Update in diagnostics, treatment and prognostic outcome in neonatal seizures

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PD Dr. med. **Alexandre N. Datta**

Stv. Abteilungsleiter, Leiter Epileptologie und EEG,

Co-Leiter Zentrum für Schlafmedizin der Basler Universitätskliniken USB, UKBB, UPK

Abteilung Neuro- und Entwicklungspädiatrie

Universitätskinderspital beider Basel (UKBB) Basel, Schweiz

Introduction

Characterisation of neonatal seizures and their treatment using continuous EEG monitoring: a multicenter experience

- Methods: Multichannel cEEG monitoring, 72 hours, started as soon as possible.
- Population: 214 neonates, at least 35 weeks of gestation
  - Etiologies: HIE (59%), metabolic/genetic disorders (21%), stroke (13%)

Rennie et al, 2019

Introduction

- Seizures confirmed in EEG in 35%
- median number of seizures: 24
- maximum hourly seizure burden in minutes per hour (21 min)
- status epilepticus in 28%!
- 52% were given antiseizure medication (ASM):
- 31% of all neonates without electrographic seizures received ASM.
- 19% of all neonates under EEG with **no** electrographic seizures received ASM.
- 9% of those who had electrographic seizures during EEG did **not** receive ASM.

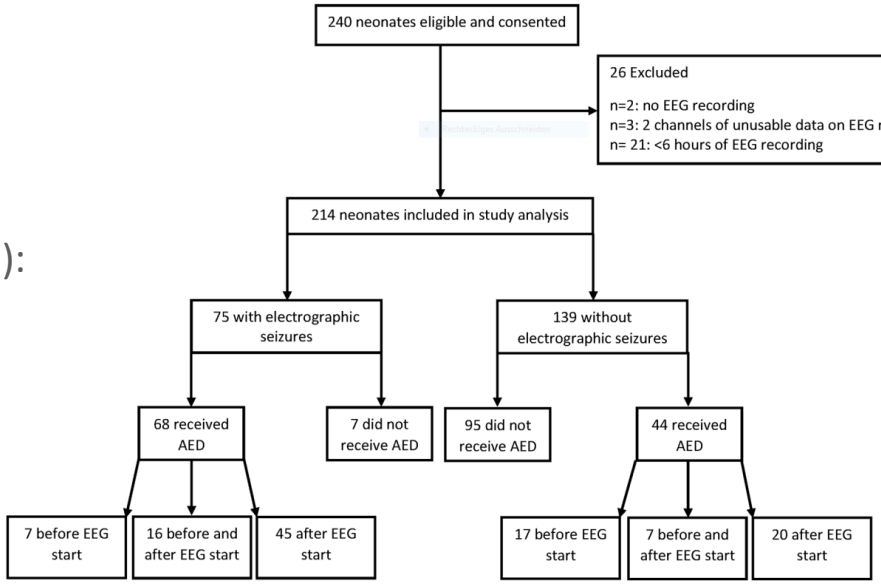


Figure 1 Flow diagram of recruitment, seizures and antiepileptic drug (AED) use in the cohort. EEG, electroencephalography.

Facit: Subtle nature of seizures in neonates: Overdiagnosis and under-recognition at the same time!

Rennie et al, 2019

Introduction and outline

What are the aspects I would like to point out in this talk:

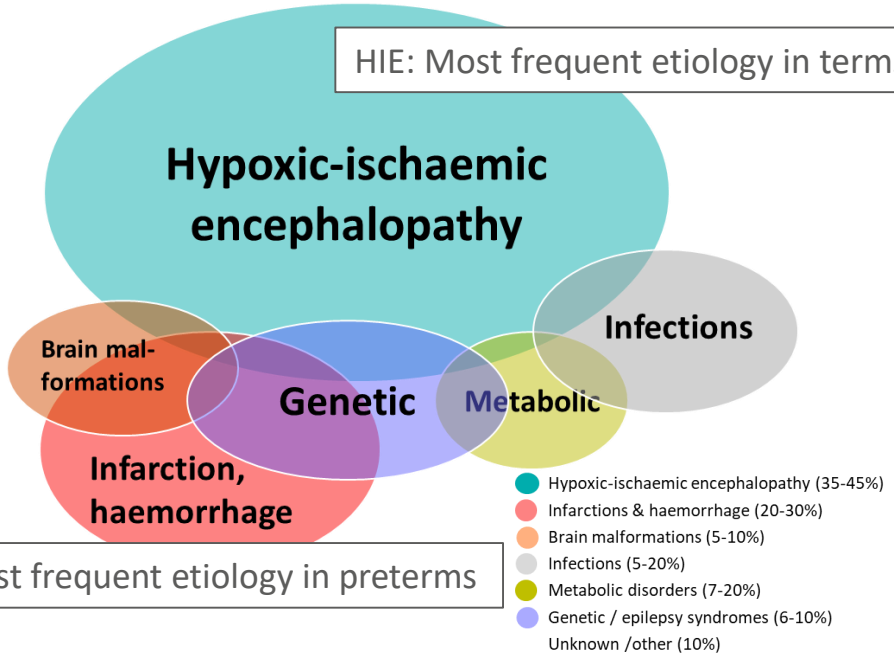
1. seizure incidence and prevalence in preterms and terms
2. epilepsy prevalence in neonates
3. what is a seizure – new classification
4. seizure burden in terms in HIE and in preterms: when do we expect most seizures?
5. methods and recommendation how to detect seizures: aEEG, cEEG, automatized seizure detection: When and how long?
6. new recommendations for treatment
7. Outcome
8. Conclusion

