Seizures in Neonates: Challenges in Diagnosis and Treatment

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Disclosures

- CLN2 Advisory Board
- UCB Advisory Board

- ANZCNS Executive Board
- ILAE task force for development of Guidelines for Neonatal Seizures
- ICNA Executive Board

Szs in Neonates

▶ Challenging to diagnose and treat.

   NS are common, estimates of incidence variable

▶ Controversies in definition of a Neonatal Seizure

   Types of events included: Electroclinical, Electrographic, Clinical

▶ Role of the EEG in Neonatal Seizures

▶ Debate and uncertainties prevail regarding treatment

   What to treat, With what to treat and how long to treat for

   Is the remedy worse than the disease

▶ NS are associated with adverse neurodevelopmental outcomes

NS – Clinical and EEG Features

▶ May be difficult to recognise and diagnose accurately.

▶ Non epileptiform events may mimic NS
    some benign paroxysmal phenomenon
    some attributed to brain stem release phenomenon
    some? subcortical seizures

▶ Clinical Seizures, with EEG correlates, at times subtle

▶ EEG szs without clinical correlates: 20 - 90%

▶ Seizure discharges may be variable in field, morphology, amplitude and clinical correlates
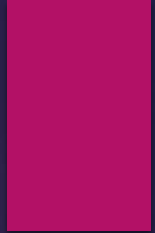
Role of V-EEG in Diagnosis of Seizures in Neonates

Ns or not? : Videos
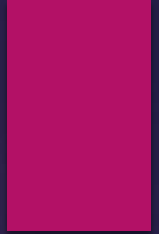
Szs in neonates

videos

Inter observer agreement in neonatal seizure identification. Malone, et al. Epilepsia 2009

- Clinical histories and video recordings of paroxysmal movements in (twenty) term and preterm infants were presented to 137 health care professionals (91drs + 46 nurses) from eight neonatal intensive care units.

- The average no of correctly identified events was 10/20.

- Inter-observer agreement was poor

- Without neurologic monitoring babies with szs may remain undetected and others treated with AEDs for non seizures

Defining the gap between electrographic sz burden, clinical expression and staff recognition of neonatal seizures.

526 EEG szs on V EEG monitoring in 9 babies

▶ Over diagnosis occurs frequently

▶ 177 clinically suspected sz episodes
   only 27% had EEG sz

▶ 1/3 of the EEG szs have clinical signs
  ▶ 2/3 are unrecognized or misinterpreted by experienced clinical staff
  ▶ 9 % of EEG szs with clinical correlates were identified.

  ▶ Murray et al. *Arch Dis Child Fetal Neonatal Ed*. 2008

Volpe's Classification of NS

- ## A seizure is defined clinically as a paroxysmal alteration in neurological function
  - Includes clinical phenomenon that are associated temporally with EEG sz activity and therefore epileptic
  - But also includes paroxysmal clinical events that are not consistently associated with EEG sz activity on surface EEG

Clonic

Tonic

Myoclonic

Subtle

Classification of clinical semiology in epileptic seizures in neonates.

▶ We used an extended classification scheme
Clonic:
Tonic:
Myoclonic:
Ocular-orbital:
Orolingual:
Autonomic:
Hypomotor:
Other:

Nagarajan et al, Eur J Paediatr Neurol. 2012.

Classification of clinical semiology in epileptic seizures in neonates.

▶ The clinical features of 61 NS with EEG correlates
   was analysed.
   43 babies had 161 EEG Szs : ECSz:12, ECSz & ESz:12, ESz :19

▶ Seizures were classified
   1. Clinical feature **at onset**
   2. **All** clinical features seen during the seizure

▶ Most ECSz (89%) had multiple clinical features.

Nagarajan et al, Eur J Paediatr Neurol. 2012.

Classification	Subcategory
Clonic	
	Focal: L and R
	Multifocal
	Generalised
Tonic	
	Focal: L and R
	Multifocal
	Generalised
Myoclonic	
	Focal: L and R
	Multifocal
	Generalised
Ocular-Orbital	
	Eye Opening
	Eye Flickering
	Eye Deviation
	Nystagmus
	Other
Orolingual	
	Mouthing / Chewing
	Tongue Movements
	Crying
	Yawning
	Noises or Vocalisation
	Dry Retching
	Other
Autonomic	
	Colour Change
	Sigh / Gasp / Breathing Change
	Oxygen Desaturation
	Apnoea
	Heart Rate (Change by >10)
	BP Increase
Hypomotor	
	Motionless, marked reduction in activity
	Staring
Other	
	Jitteriness
	Restless
	Other

Classification of clinical semiology in epileptic seizures in neonates. Nagarajan et al, Eur J Paediatr Neurol. 201

- Orolingual features were the most frequent clinical phenomenon at seizure onset (30%)

- Orolingual Seizures started frequently from the Right hemisphere (78%)

- video

Classification of clinical semiology in epileptic seizures in neonates.

Ocular manifestations occurred in 12% at onset.

Ocular features were the most frequent clinical phenomenon during the EEG discharge (70%)

Ocular and autonomic seizures had EEG sz onset from either hemisphere

Nagarajan et al,

Eur J Paediatr Neurol. 2011

▶ video

Clinico-electrical correlations of neonatal seizures.

- Focal clonic szs were associated with EEG sz onset from the contralateral side.

- EEG discharge involved both hemispheres in 54% of all ECSZ, in szs with clonic features this was 93%.

- Do babies with clonic seizures have a better prognosis?

- video

▶ Most ECSz had multiple clinical manifestations.

▶ video

▶ video

Nagarajan et *al*, Eur J Paediatr Neurol. 2012

EEG essential for diagnosis of neonatal seizures

▶ Ictal EEGs in NS may be unique and complex

▶ Electroclinical dissociation occurs commonly
  ▶ with some having only ECSZs, some ESZs only & some both.
  ▶ In our study of 43 babies with 163 seizures,
  ▶ there were 100 ESZs and 63 ECSZs,
  ▶ with ECD in ~ 70% babies

▶ We analysed the ictal EEG features of 160 neonatal seizures

▶ Nagarajan et al, J Child Neurol. 2010
▶ Nagarajan et al., Pediatric Neurol 2011

Ictal EEG in Neonates. Nagarajan et al. Ped Neurol. 2011
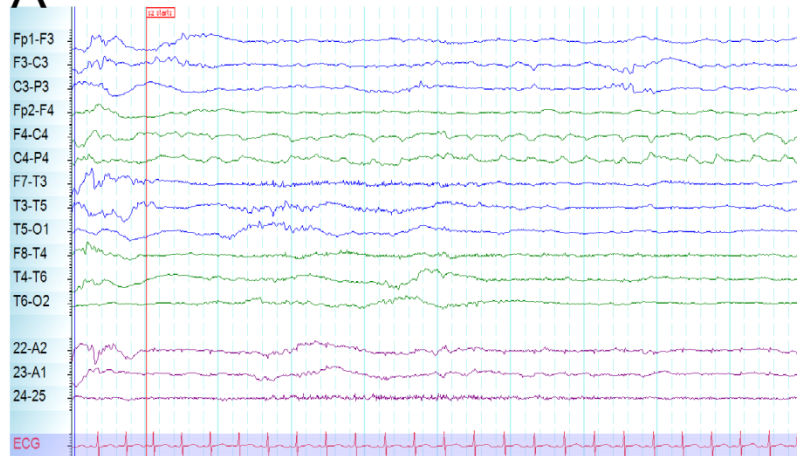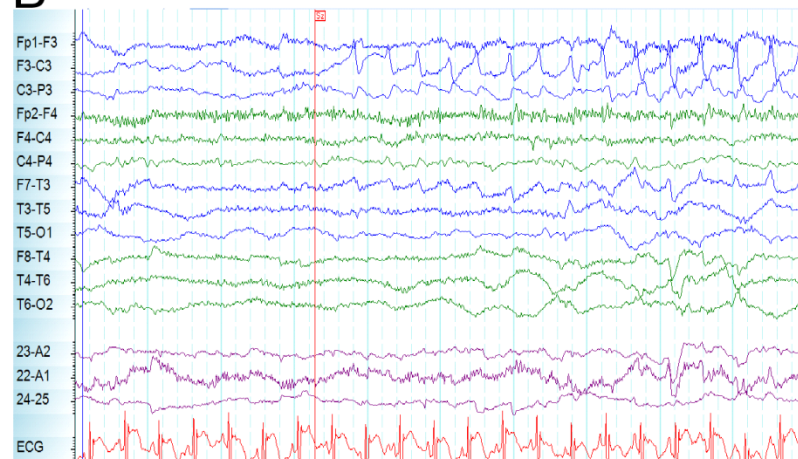
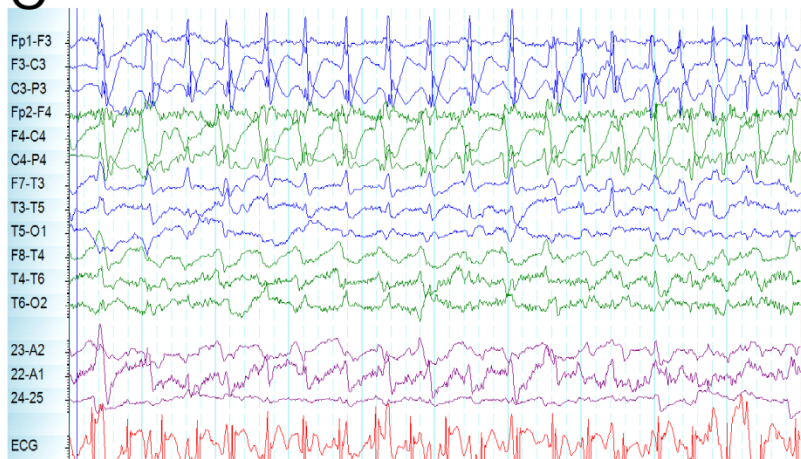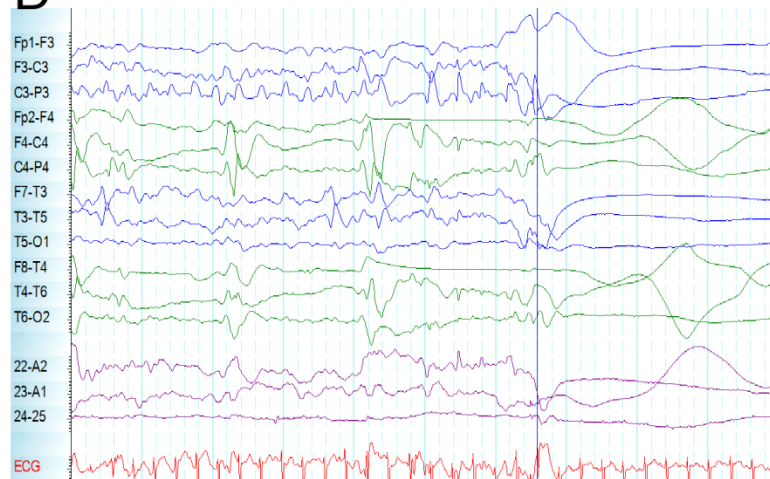# Seizure Onset

