UNIT

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**Aim:** To determine the frequency of neurologic disease in hospitalized newborns

**Methods:** Observational, descriptive, retrospective study. Pediatric neurology evaluations were reviewed for all babies admitted between June 2008 and September 2012.

**Results:** 1626 neonates (11.1% of total hospitalized population) required neurologic evaluation. 803 of these were VLBW babies. 877 neurologic problems diagnosed before discharge. 178 cases of intraventricular hemorrhage (20.29% of total neurologic cases) were detected by routine ultrasonography, 29.8% were bilateral. 39.8% IVH cases were severe (III grade IVH or periventricular infarction). IVH was present in 19.7% of VLBW babies and 33.7% of ELBW babies. Periventricular leucomalacia was present in 28/803 VLBW babies (3.48%). Most common problem in term babies was neonatal encephalopathy (190 patients, 21.6% of neurologic disease), 24.7% cases (47 newborns) were definite or probable cases of hypoxic ischemic encephalopathy. CNS malformations were frequent (123 patients, 14% of neurologic diseases), neural tube defects were the most common (28/123, 22.7%), as were corpus callosum anomalies (20 cases), holoprosencephaly (15 cases) and Moebius syndrome (16 cases). 49 patients were diagnosed with perinatal trauma, most frequent lesion was brachial plexus injury (30 patients). 41 patients had CNS infections (4.6% of neurologic disease), 31 of them presented acute meningitis. Stroke was diagnosed in 29 patients, 13 of which presented as hydranencephaly. 5 patients were admitted for cranial injuries. 25 patients had neonatal seizures for causes not listed above.

**Conclusions:** Neurologic disease is frequent in hospitalized newborns. Attention must focused on severe, preventable injury and follow up.

### FP102

#### EXPERIENCE WITH INDUCED HYPOTHERMIA AT A TERTIARY HOSPITAL IN A RESOURCE LIMITED SETTING: PRELIMINARY RESULTS

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**Background:** Induced hypothermia has recently been introduced as one of the interventions used in management of neonates with intrapartum asphyxia at the institution.

**Aim:** To describe infant characteristics (demographics and cooling criteria), during induced hypothermia and outcomes to hospital discharge.

**Method:** Retrospective record review of infants who had asphyxia and were managed with whole body cooling. Patients were cooled according to the modified TOBY criteria. On discharge all patients had a neurological examination.

**Results:** From October 2011 to April 2013, 52 patients had been cooled. The median birth weight and gestational age was 3149 grams and 39 weeks respectively. The median 5 minute Apgar score was 5 and 21% required resuscitation for >10 minutes. The mean pH was 7.021 and base deficit was 20.4 mmols/ L. Moderate and severe encephalopathy were noted in 79% and 19% patients before cooling respectively. Only 53% of patients had an aEEG performed before induced hypothermia (shortage of machines). None of the patients required mechanical ventilation except one who was put on nasal continuous positive airway pressure during cooling. Five patients died (9%) died before discharge. Among the survivors 18% were discharged with mild neurological abnormalities on examination and 28% had moderately abnormal neurological findings, 16 patients were not examined by the neurologist on discharge.

**Conclusion:** Induced hypothermia is feasible within a resource poor setting. Resources remain a major factor in managing these patients according to the protocol. Short term results are promising but follow up of the patients is vital.

### FP103

#### FETAL VENTRICULOMEGALY INVESTIGATIONS AND OUTCOMES - 5 YEAR EXPERIENCE

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**Background:** Ventriculomegaly is defined as a dilatation of 10 mm or more of the foetal lateral cerebral ventricles on ultrasound at 20 weeks gestation. It can be isolated benign finding or associated with chromosomal abnormalities, congenital infections, malformations or cerebral haemorrhage. It is graded as mild (10 -12 mm), moderate (13-15 mm) and severe (> 15 mm) based on atrium width measurement.

**Aim:** To assess the etiology, investigations and neurological outcome of fetal ventriculomegaly cases in our centre from 2009 to 2013

**Methods:** 35 women with ventriculomegaly on 20 week anomaly scan were identified from fetal medicine database. Electronic and clinical records of mother & baby were reviewed to collect data on antenatal investigations, delivery details, discharge outcome and long term neurological outcome. Three cases underwent termination of pregnancy & 32 babies were born. All women had serial USS to determine if the ventriculomegaly had returned to normal, was stable or was progressive.

**Results:** 32 fetuses had ventriculomegaly (21 mild, 9 moderate & 2 severe). Fetal chromosomes were normal in 9 cases. TORCH screen was normal in 30 women. 13 women had fetal MRI scans.