1. Incidence and prevalence of neonatal seizures

Seizures at neonatal age

- Incidence of seizures: 1-5/1000 births:
  - 85% with provoked/ acute symptomatic seizures (HIE, etc)
  - 13-15% (-30%) later develop a structural epilepsy, 68% in the first year of life.
  - Large range of postnatal epilepsy severity: 1/3 are pharmacoresistant
  - More than 51% have good seizure control before age 24 months

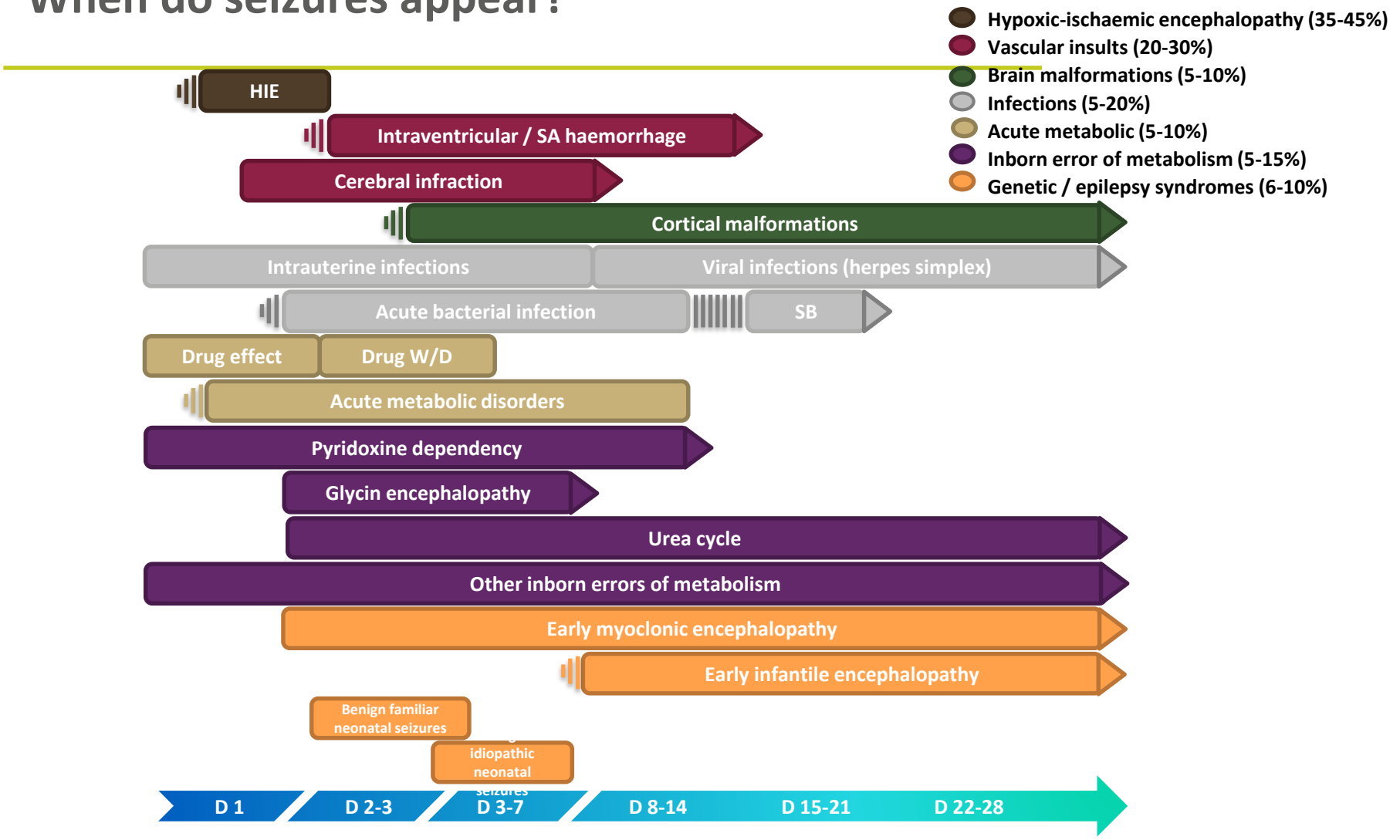