	ECSz				ESz				ECSz+ESz	
Ictal EEG	Left	Right	Vertex	Percent	Left	Right	Vertex	Percent	Total	Total (%)
Frontal	9	7		26.2	20	9		29.3	45	**28.1**
Paracentral	8	10		29.5	9	16		25.3	43	**26.9**
Parietal	0	1		1.6	0	0		0.0	1	0.6
Temporal	16	10		**42.6**	21	19		**40.4**	66	**41.3**
Occipital	0	0		0.0	3	0		3.0	3	1.9
Vertex			0	0.0	0	0	2	2.0	2	1.3
Total	33	28	0		53	44	2		160	

Seizure spread

Seizure spread		
Ictal EEG	ECSz (%)	ESz (%)
Focal	0.0	23.2
Regional	3.3	17.2
Unilateral	42.6	35.4
Contralateral	6.6	9.1
Flip-flop	4.9	10.1
Bilateral	42.6	5.1
One side	45.9	75.8
Both sides	54.1	24.2
No of seizures	61	99

Amplitude and Frequency of EEG Discharge during NS

Ictal EEG of electroclinical and electrographic szs					
	Frequency at onset	**Maximum frequency**	**Minimum amplitude**	**Maximum amplitude**	**Duration**
ECSz	3.2	5.4	29.1	124.3	252.9
ESz	3.3	3.9	20.5	63.7	213.9
p value	0.94	**0.01**	**0.05**	**0.00002**	0.68

NS – Sleep Wake State

Sleep/Wake State at Seizure Onset			
State	**ECSz (%)**	**ESz (%)**	**All Szs%**
Sleep	34.4	45.5	41.3
Wake	41.0	24.2	30.6
Undetermined	24.6	30.3	28.1
No of Szs	61	99	160

Ictal EEG in Neonatal Seizures.

▶ Neonatal seizures almost always have a focal onset

In our study of 160 NS,

>40% started from the temporal region, the next most frequent foci of onset were the frontal and paracentral areas.

  ▶ Most other studies have also shown the temporal and paracentral areas to be frequent foci of Sz onset, with occipital foci being infrequent.

  ▶ The data regarding frontal onset is variable.

▶ Neonatal seizures occur more frequently from sleep than the wake state, when state can be established.

▶ Electrographic only seizures are more contained than electroclinical.

▶ The highest frequency and minimum and maximum amplitudes of the EEG szs were significantly higher during electroclinical seizures.

Does V-EEG help prognosticate neurodevelopmental outcome in babies with NS

- EEG background is a good predictor of outcome

  Continuity, amplitude, frequency, synchrony, symmetry, sleep, sharps, interburst intervals, maturation patterns

  - Holmes, 1982; Rowe, 1985; Takeuchi, 1989; Sinclair, 1999; Khan, 2008;

    Lombroso, 1993; Laroia, 1998; Nagarajan, 2010….
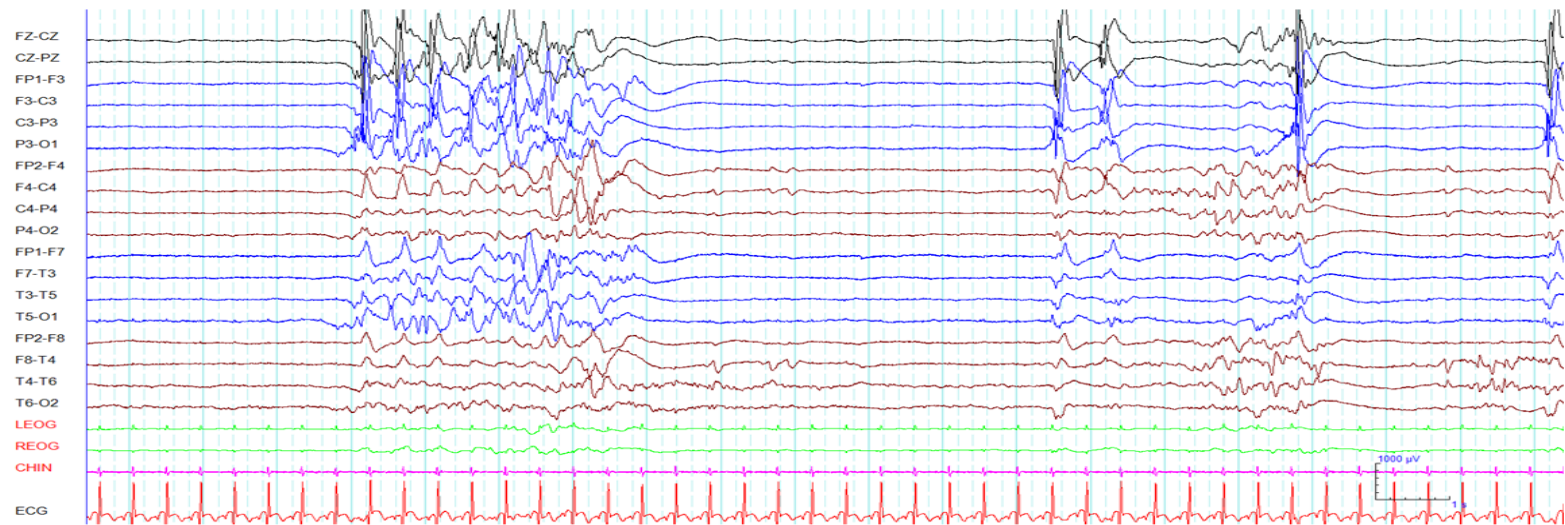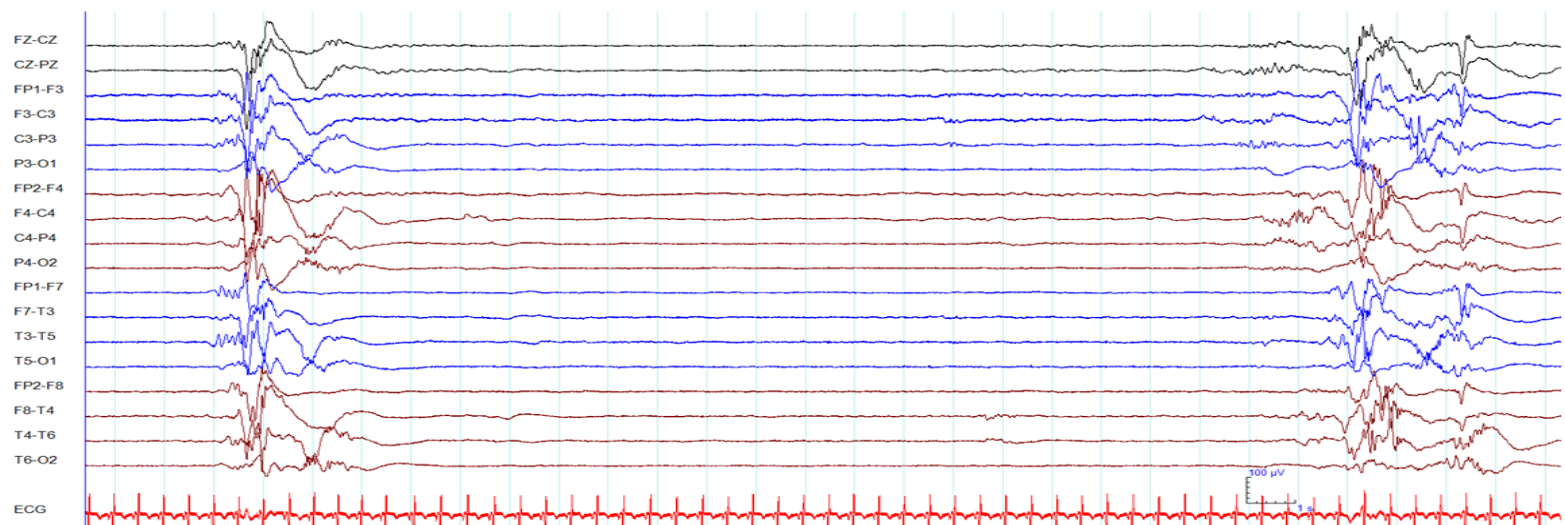
- Are Features of the Ictal EEG useful in prognostication