All 16 babies in whom mild ventriculomegaly returned to normal or was stable on serial scans were neurologically normal at birth and did not have developmental abnormality. All 5 babies with mild but progressive ventriculomegaly were neurologically normal at birth but one of these baby required insertion of VP shunt. 4 out of 11 Babies with moderate or severe ventriculomegaly had delayed development.

**Conclusion:** Fetuses with non-progressive isolated ventriculomegaly have good prognosis but those with moderate or severe ventriculomegaly are at risk of neurodisabilities.

**FP104**

**EMERGENCE AND EVOLUTION OF NEUROLOGICAL DEFICITS FOLLOWING ACUTE NEONATAL ARTERIAL ISCHEMIC STROKE**

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**Introduction:** Neonatal Arterial Ischemic Stroke (NAIS) causes significant long-term morbidity. Information on evolution of neurological deficits after acute NAIS is lacking.

**Aim:** To study the emergence and evolution of neurodeficits over time following acute NAIS.

**Methods:** Retrospective analysis of neonates with acute AIS from 1999–2009 was conducted. Outcome was assessed by the validated Pediatric Stroke Outcome Measure (PSOM), administered prospectively during follow-up. PSOM scores between 3–6months, 6–12months, 1–3years, 3–5years and after 5-years were analyzed. Only patients with minimum 3 assessments, each during different time-interval, were analyzed. Within individual PSOM sphere, *any* neurodeficit was considered abnormal.

**Results:** Fifty-two (27 males) of 87 acute NAIS were included. The table depicts our salient findings on interim analysis.

**Neurological Deficits**

Sensorimotor and language deficits emerge over early infancy and between 1–3years respectively; these remain persistent in many thereafter. Cognitive/behavior problems surface in pre-schoolers and worsen during school age. Predictor testing is under way.

**Conclusions:** A distinct pattern of emergence and evolution of neurodeficits is evident following NAIS. This information can be helpful for timing of rehabilitation interventions.

**FP105**

**A RETROSPECTIVE ANALYSIS OF ETIOLOGICAL FACTORS ASSOCIATED WITH NEONATAL SEIZURE, TYPE OF ANTI-EPILEPTIC MEDICATIONS USED AND THE DURATION OF TREATMENT.**

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**Objectives:** To identify the etiological risk factors associated with neonatal seizures from the history, physical examination, lab findings, imaging studies and EEG in NICU setting, to identify the type of anti-epileptic medications used for treatment in NICU setting, to find out the duration of anti-epileptic medications during hospital stay and to ascertain any association between the etiological factors, type of anti-epileptic medications and the duration of treatment

**Materials/Methods:** Charts were retrospectively reviewed for those infants with an ICD -9 code of (ICD-9 CODE -779.0) from January 1, 2005 to December 31, 2010 at Women and Children hospital's NICU division.

**Results:** Eighty-one neonates, less than 1 year of age, were diagnosed with neonatal seizures during the 5 year period. Three patients were excluded due to duplication. Our study focused on 78 infants, both term and preterm, with a history of clinical seizures. The seizure types that were identified from the charts reviewed included generalized (51.61%), clonic (25.81%), focal (9.68%), tonic (9.68%), myoclonic (3.23%) among documented types and undocumented (60.26%). Factors taken into consideration in prenatal history included instances of maternal

tobacco use (19.74%), maternal drug use (21.05%) and maternal alcohol use (0.0%). Imaging studies performed included abnormal EEG results (61.76%), abnormal CT head (50.88%), abnormal MRI head (73.33%) and abnormal cranial ultrasound (43.59%). Among the patients who were treated with Phenobarbital, 6.41% of them were given only one dose and 7.69% of them were treated for duration of less than one week. Also, 50% of the patients were discharged on Phenobarbital and the mean duration of treatment while in hospital was found to be 3.15 weeks with standard deviation of 2.995. Out of the total number of patients, 92.31% of patients were discharged from the hospital, 6.41% died and 1.28% got transferred to higher centres of care.

**Conclusion:** The common etiological risk factors that we identified in our NICU division based on the chart review include prenatal history, type of seizures, lab findings, EEG, imaging studies. Based on the chart reviews, the most commonly associated risk factors that were identified from pre-natal history are maternal drug abuse and maternal smoking. In addition, EEG and imaging studies play a crucial role in the diagnosis of neonatal seizures. Phenobarbital is the most frequently used drug in the NICU setting with a mean duration of 3.15 weeks during hospital stay. Finally, infants with abnormal imaging results were more likely to have started Phenobarbital while in the hospital and also be discharged on Phenobarbital.

**FP106**

**LEVETIRACETAM AS A TREATMENT OF NEONATAL SEIZURES**

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**Introduction:** Seizures in neonatal period are often difficult to control and are associated with a high rate of poor long-term neurological outcomes. The efficacy of Phenobarbital and phenytoin, the two standard antiepileptic drugs used to treat neonatal seizures, is often poor. Furthermore, in experimental studies, phenobarbital has a deleterious effect on developing brain. Levetiracetam is a wide spectrum anticonvulsant, that has a potential to represent safe and effective therapeutic option to treat neonatal seizures.