HIE: Most frequent etiology in terms



IVH: Most frequent etiology in preterms

Glass et al, 2021; Ronen et al, 2007; Lay et al, 2013; Garfinkle et al, 2011; Pisani et al., 2021; Pressler, 2021; Rennie et al, 2019, Nagarajan et al, 2010; Ramantani et al, 2019

When do seizures appear?



Courtesy R. Pressler

2. Prevalence of neonatal epilepsies

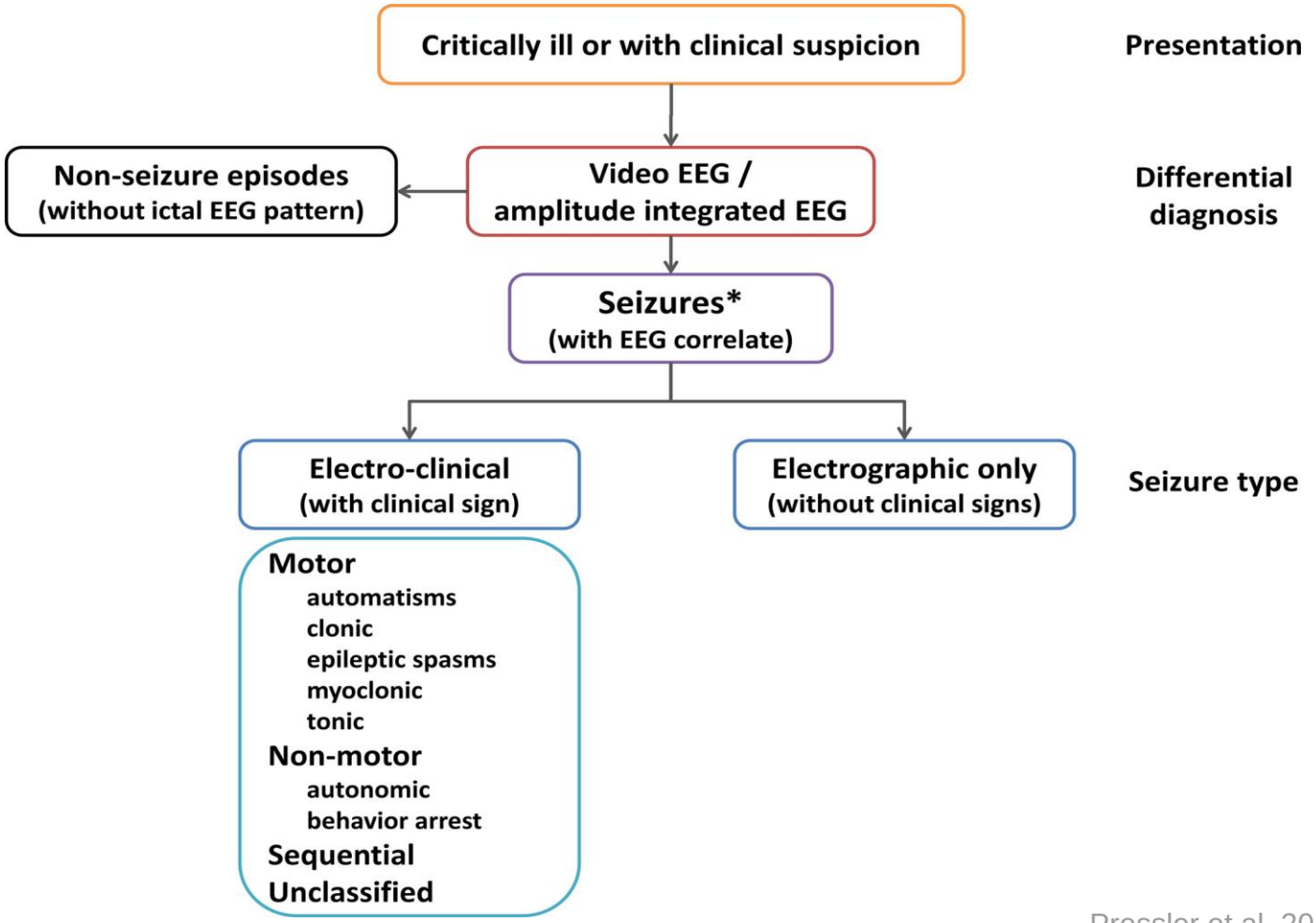
Epilepsies at newborn age:

Only 10-15% of all neonatal seizures are non provoked seizures → epilepsies

- Self limited epilepsy syndromes
  - self limited familial neonatal epilepsy (day 2or 3): KCNQ2, KCNQ3
  - self limited familial neonatal-infantile epilepsy: PRRT2, KCNQ2, KCNQ3, SCN2A
  - self-limited non-familial neonatal epilepsy (5th day fits)

- Early-Infantile Developmental and Epileptic Encephalopathy
  - Early infantile epileptic encephalopathy with suppression burst pattern (Ohtahara Syndrom): often structural, less often metabolic: ARX, STXBP1, KCNQ2, KCNT1, NECAP1, PIGA, PIGQ, SCN8A, SIK1, SLC25A22
  - early myoclonic encephalopathy: often metabolic or genetic: PIGA, SETBP1, SIK1, SLC25A22

3. Definitions and classification



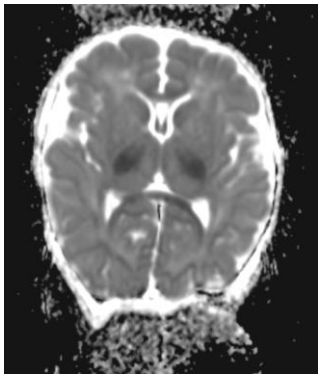
Pressler et al, 2021

4.a. aEEG/ EEG in HIE: Seizure detection

When do we expect most seizures?

- The first hour of continuous EEG detects (or predicts) most neonates who will have seizures in the first 96 hours.
- 50% of neonates who develop seizures have their first seizure during the first hour of recording, 45% between 1-24 hours, 5% between 24-96 hours.
- Abnormal background 2.4x increased risk for seizures, in severely abnormal background 7x increased risk for seizures.

Macdonald-Laurs et al, 2021



Regular EEG in the first 24 hours; a EEG at least 96 hours; MR scan after 96 hours

How accurate do we detect them by aEEG?

- Presence of seizures was rather overdiagnosed by aEEG (63.6 vs 45.5%).

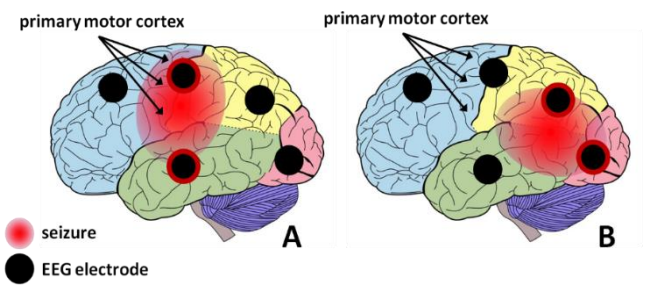
Before treating a child EEG should confirm seizures.

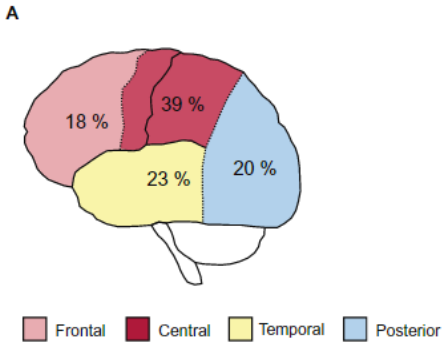
Evans et al. 2010

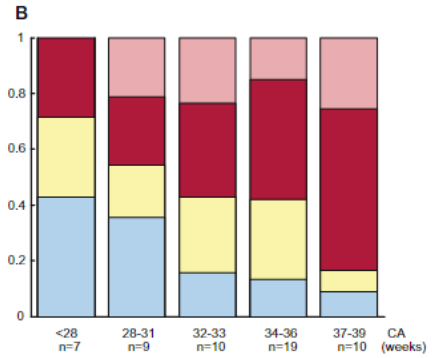
4.b.EEG in preterm babies: Neonatal seizures