Figure 1. A, B: Electrographic seizure in a term neonate. The EEG at A shows onset of the seizure from the right parieto-central region, and B shows the discharge about 5 minutes later, towards the end of the seizure.
C, D: Background EEG abnormality in 2 term neonates. C shows asynchrony in quiet sleep, which was persistent. D shows a low amplitude background.
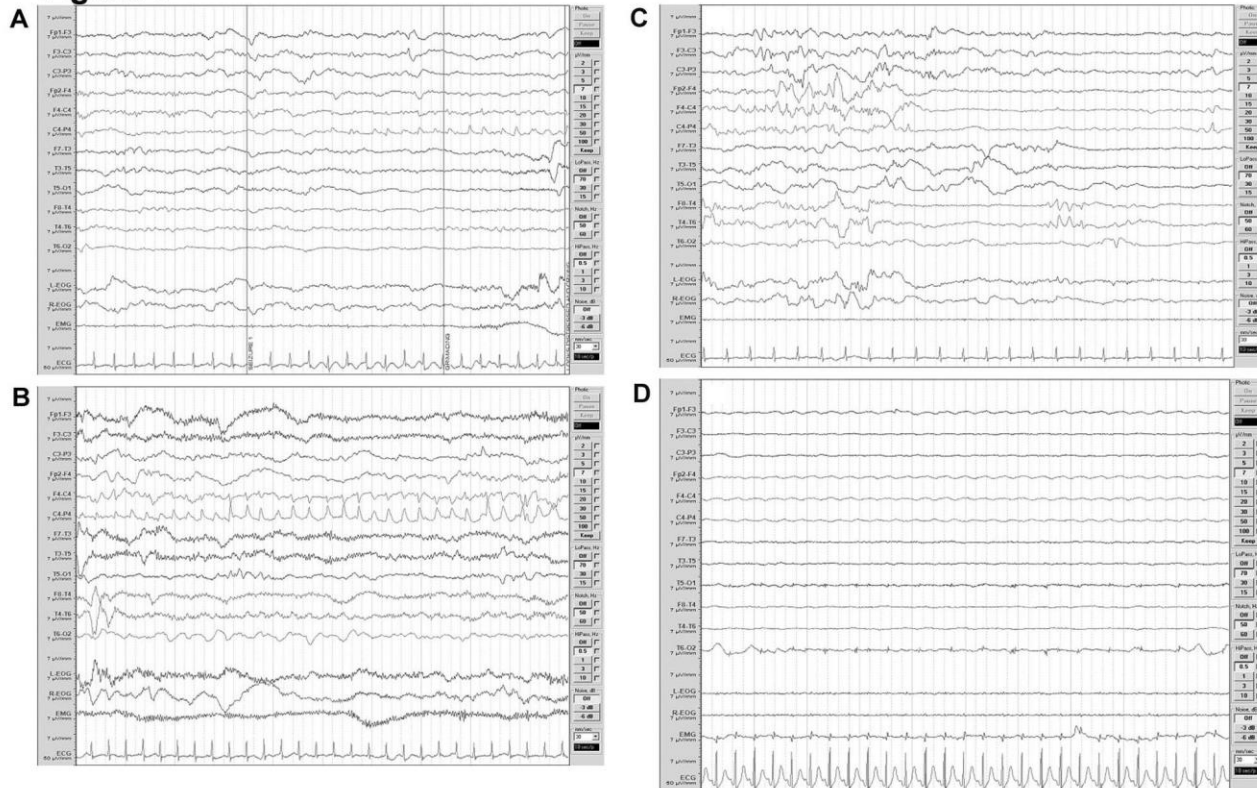
Neurodevelopmental outcomes in babies with neonatal seizures : A Numerical score of Background EEG score to help Prognosticate. Nagarajan et al, JCN 2010

- EEG background good predictor of outcome
    - Severely abnormal background – poor prognosis,
    - Normal background – good prognosis
    - Moderate abn – difficult to predict

- Numerical Score proposed to improve reproducibility, categorisation and prognostication

- The numerical score was a good predictor of outcome :

    increasing percentage scores,

    reflecting greater background abnormality,

    was associated with increasing incidence of mortality, neurodevelopmental impairment, cerebral palsy, epilepsy, hearing and vision impairment.

Background EEG Score

1. Table 1. Numerical scoring of background EEG in neonates >35 weeks post-conceptional age

Abnormalities of Amplitude	Abnormalities of Continuity	Duration inter-burst intervals during TA⁺	Frequency	Symmetry	Synchrony	Abnormalities of Sleep	Sharps	Maturation
1. WNL	1. WNL	1. <10s	1. WNL	1. WNL	1. WNL	1. WNL	1. WNL	1.WNL
2. Mildly ABN	2. Mild Excess discontinuity (infrequent)"	2. 10-20s	2. Excess slow	2. Inter-hemispheric Voltage Asymmetry >25%	2. Inter-hemispheric asynchrony <25%	2. Excess Transient State#	2. Mildly increased sharps (<5/hr)	2. Lag*
6. Predominantly low amplitude bilaterally (mostly< 30µV)	6. Marked Excess discontinuity (frequent)	4. >20s	4. Diffuse delta	3. Focal Slowing	3. Inter-hemispheric asynchrony 25-49%	2. Excess Labile State##	4. Frequent or Multifocal sharps	4. Delayed**
6. Very low amplitude unilaterally (6-10µV)	8. Permanent discontinuity			4. Focal Attenuation	4. Inter-hemispheric asynchrony >50%	4. No Recognisable Sleep State		
8. Unilateral inactivity (<5µV)	10. Burst suppression" "							
8. Low amplitude bilaterally (10-20µV)								
10. Very low amplitude bilaterally (6-10µV)								
12. Electrocerebral inactivity bilaterally (<5 µV)								
Total: /12 or N/A	Total: /10 or N/A	Total: /4 or N/A	Total: /4 or N/A	Total: /4 or N/A	Total: /4 or N/A	Total: /4 or N/A	Total: /4 or N/A	Total: /4 or N/A
							Total:	%

Abbreviations: WNL = within normal limits, ABN = abnormal

"Discontinuous patterns: Bursts containing high to medium voltage activity of various kinds including normal activity interrupted by abnormally attenuated portions

" "Burst Suppression: Non Reactive Discontinuous tracing with periods of suppression < 5µV in amplitude interrupted by asynchronous bursts of poorly organised activity of 1-10s duration.

⁺TA: Trace Alternans in quiet sleep

#Excess transient state is defined by >20% indeterminate sleep

##Excessive labile state is characterised by rapid transition between sleep states over seconds to minutes

*Maturational Lag: Immature for gestational age by <2 weeks

**Maturational Delay: Immature for Gestational Age by > 2 weeks

Figure 5. Statistical analysis (Mann Whitney ranksum test, box and whiskers plots) of percentage scores of EEG background abnormality (median, interquartile range and range) in infants who subsequently developed adverse outcomes compared to those who did not.

Figure 5   **Background EEG and outcomes**

$P < 0.0001$
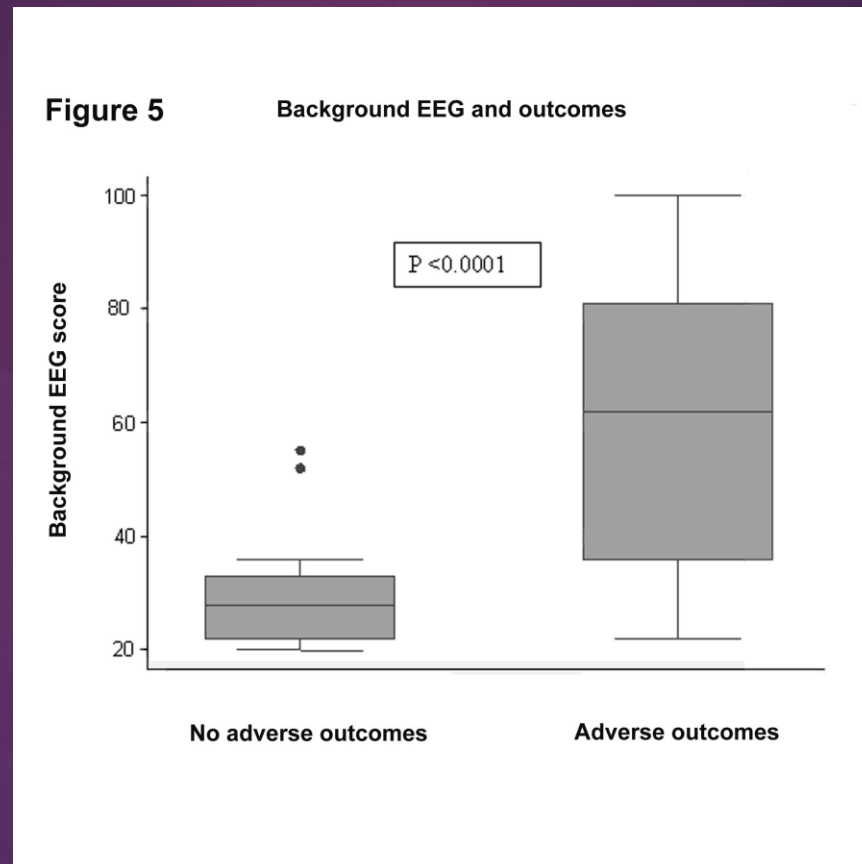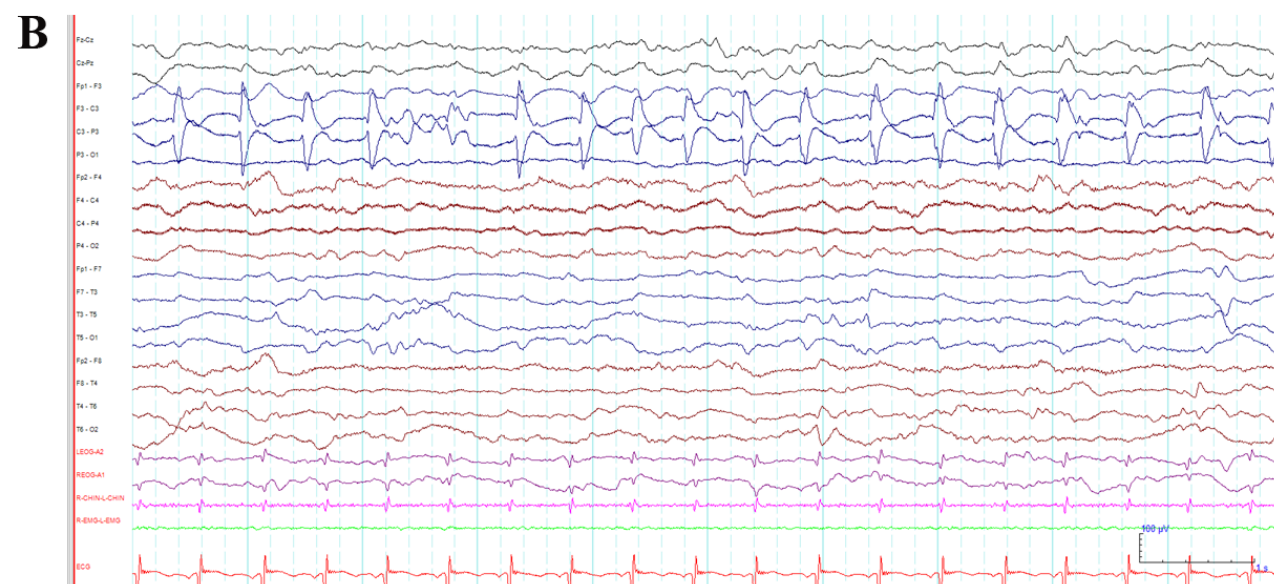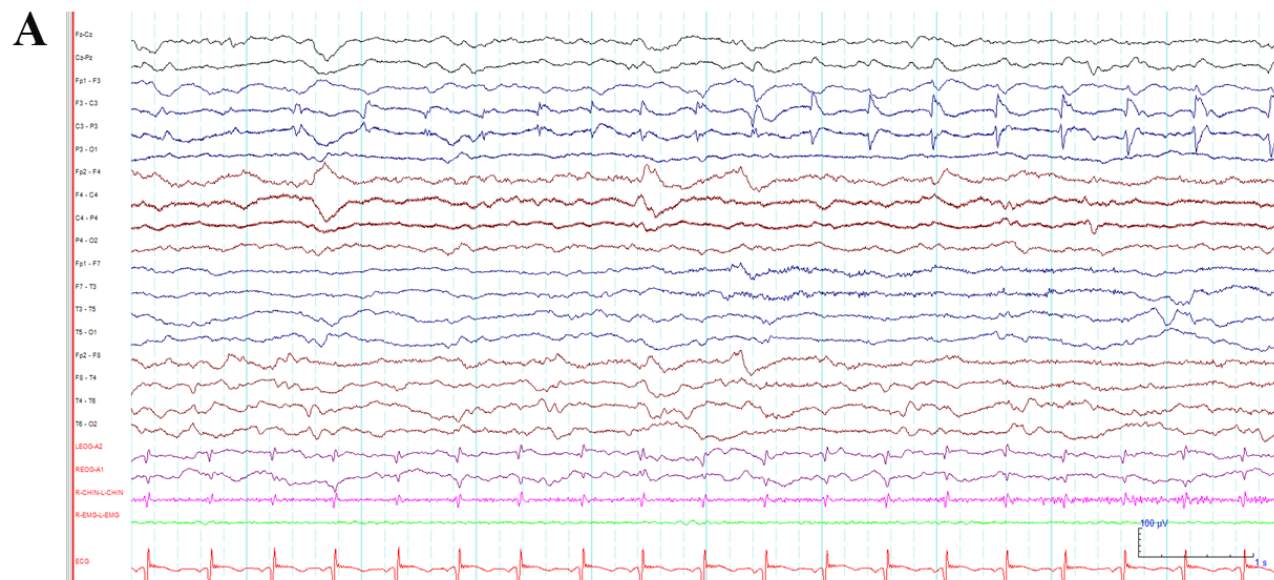
Does Ictal EEG help prognosticate neurodevelopmental outcome in babies with NS