**Methods:** We retrospectively reviewed the charts of neonates, who were admitted to our neonatal intensive care unit, failed at least one anti-epileptic drug and received levetiracetam for the treatment of seizures.

**Results:** From June 2010 to August 2013, 11 such neonates with electrographically confirmed seizures were treated with levetiracetam. We reviewed their medical records in an attempt to estimate treatment efficacy of levetiracetam. Levetiracetam was associated with seizure reduction in 36% (4 of 11) of neonates. No adverse effects were noted.

**Conclusion/Discussion:** A major limitation of our study is that the only neonates with significant seizure burden, who failed other antiepileptic agents, were included. Single blind randomized controlled trial comparing conventional antiepileptic drugs and levetiracetam is warranted.

**FP107**

**A NEONATAL SEIZURE BLINDED TREATMENT TRIAL**

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**\*FP104**

Time interval following Stroke	Left-sensorimotor	Right-sensorimotor	Language comprehension	Language expression	Cognitive/Behaviour problems
3-6months (N=20)	45%	35%	5%	0	0
6-12months (N=21)	48%	24%	10%	5%	0
1-3years (N=72)*	44%	33%	38%	18%	15%
3-5years (N=40)	40%	20%	38%	8%	18%
>5years (N=43)	35%	23%	30%	23%	42%

N= # neonates assessed, \* some neonates had ≥ 2 assessments

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**Introduction:** Neonatal seizures are a common problem within the field of child neurology and cause significant morbidity. Phenobarbital and phenytoin are effective in less than 50% of subjects, both have significant acute and chronic side effects. In neonatal animals these agents cause accelerated neuronal apoptosis. Better treatments are needed.

**Methods:** We report an on going FDA funded blinded comparison of efficacy of intravenous phenobarbital vs. levetiracetam in EEG confirmed neonatal seizures in term infants with internet video EEG monitoring and evaluation of a new seizure detection algorithm. We will recruit >200 at risk subjects to identify and treat 100 babies with seizures. There are 6 study sites, 3 in San Diego, Loma Linda University Medical Center, Oakland Children's Hospital and Auckland New Zealand.

**Results:** This study is blinded and on going however we can report that 7 of 26 infants at risk of seizures had electrographically confirmed seizures. 16 of 26 enrolled babies suffered perinatal depression and underwent whole body hypothermia; 3 had seizures acutely and 1 on rewarming. We will report our experience so far on the utility of remote video EEG monitoring. The study flow is supplementary.

**Discussion:** A blinded term neonatal seizure study comparing efficacy of phenobarbital and levetiracetam is underway at 6 neonatal units with internet continuous EEG monitoring (NEOLEV2). We report preliminary information although efficacy data on seizure control will not be available until study completion.

#### FP108

##### TOWARD PRENATAL DIAGNOSIS OF PRADERWILLI SYNDROME

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**Objectives:** To characterize the fetal phenotype of a cohort of individuals with confirmed diagnoses of PWS.

**Methods:** We interviewed mothers of 106 individuals with PWS to obtain information about the pregnancy of their affected child. For 47 pregnancies of children younger than 10 years, we also reviewed the obstetric ultrasound and detailed obstetric history from medical records. We compared the PWS pregnancies with those of the sibling closest in age.

**Results:** Decreased fetal movement, small for gestational age (SGA), asymmetrical intra-uterine growth with a significant discrepancy between abdomen and head circumferences, and polyhydramnios were found in 88%, 65%, 43% and 34%, respectively. In 101/106 (95%) pregnancies, at least one abnormality was documented prenatally. A combination of 2, 3 and 4 abnormalities were found in 27%, 29% and 24% of pregnancies, respectively. The combination of asymmetrical intra- uterine growth and polyhydramnios was found in 34% of PWS pregnancies and in 0.26% of a control group (p<0.0001).

**Conclusion:** Prenatal genetic screening for PWS by methylation testing is indicated when any combination of SGA or asymmetric intra-uterine growth, polyhydramnios, and diminished fetal movements is present, particularly when asymmetrical intra- uterine growth and polyhydramnios coexist.

#### FP109

##### NEUROBEHAVIORAL STATUS OF NEWBORNS WITH CONGENITAL HEART DEFECTS IN RURAL HOSPITAL OF CENTRAL INDIA

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**Introduction:** Neurodevelopmental disability in neonate with congenital heart defects has largely been attributed to complications of open-heart surgery, without consideration of preoperative neurologic status. So the controversy exists regarding the integrity of the nervous system in the newborn with a congenital heart defect (CHD) who must undergo corrective or palliative open heart surgery.