- Incidence of seizures in preterms: Controversary reports: **5%** (Lloyd et al, multichannel video EEG) – 13-20% (Meledin et al, aEEG with no video) → seizures rather overestimated
- Seizure recognition difficult, duration short (mean: 49.6 seconds), always focal, frontal and occipital can be missed→ some not captured in aEEG.
- Artifacts (movement, muscle, hiccup) raise EEG baseline mimicking seizures
- High grade IVH with highest incidences (up to 45-65%)
- Uncoupling and electroclinical dissociation

Seizures in preterms rather overestimated

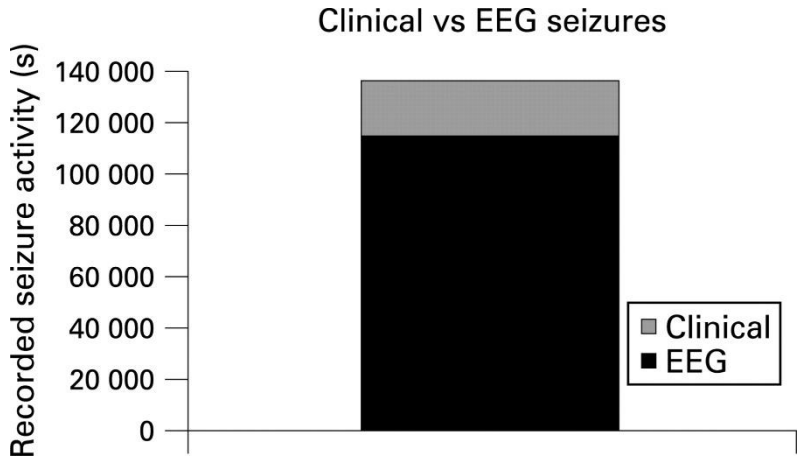






Lloyd et al, Jpeds 2017; Meledin et al, 2019; Janackova et al, 2016

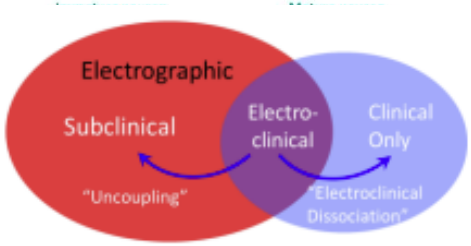
Electroclinical versus elecrographic seizures



- One third only of neonatal seizures have clinical expression on simultaneous video EEG.
- Two-thirds of these clinical manifestations are unrecognized, or misinterpreted

Murray et al, Lloyd et al, 2017; Janackova et al, 2016

Uncoupling of neontatal seizures



1. GABA signaling:
   - Low intracellular Cl → GABA-mediated inhibition
   - High intracellular Cl → GABA mediated excitation
   - Maturation rostro-caudal → GABA inhibition subcortical before cortical
2. Seizure propagation in preterms < terms, reduced by drugs like Phenobarbital

Courtesy R. Pressler

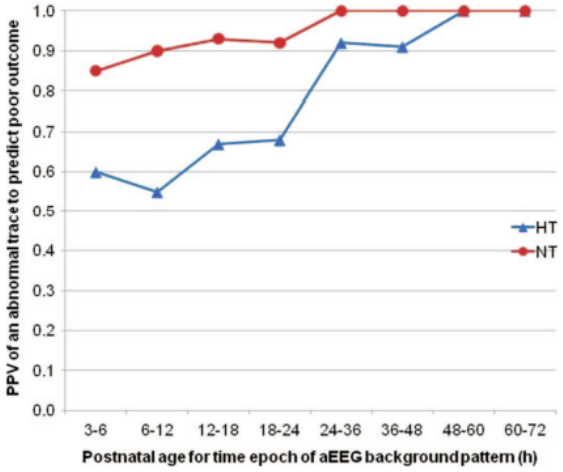
Ben-Ari et al, 2007; Kahle et al, 2008; Mathieson et al 2016