Are features of the ictal EEG of prognostic value?

► Results at times inconsistent and variable.

► Low average maximal frequency and low average maximal amplitude of seizure discharges appear to be poor prognostic indicators (Nagarajan, 2011)

► Some studies have shown that higher ictal fractions, multiple ictal foci, status, involvement of both hemispheres and electroclinical dissociation are associated with adverse outcomes. (Volpe, 2008; Scher, '93; Bye, '97; Pisani,'07, '08; Ortibus,'96; Scher,'03).

Our data does not support this. (Nagarajan, 2010, 2011,2012)

Brief Electrographic Rhythmic Discharges in Neonates.

- Conventionally (rather arbitrarily) neonatal Szs defined as being > 10 second duration

    - Shewmon, *Electroencephal Clin Neurophysiol*, 1983; *J Clin Neurophysiol*, 1990.

- Brief rhythmic discharges of 5 - 10 seconds may also be an indicator of epileptic neuronal networks in the newborn.

Nagarajan et al. J Child Neurol 2011
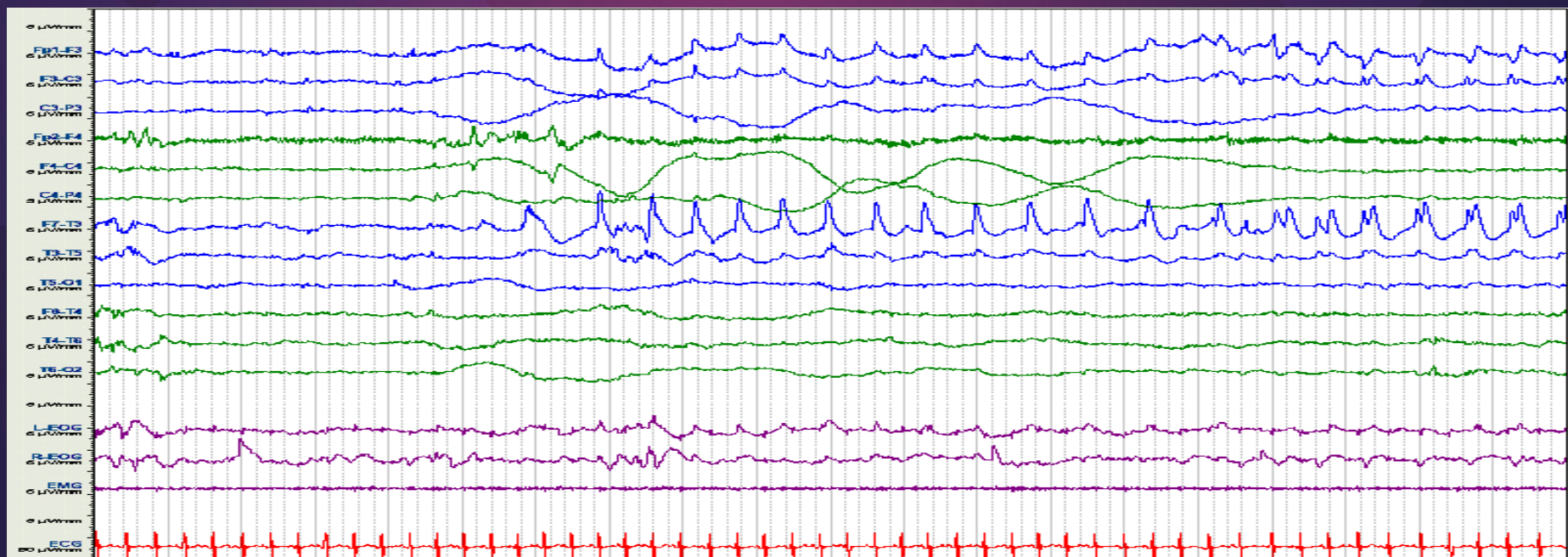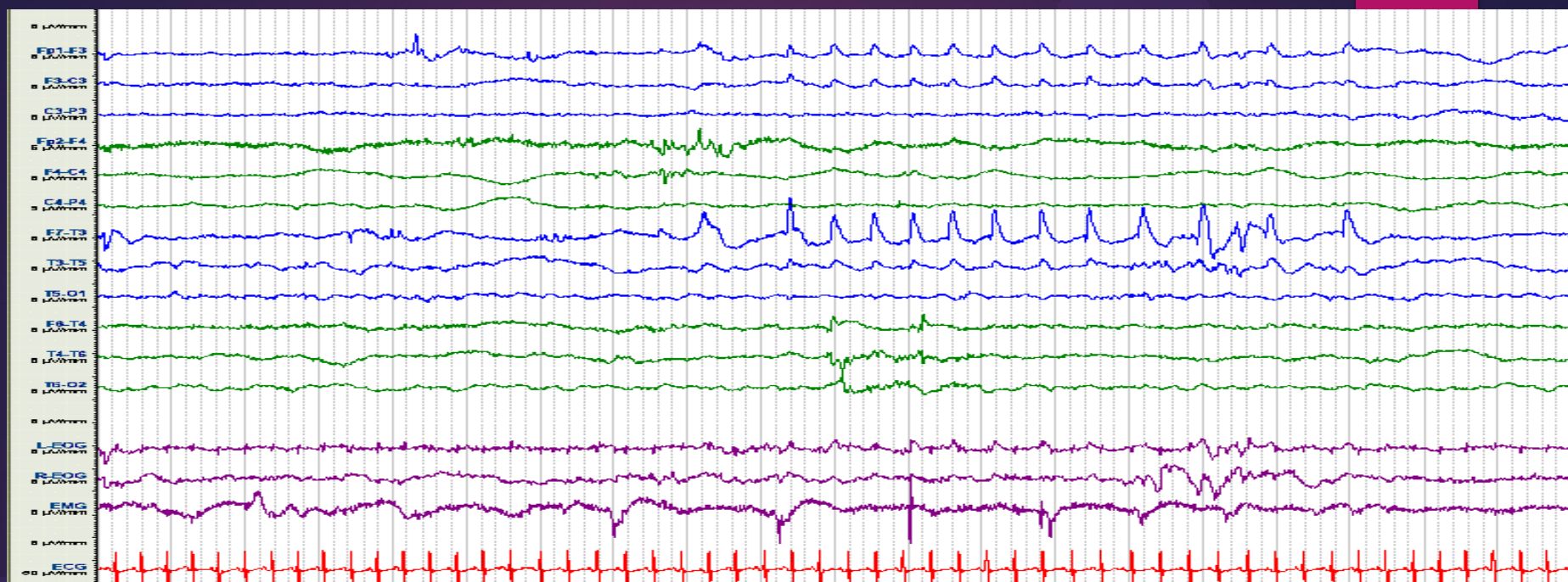
Brief EEG Rhythmic Discharges in NS

52 babies with EEG Szs, BERDs, or both

- 32 babies had EEG Szs only
- 11 had EEG Szs + BERDs
- 9 had BERDs only

- BERDs of 5- 10 second duration
  - are associated with increased mortality and morbidity,
  - background EEG abnormalities,
  - neuroimaging abnormalities,
  - just as conventional neonatal seizures are.

- Are they mini seizures ?
  - Nagarajan et al. J Child Neurol 2011

Ictal Fast activity during Neonatal Seizures..

- ▶ High Frequency Oscillatory Activity (80-500Hz), recorded from intracranial EEG mostly, has been associated with seizure genesis and implicated in epileptogenesis.

- ▶ Paroxysmal Fast Activity in the beta and gamma range, detected on scalp EEG, in children, has been proposed as a marker for epileptic networks in a few studies

- ▶ Ictal fast activity in neonatal seizures has not been explored previously.