**Aim:** To determine the neurobehavioral status of newborns with CHD.

**Material and Methods:** In this prospective study, a new neonatal neurobehavioral examination (NNE) was conducted independently in a consecutive series of 40 neonates with congenital heart defects. The

NNE consists of 27 items divided into three sections: 1) tone and motor patterns, 2) primitive reflexes, and 3) behavioral responses. Neurologic examinations were carried out as well. Cardiorespiratory status was determined at the time of assessment.

**Results:** Neurobehavioral abnormalities were documented in 62% of newborns and included hypotonia, hypertonia, jitteriness, motor asymmetry, and absent suck. Poor state regulation (n=16) and decreased feeding efficiency (13) were commonly observed as well. In addition, 10% neonates had seizures and 24% were microcephalic. The overall likelihood of neurobehavioral abnormalities was not enhanced by indicators of cardiorespiratory compromise. Interestingly, newborns with acyanotic congenital heart defects were more likely to demonstrate neurologic compromise than were those with cyanotic defects.

**Conclusion:** Neuromotor abnormalities are common in neonates with congenital heart defects. These developmental deficits are under-recognized clinically, and may suggest the need for early systematic developmental screening in neonates with CHD.

#### FP110

##### ALTERED EXPRESSION OF NON-NEURONAL CELLS IN NORMAL AND DOWN SYNDROME DEVELOPING BRAIN

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**Introduction:** Down syndrome (DS) is the most common causes of mental retardation and early Alzheimer' disease (AD). Brain pathology of DS is characterized by reduced number of neurons and delayed myelination. Though on-neuronal cells in the brain are important for the development, survival and function of neurons, there are a few comparative studies of normal development and DS fetal brains,

**Methods:** We observed and compared with immunoreactivity for CD68 (marker for macrophage), HLA-DR (marker for microglia), Olig2 (marker for oligodendrocyte) and GFAP (marker for astroglia) in the germinal matrix (GM), temporal lobe white matter (TeWM) and hippocampus from 14 weeks of gestations to newborn in 28 DS patients and 30 age-matched controls.

**Results:** The rate of increase of CD68 positive cells in the GM, CA1 hippocampal sub region and subiculum was significantly higher in DS. Interestingly, the density of Olig2 positive cells in the GM was lower in DS brains at early stages, then showed a transient increase contrasting controls. Olig2 expression increased more in the TeWM in DS.GFAP-immunoreactivity in DS was significantly lower in the middle pregnancy period in the TeWM and did not increase between early and middle periods in the GM compared to controls, likely reflecting a defect in astrocyte production.

**Conclusion/Discussion:** The altered expression of non-neuronal cell markers during normal development and DS may cause the defective neurogenesis, leading to reduced number of neurons and delayed myelination in the developing DS brain. This has implications for the understanding of the mental retardation in DS patients.

#### FP111

##### TRANSCRIPTION REGULATION OF THYROXIN PROTECTIVE EFFECT ON WHITE MATTER INJURY

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Premature babies with periventricular white matter injury (PWMI) exhibit spastic motor deficits and cognitive or behavior deficits without effective treatment. Our in vivo study highlighted the therapeutic role of thyroxin (T4) on PWMI. We demonstrated T4 post-treatment decreased pre-OLs proliferation and may drive them toward maturation. To understand the maturational status, we analysed the oligodendrocyte maturation –dependent transcription factors after T4 treatment. Materials and Methods: A PWMI animal model was established by unilateral carotid artery ligation followed by 6.5% 1 hour of hypoxia (HI) in P7 rat pups. The pups were subjected to normal saline (NS), T4200µg/Kg (T4-0.2), and T41 mg/Kg (T4-1) after HI. At 96 hrs after HI, the cerebral white matter was dissected out for RNA extraction. Total RNA were isolated from the white matter for quantitative real-time PCR. The following transcription factors were analysed: PDGFα SOX8 SOX10

Nkx2.2. Each sample was tested in triplicate and data analysis used the  $2^{-\Delta\Delta CT}$  method. Results: SOX10 mRNA was up-regulated from P9 during immature brain development. PDGF $\alpha$  and SOX10 mRNA expression increased significantly at 96 hrs after HI. T4 treatment after HI increased NKx2.2 mRNA expression compared with NS- and T4-0.2-treated rats.

Conclusion: Sox10 gene plays an important role during brain development in immature rat pups. HI increases PDGF $\alpha$  mRNA expression may indicate replenishment of pre-OLs in the white matter. T4 post-treatment after HI would up-regulate SOX10 and Nkx2.2 gene expression. The SOX10 and NKx2.2 genes are turned on after T4 post-treatment in the rats with HI insult.