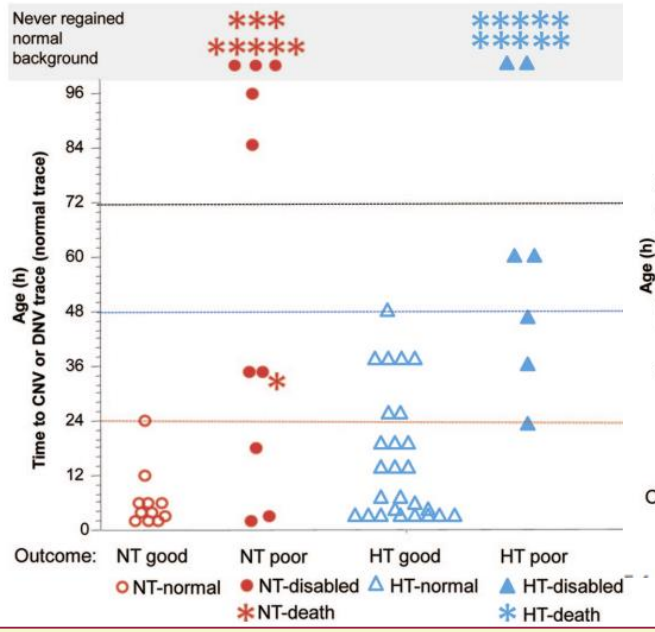
4.c. aEEG/ EEG in HIE: Prognosis

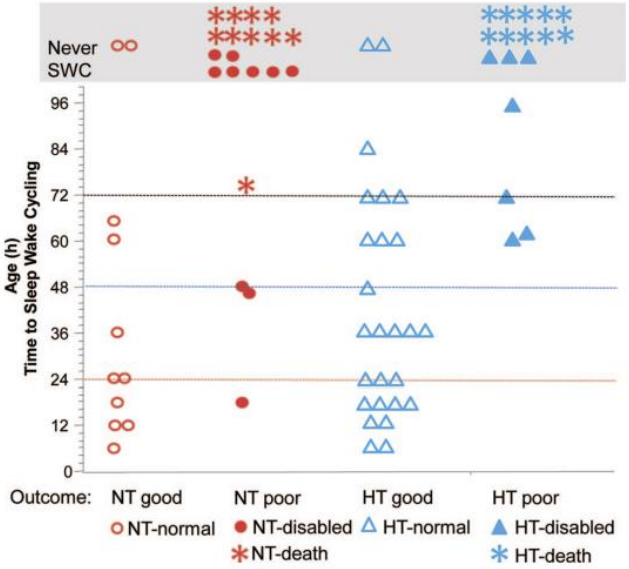
Table 3
Pooled sensitivity and specificity with confidence interval for different EEG background patterns.

EEG background patterns	No. of studies	No. of neonates	Pooled sensitivity		Pooled specificity	
			Point estimate	95% CI	Point estimate	95% CI
Burst suppression	29	914	0.87	0.78–0.92	0.82	0.72–0.88
Low voltage	19	566	0.92	0.72–0.98	0.99	0.87–1.0
Flat trace	13	493	0.78	0.58–0.91	0.99	0.88–1.0

Awal et al, 2016





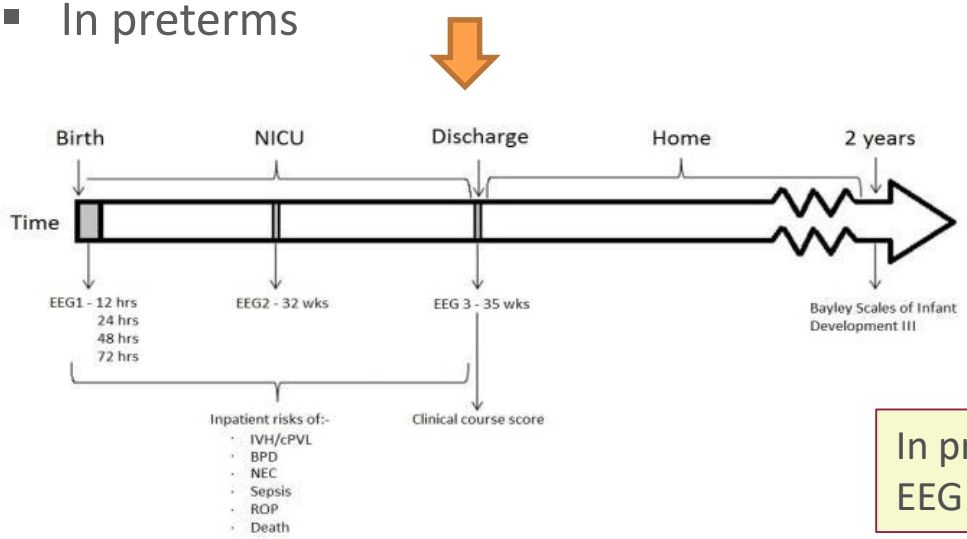


Thoresen et al, 2010

In terms with HIE: Background activity at 3-6 h in normothermia (NT) and hypothermia (HT)
Regain of normal background activity in 24h in NT, 48h in HT
Regain of normal sleep wake cycling in 24h for NT, 48h for HT