- ▶ Nagarajan et al. Epilepsy Research, 2011
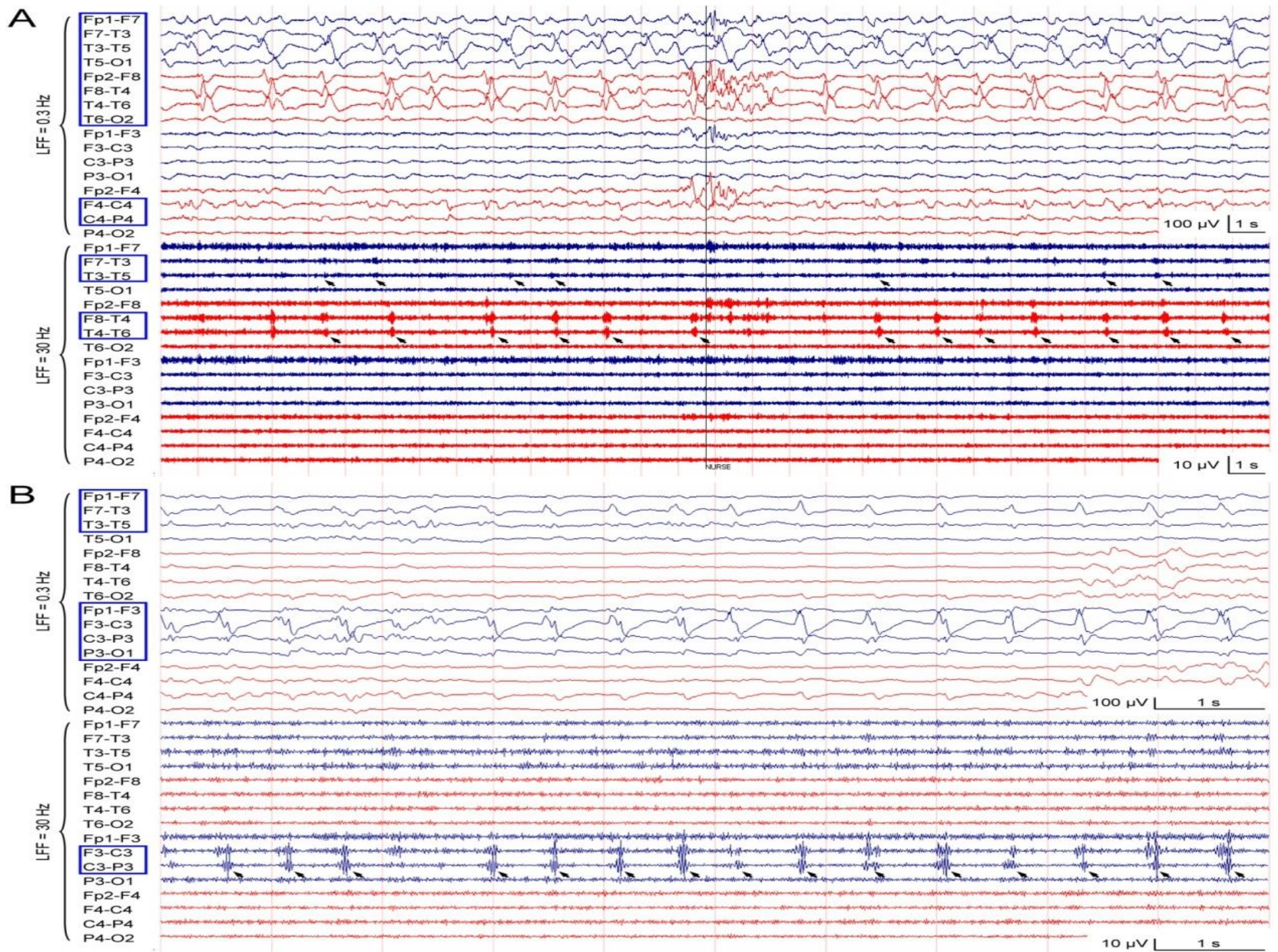
Ictal Fast Activity occurred in 62 (39%) of the 159 EEG Szs.

- Ictal FA is highly correlated to the presence of clinical features during an EEG Sz (p=.0006)

- Ictal FA may be related to symptomatogenesis in neonatal seizures

- Ictal FA not correlated to Phenbarbitone

Ictal Fast Activity in Neonates.

Nagarajan et al. Epilepsy Research, 2011.

- ▶ Ictal FA was present in 40.5% of the babies

- ▶ The presence or absence of ictal FA does not appear to influence
  - ▶ mortality,
  - ▶ neurodevelopmental outcome
  - ▶ the occurrence of postneonatal seizures _ why?

- ▶ Ictal FA may not be a biological marker for epileptogenic tissue in neonates

Neonatal seizures

▶ **Most electrographic seizures in critically ill children with acute encephalopathy have no clinical correlate so identification requires EEG monitoring**

▶ Recent guidelines recommend EEG monitoring of at-risk encephalopathic children for 24-48 hours

▶ **Conventional EEG (VEEG)** and **amplitude-integrated EEG (aEEG)** are currently the two main methods used in the newborn infants for detection and monitoring of neonatal seizures.

Amplitude-integrated EEG

▶ aEEG is now a part of clinical management in most NICUs

▶ It is thought to be a practical method of continuous evaluation of brain function in a neonate

Hellström-Westas, 2016 , Rakshasbhuvankar et al, 2015, 2016.

Conventional V-EEG for Neonatal seizures

- ▶ VEEG the gold standard

- ▶ VEEG needs special expertise

- ▶ Not easily available

aEEG for neonatal Seizures

▶ aEEG is widely used in NICUs world over

▶ aEEG is an asymmetrically filtered, rectified, compressed, semi-logarithmic trend measure of the EEG background amplitude.

  ▶ Time compressed (traditional 6 cm/hr),

  ▶ Semi-logarithmic scale (linear 0-10, logarithmic 10-100)

  ▶ displays peak to peak amplitude values of a filtered and rectified EEG

  ▶ Filtered with LFF:2Hz, HFF:15Hz

▶ New aEEG machines also display raw EEG trace/s

▶ 0ften equipped with seizure-recognition algorithm software

A diagnostic accuracy study

▶ Compared the diagnostic accuracy of aEEG vs VEEG for detecting seizures in neonates

▶ Rakshasbhuvankar et al. J Child Neurol 2017

Methodology

- Neonates recruited to the study, after informed consent
- 24 hours of simultaneous aEEG and VEEG were acquired.
- C3, P3, C4, P4 electrodes from VEEG (PSG, Compumedics) were fed to the aEEG (Brainz)
- aEEG was interpreted independently by neonatatologist
- VEEG was interpreted by a paediatric neurologist with expertise in neonatal EEG
- The aEEG and VEEG studies were interpreted blindly, later.

|	
Number of infants studied	35
Sex	M 22, F13
Birth weight (g), median (range)	3310 (2385-4375)
Gestational age at birth (week), median (range)	39^{+4} (36-41 $^{+3}$)
Age at the start of study (hours) , median (range)	32 (7- 480)
Apgar score at 5 min, median (range)	8 (0-9)
Diagnosis / cause of seizure	
HIE stage 2 or 3 (n)	16
IVH/infarct (n)	5
Other (n)	14
Therapeutic hypothermia (n)	14
Infants treated with AEDs	
Before the study	23
During the study	12

Results: Babies with seizures

- A total of 855 hours of aEEG and VEEG traces from thirty-five infants were analysed.

- Seven babies were identified to have seizures on VEEG and aEEG picked all 7: Sensitivity for babies with seizures: 86%

- However, 7 other infants were incorrectly diagnosed to have seizures on aEEG: Specificity: 75%, PPV:46%

Results: INDIVIDUAL SEIZURES
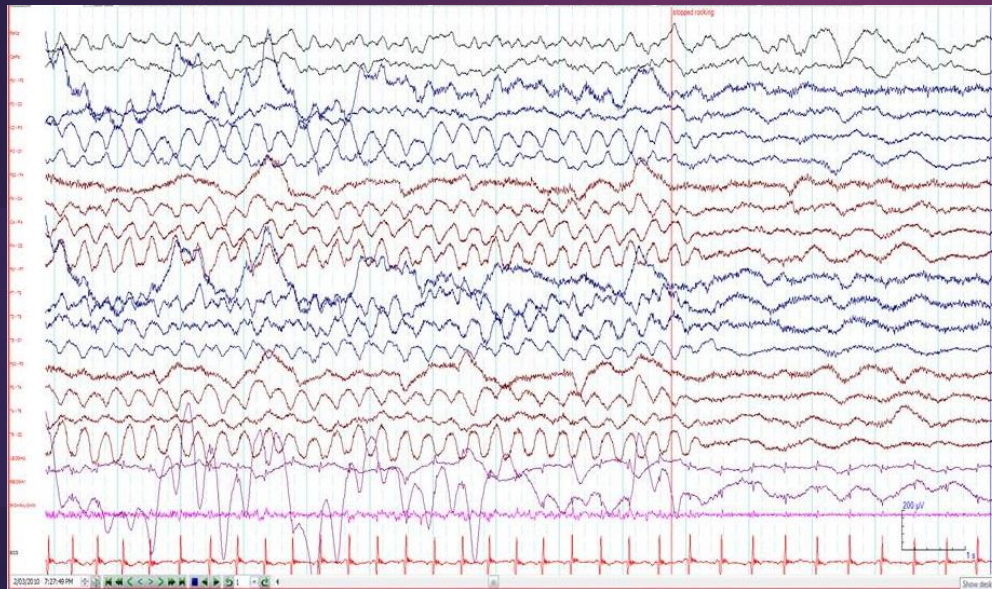
- There were 169 seizures on VEEG

- aEEG correctly identified 57 of these 169
  - **The sensitivity for individual seizures was only 34%**

- aEEG also falsely identified 50 other events as seizures
  - **PPV was 53%**

- For individual seizures 112 seizures detected by VEEG were not identified by aEEG
  - **False negative rate was 66%**

True positive
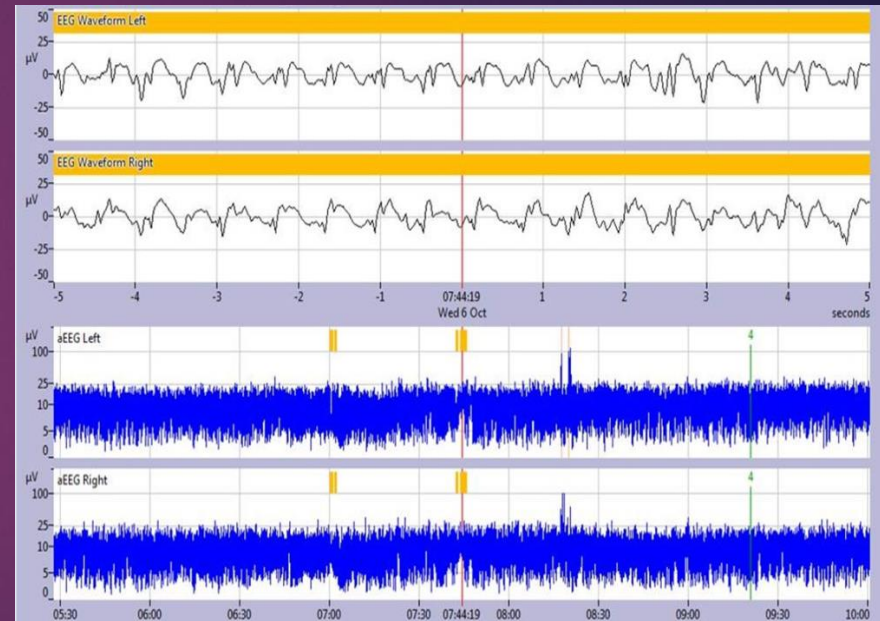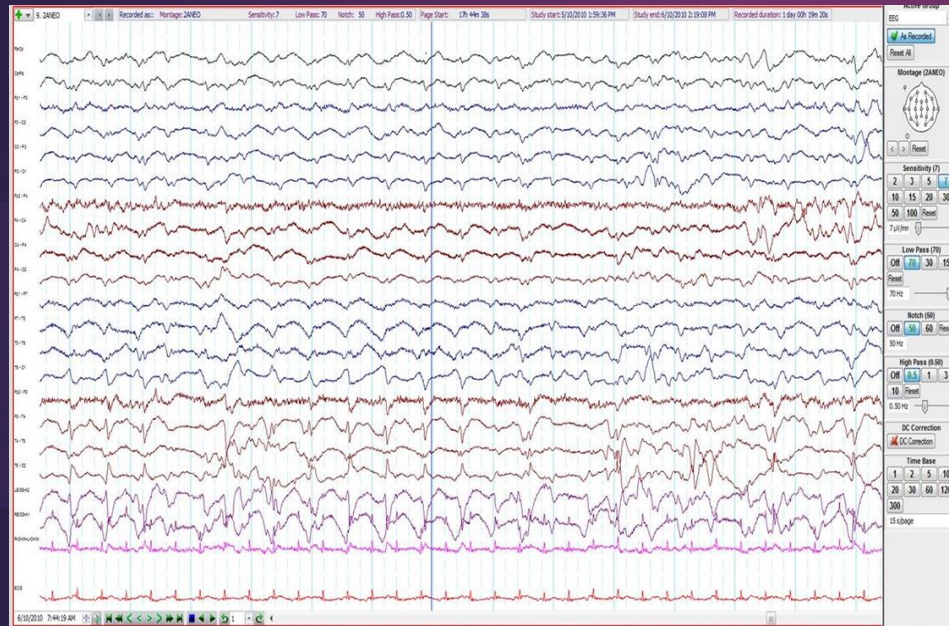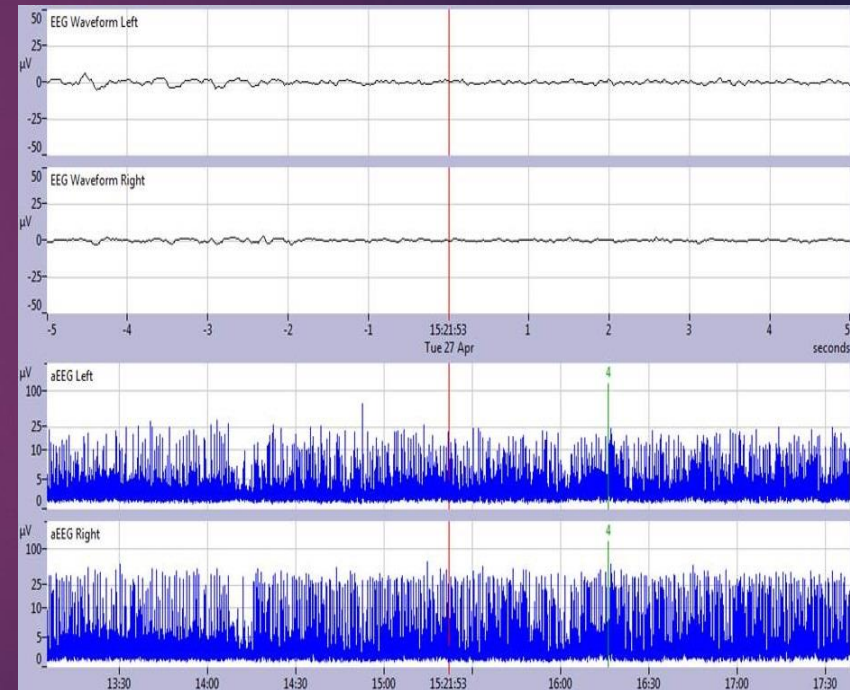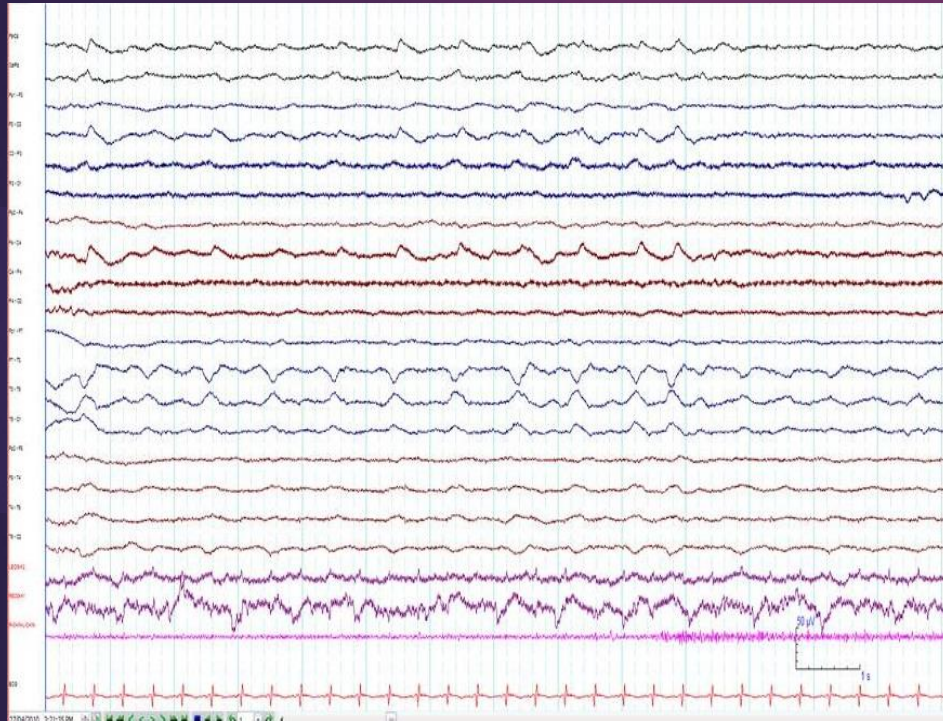
False positive
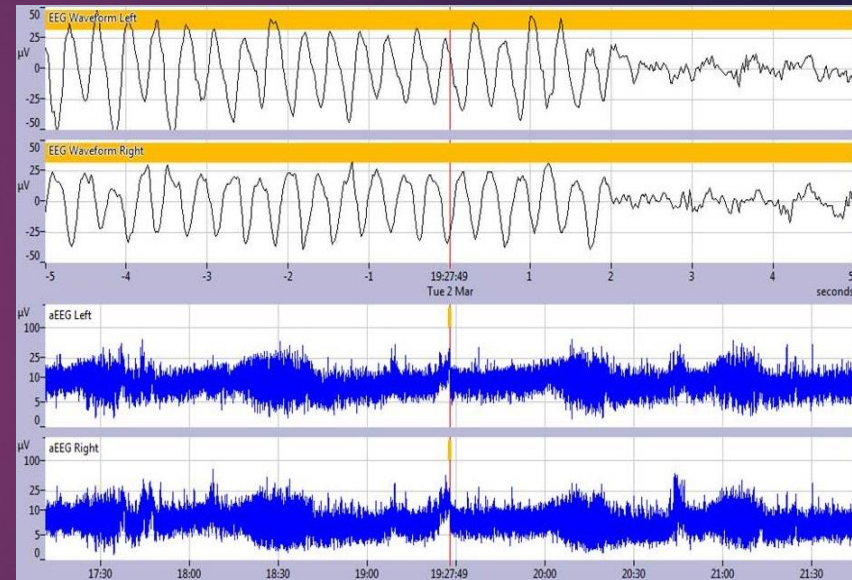
False negative

Results

▶ Seizures were more likely to be identified on aEEG

   ▶ If they were of longer duration

   ▶ occurred on an abnormal aEEG background

   ▶ in babies that are not cooled

Limitations of aEEG in Neonatal Seizures

▶ Amplitude-integrated EEG for detection of neonatal seizures: a systematic review. Rakshasbhuvankar et al, Seizure 2015

▶ aEEG compared with conventional V-EEG for neonatal seizure detection; a diagnostic accuracy study. Rakshasbhuvankar et al. J Child Neurol 2017

Conclusions:

Studies included in the systematic review showed aEEG to have relatively low and variable sensitivity and specificity.

Based on the available evidence, aEEG cannot be recommended as the mainstay for diagnosis and management of neonatal seizures.

▶ **Neuromonitoring is essential.**

▶ Clinical acumen alone – clearly not adequate.

▶ Neonatal Seizure Detection Alogarithms: Stevenson, 2106

▶ The most effective paradigm for neuromonitoring – ?

Boylan, 2011, Wusthoff, 2013. Rennie, 2004; Shellhaas , 2007; Silverstein, 2008; Shah, 2009; Evans, 2010; Elke, 2011; Kato, 2011; McCoy, 2013, Rakshasbhuvankar 2016, 2017, Nagarajan 2016.

Treatment of Seizures in Neonates

- Therapeutic options limited

- Frequently used AEDs not very effective

- Concerns regarding the safety and adverse effects – short and long term, including effects on neurodevelopment

- Under and over treatment may have adverse consequences

- Pressler, 2013, Slaughter 2013, Shetty, 2015, Velez-Ruiz and Meador, 2015, Bittigau, 2002, Maitre 2013, Pennell, 2012.

Treatment of seizures in the neonatal period

- Identification and treatment of underlying or contributory disorders essential

- HIE most common cause, with PAIS, ICH, infections, metabolic perturbances and disorders, epileptic electroclinical syndromes, brain malformation disorders, channellopathies…

- Supportive treatment very important: ABC….