4.d. EEGs in preterms: Prediction of outcome

- In preterms



In preterms:
EEG at 35 weeks is best for predicting outcome

EEG Recording	Number	AUC	Sens	Spec	PPV %	NPV %
Early EEG first 72h	57	0.68	0.94	0.43	41	94
EEG - 32 weeks	53	0.84	1.00	0.68	50	100
EEG - 35 weeks	**45**	**0.91**	**1.00**	**0.83**	**63**	**100**

Lloyd et al. Arc Dis Child 2021

5.Indications to perform an EEG in neonates

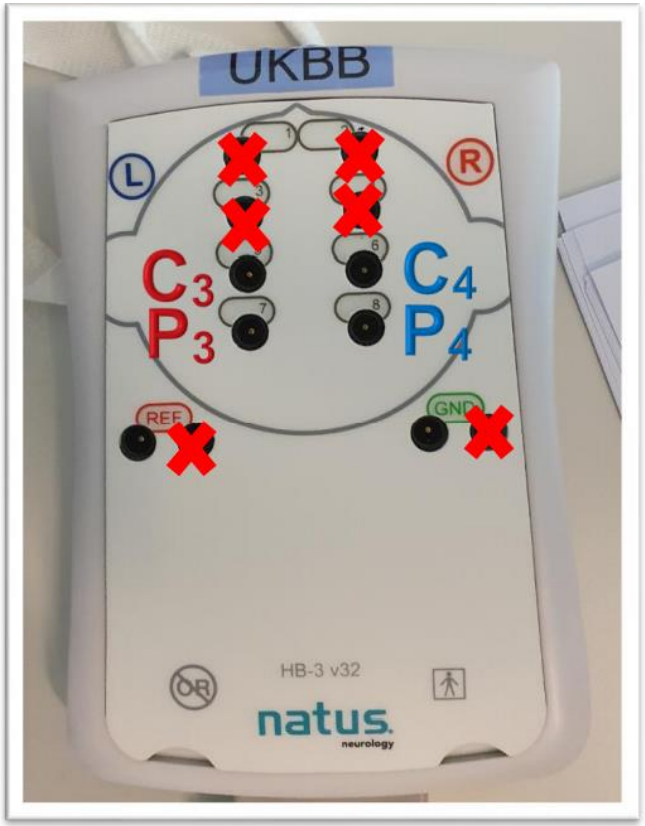
- maturation
- prediction of developmental outcome
- brain dysfunctions: focal or more diffuse
- clinical seizures
- epileptic activity
- electroclinical uncoupling (preterm)
- EEG pattern genetic and metabolic entities
- documentation of successful antiseizure treatment
- coma or altered consciousness, brain death

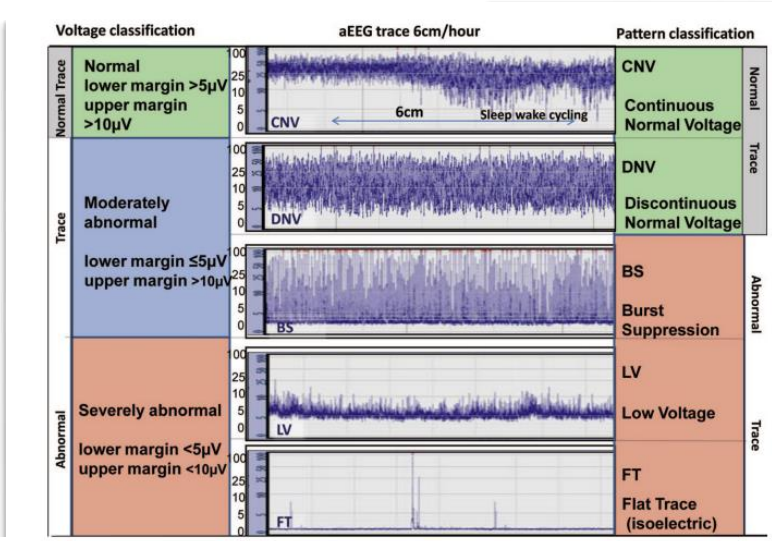
Recommended definitions of EEG background feature.