- Specific treatment for the seizures

- Nagarajan, L. 2016.

Current practice for seizures in neonate

Phenobarbitone remains first line drug internationally

Efficacy of PB ~ 50% at best

PHT, Benzodiazepines, Lignocaine, LEV are other medications being used

Need for newer options

First line AEDs: PB AND PHT

- Phenobarbitone: most frequently used AED and remains drug of first choice

- In Painter's RCT('99) , szs were controlled in 43% of neonates treated with PB, cf to 45 % with PHT

- Studies suggest efficacy of PB and or PHT <50%

- PB reasonably good safety profile, however there are concerns that it may increase neuronal apoptosis and adversely affect neurodevelopmental outcomes.

- Boylan, 2004, Pathak 2013, Slaughter 2103, Shetty 2015, Nagarajan 2016, Torolira 2017.

PHENOBARBITAL PLUS OTHER INTERVENTIONS

- **Therapeutic Hypothermia**: has been shown to be beneficial in many trials (Gano, 2014).

- Reduction in sz burden, alteration of temporal evolution of szs, increase in ECD have been demonstrated (Boylan, 2015, Lynch, 2012, Srinivasakumar, 2013, Kharoshankaya, 2017).

- TH may alter the pharmacodynamic and pharmacokinetic properties of AEDs (Pokorna, 2015, Boylan, 2015).

- It has been suggested that PB alone or in conjunction with **Bumetanide** may augment the beneficial effects of TH, in animal models (Barks, 201, Lui, 2012)

- In neonates the combination (TH+PB) may have a neuroprotective effect (van den broek, 2012)

PB and Bumetanide

- Bumetanide is a loop diuretic, previously used in neonates, with rapid onset, short duration of action, as well as a relatively good safety profile (Pressler & Magnum, 2013).

- BTN inhibits NKCC1, reduces intraneuronal CL and hence the depolarising effect of GABA activation.

- In some animal studies and vitro models (not all), BTN in combination with PB was effective in reducing szs without increasing apoptosis (Cleary, 2013, Vanhatalo, 2009).

- These studies provided support for clinical trials of BTN in neonatal seizures

PB AND BUMETANIDE
CATION CHLORIDE CO-TRANSPORTERS.
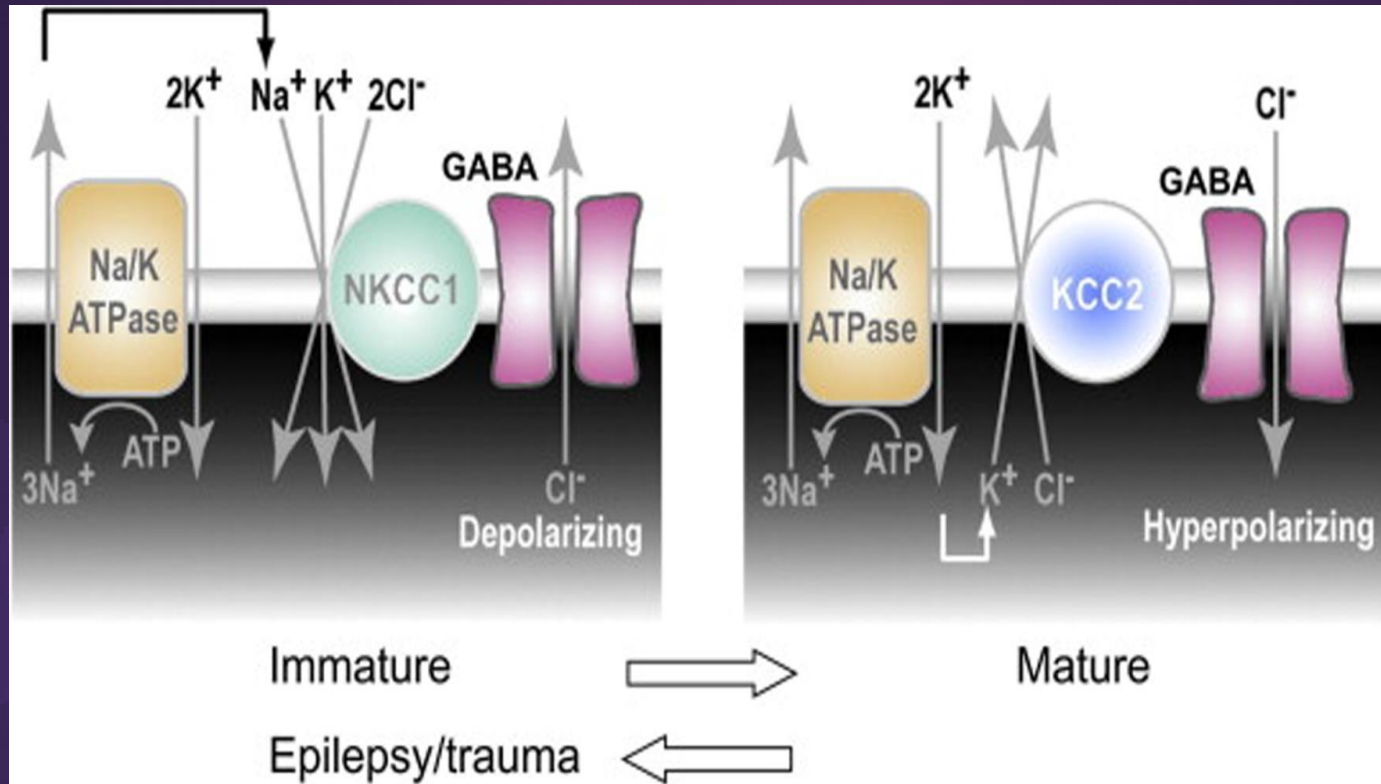
Puskarjov et al, 2013

IN THE IMMATURE BRAIN THERE IS OVER EXPRESSION OF THE NKCC1 AND RELATIVELY LOW EXPRESSION OF THE KCC2. THIS RESULTS IN HIGH INTRANEURONAL CHLORIDE, CAUSING GABA ACTIVATION TO HAVE A PARADOXICAL EXCITATORY/DEPOLARISING EFFECT.

NEMO Trial

- A trial of BTN for neonatal seizures refractory to PB was stopped early because of reported lack of efficacy and increased incidence of adverse effects such as hearing impairment, dehydration, hypotension and electrolyte imbalance (Pressler, 2015).

- Thoresen and Sabir (2015), feel the decision to stop the trial may have been overcautious.

- Efforts to find other drugs that may target the CCCs continue (Puskarjov, 2014).

- Modulation of CCCs with or without PB/TH remains a novel therapeutic option to be explored further.

PB and Caffeine

- Caffeine is used for Rx of apnoeas in newborns
- Caffeine appears to be neuroprotective
  - In animal models antiapoptotic and anti-inflammatory effects
- In human neonates -? Caffeine reduces CP
- PB increases apoptosis inducing factor, and cleaved caspase3 ,
  - this is reduced by co-administration of caffeine
- Down regulation of adenosine A1 and A2 receptors by phenobarb,
  - also partly anatgonised by caffeine
- ? PB induced adverse effects be reduced by co Rx with caffeine
- Endersfelder et al, 2017

Phenytoin

- Has been one of the mainstays of NS management

- However efficacy not more than 50%

- Enteral and parenteral preparations available

- IV PHT cannot be mixed with other drugs, has to be administered slowly, may cause tissue irritation and discolouration

- PHT infusions have been associated with hypotension, cardiac arrhythmias and collapse.

- These problems and the availability of other Rx options have resulted in some waning of the use of PHT for NS

Benzodiazepines

- Midazolam – most frequently used BZD for NS.

- Reported efficacies have varied from 0-100% . Reasonably well tolerated, respiratory and cardiac depression may occur. Occasional sz exacerbation especially in preterms.

- Clonazepam, Diazepam

- Gelissen, 1996, Montenegro, 2001, Sheth, 1996, Boylan, 2004, van leuven, 2004, Shany, 2007, Nagarajan,2016

Lignocaine

- Second line in some parts of the world, mostly third line
- Lidocaine efficacy 60-90% (with PB).
- Cardiovascular adverse effects may occur, especially in babies with cardiac problems, concurrent PHT, hypokalaemia
- Cardiac monitoring recommended
- Guidelines and protocols available
- Probably underutilised, in view of efficacy, safety profile with current guidelines (with and without TH), should be considered in future trials
- (Weeke, 2015, van den Broek, 2013, Lundqvist, 2013)

LEVETIRACETAM

- Most promising new AED for Szs in the neonate
- Good safety profile,
- has IV and enteral forms.
  - No requirement to monitor levels,
  - twice daily dosage,
  - renal excretion,
  - minimal protein binding,
  - lack of significant interaction with other drugs,
  - lack of neurotoxic effects make it an attractive AED
  - (Mruk, 2015)

Levetiracetam for szs in neonates

- Levetiracetam is a pyrrolidine derivative that is chemically related to piracetam, a nootropic drug. Unique MOA

- Thought to act primarily through the synaptic vesicle protein 2A, involved in synaptic fusion, exocytosis and neurotransmitter release. May affect GABAnergic pathways, Excitatory pathways and Ca channels

- ? Alters epileptiform burst firing without affecting normal neuronal activity

- with linear pharmacokinetics, renal metabolism, and minimal protein binding, attractive.

Animal studies with LEV

- Unlike phenobarbital, levetiracetam does not increase apoptosis in the developing brain in animal models

- In rat pups with HIE- decrease in no. of apoptotic neuronal cells in LEV group ? Neuroprotective effect (Killigdac et al,2013)

- Does not cause neuronal apoptosis in the immature brain or disrupt synaptic development (Forcelli, 2013)

LEV for szs in neonate

- Khan et al, Pediatr Neurol, 2011.
  - Retrospective, 32% sz (ECSzs and ESz) cessation after 10-50mg/kg loading in 22 term neonates , maint: 25mg/kg bd or tid
- Khan et al, Pediatr Neurol, 2013.
  - 12 preterm patients – loading doses of 25-50mg/kg, 25mg/kg maint
  - 82% sz cessation
- **Rakshasbhuvankar et al**, Journal of Clin Neuroscience, 2013
  - 5-10mg/kg good response in 6/8, maint upto 35mg/kg/day
- Shin et al, Korean J Pediatr, 2017
  - 18 babies, loading dose 10 -20 mg/kg and mean maintenance of 29 mg/kg (20-60)
  - Sz cessation 94% within one week
- Falsaperta et al, J Pedaitr NeuroSci, 2017
  - 16 , 10 mg/kg/twice daily, increased every 24 hours upto 40 mg/kg
  - Sz cessation in all.
- **Two phase 2 studies cf PB and LEV as first line results awaited**

LEV in Szs in neonates

- Mehra et al, J Pediatr, 2011

    - 15-40mg/kg loading dose in 18 neonates, somnolence only side effect

- Ramantani et al, Eur J Paediatr Neurol,2011

    - Prospective, Initial dose 10mg/kg/ as twice daily, maint upto 30-60mg/kg/day

    - 79% of 38 infants sz free at the end of first week

- Abend et al, J Child Neurol, 2011

    - Retrospective, 10mg- 20 mg/kg loading, > 50% reduction in 8/23 , in 7, cessation:30% Maintenance: 5-40mg/kg/bid

- Sharpe et al, Pediatr RESEARCH, 2012

    - 18 infants 20 or 40mg/kg loading dose and maint of 5-10mg/kg/d

    - cessation of szs in 30%

Efficacy of LEV for szs in the neonate

- As first line drug: 25-100%

- As second or> line: 32-84%

# Optimal dose of LEV for szs in neonates still not clear

- No clear dosing guidelines, loading doses of 10-70mg/kg/day, 2/3 excreted in urine unchanged, 1/3 hydrolysed into three inactive metabolites (UCBL057 one of them). Neonate volume of distribution high. Renal clearance low in neonate compared to older infant. Renal reabsorption low. Esterase level low

- Studies looking at pharmacokinetics – some unexpected results and variability, change in pharmacokinetics in first week of life

- Half life: 18.5 h – 8.9h, higher than in older children, ? Changes rapidly first week. Clearance increases in first week of life, half life may be prolonged in neonates and especially preterms due to immature renal function.

- Value of therapeutic monitoring????

- # Dosage information from the studies suggest

- loading doses of 10 to 20 mg/kg are appropriate and effective in neonates,

- maintenance dose range of 10 to 50(?80) /kg/day divided twice daily.

Sharpe, 2012,   Murk, et al, 2015, Nagarajan, 2016.

Safety profile of LEV in neonates and children

- Children exposed to LEV in utero not at increased risk of early(<2 year) delayed development.

- LEV may be the preferred AED, when apt, in WWE (Shallcross et al, Neurology 2011)

- Maitre, et al, J of Perinatol, 2013 .

    - A retrospective paediatric study looking at exposure to AEDs in the neonatal period (106 only PB, 33 LEV alone & 141 neonates received both), found greater neurotoxicity and poor neurodevelopmental outcomes with phenobarbital compared to LEV….. Mortality outcome not associated with either drug

Other AEDs
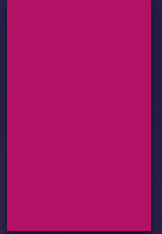
Other drugs and therapies

- Topiramate

- Valproate

- Carbamazepine, Oxcarbazepine

- Vigabatrin

- Lamotrigine

- Zonisamide

- Paraldehyde, Thiopentone

- **Xenon**

- Tulloch, 2012, Azzopardi, 2013, Slaughter, 2013, Nagarajan, 2016

Inborn Errors of Metabolism

- The cumulative incidence of IEM is low: 1:2000-3000 live births
  - ~25% present in the newborn period and ~40% having SZs

- Early Diagnosis important as some may have specific treatment options

- Treatable metabolic causes for NS are uncommon,

- Abnormalities in Ca, Mg, Sugar should be looked for and treated

- Campistol, 2016.

Metabolic Disorders and Vitamin responsive Szs

Pyridoxine Dependant Epilepsy:

- Antiquitin deficiency main cause

- Responsiveness may be seen in a number of disorders, PNPO deficiency, hypophosphatasia with TNSALP mutation, familial hyperphosphatasia, hyperprolinaemia type 2

- Restriction of lysine and fortification with arginine may be considered

- Folinic acid responsive szs are thought to be identical to PDE, folinic responsiveness may be seen in other conditions

- **PNPO** may only be responsive to pyridoxal phosphate

Campistol, 2015, Ficicioglu, 2011, van Karneberg, 2015, Mills, 2014, Tso, 2014

Treatment of Szs in Neonates with IEM

- Supplementation with selected drugs in specific conditions such as creatine def syndromes, serine and glycine in defects of their biogenesis

- PKU , biopterin defects with dietary restrictions and apt supplements

- Benzoate and dextromethorphan in NKH, Biotin in biotinidase def., cyclic monopterin pyrophosphate in MOCODType1, folate in cerebral folate deficiency

- B12, Betaine, Vigabatrin, riboflavin in some IEMs, such as organic acidurias

- Ketogenic diet in Glut -1 , NKH, mitochondrial disorders.

- Exchange transfusions, PD, to get rid of toxic metabolites, in MSUD, Urea cycle and related disorders

Novel therapies

- Melatonin
- Erythropoietin
- Anti inflammatory compounds
- AMPAR antagonists
- NMDA inhibitors/antagonists
- Cell based therapies

Kadam et al, 2016, Nagarajan, 2016.

Genes and Epilepsy

- With the advent of next generation sequencing rapid advances in genetic cause of epilepsies (Mastrangelo, 2015)

- Among 611 consecutive newborns with seizures, in a neonatal seizure registry, 79 (13%) had epilepsy. (Shellhass 2017)

  - 35 epileptic encephalopathy, 32 congenital brain malformations, 11 benign familial neonatal epilepsy, 1 benign neonatal seizures.

  - 83% with epileptic encephalopathy had genetic testing and 83% had a genetic aetiology

- Targeted therapies emerging (Milligan, 2014, Pearson 2014)

  - eg Quinidine for KCNT1 mutations,

  - Memantine for GRIN 2A mutations

Duration of Therapy

- Lack of guidelines, optimal duration of therapy not known.

- Dependant on aetiology – acute symptomatic seizures vs epilepsy

- In acute symptomatic szs one often considers cause, ease of obtaining sz freedom, SE, neurological examination at discharge from NICU, follow up EEG……

- Preliminary evidence suggests that early discontinuation may not be harmful

- Shellhaas reports, in the neonatal Sz registry 71% of survivors went home on AEDs: study site and Sz aetiology influenced decision making

- Shellhaas, 2017, Nagarajan, 2016, Volpe.
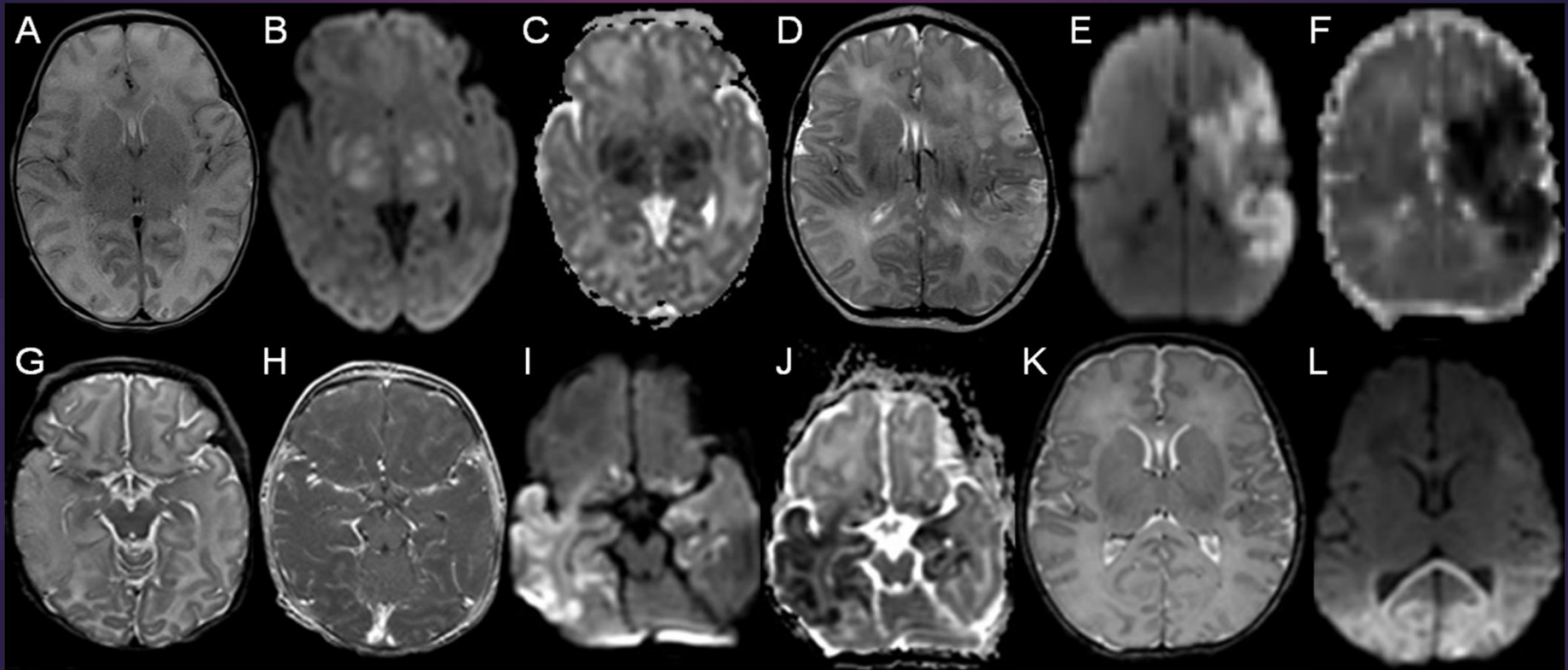
Prognosis in neonates with seizures

▶ Aetiology

▶ Clinical profile and response to interventions

▶ VEEG

▶ Imaging

▶ Epileptic Burden   (ESZ or ECSZ or BERDS)- adds to neurodevelopmental impairment

▶ Geographical profile

Seizures in the neonate

- Many advances
  - Basic neurobiology and developmental profiles of the brain
  - Better understanding of NS
  - Recognition of the importance of EEG in diagnosis, Advances in neurophysiology
  - Treatment options – old and new, neuroprotective strategies

- Many challenges too
  - Better prevention,
  - Availability of diagnostic tools
  - New Rx options required, optimal durations to be determined
  - Does management need to be tailored to the gestational age, the aetiology
  - Improve long term neurodevelopmental outcomes

- ILAE Neonatal Seizures Task Force for development of guidelines

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