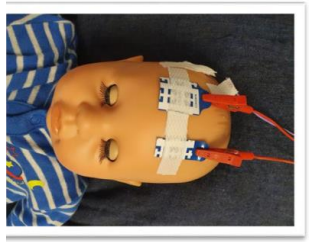
Patterns	Amplitude, duration or characteristics of EEG activity*
CNV[&]	Continuous background activity with voltage 10–25 (−50) μV but without sleep stages
DNV	Discontinuous trace, with voltage predominantly >5 μV
Burst suppression[#]	High voltage (>30 μV) delta (0.4–4 Hz) and theta (4–8 Hz) activities lasting 1–10 s with suppressed activity of <5 μV lasting >2 s
Modified burst suppression	High voltage (>30 μV) delta (0.4–4 Hz) and theta (4–8 Hz) activities lasting 1–10 s with suppressed activity of >5 μV lasting >2 s
Asymmetry	Consistent asymmetry by 20–50% between homologous areas of the brain can be treated as abnormal. Asymmetry should be present in all states (Holmes and Lombroso, 1993)
Asynchrony	Bursts are classified 'asynchronous' if their onset between hemisphere is separated by >1.5 s and exist unequally between the hemisphere. To measure asynchrony, 5 consecutive minute should be used (Holmes and Lombroso, 1993)
Low voltage	Continuous background patterns around 5 μV throughout the record
Flat trace	Mainly inactive (isoelectric tracing) with consistently <5 μV

* Age related issue need to consider while defining abnormal background feature. This is because pattern which is normal at preterm and may be treated as abnormal in term neonates (Hellström-Westas et al., 2006).

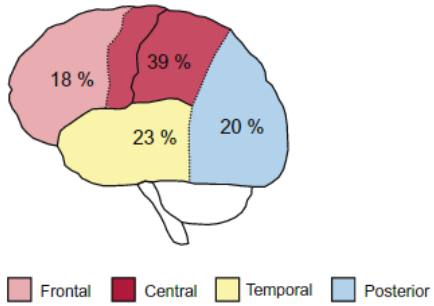
5.aEEG



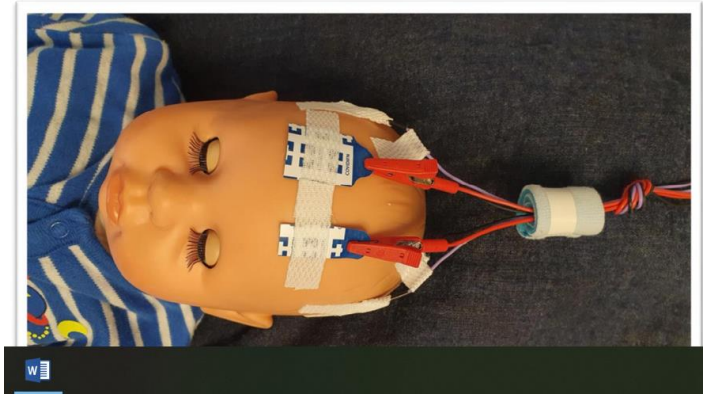




A Thoresen et al, 2010

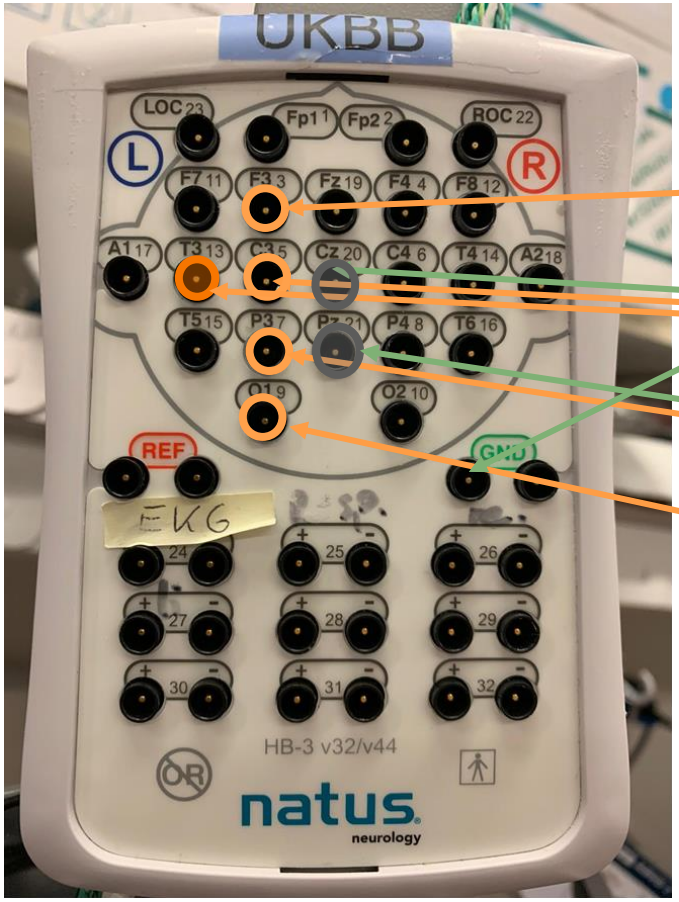


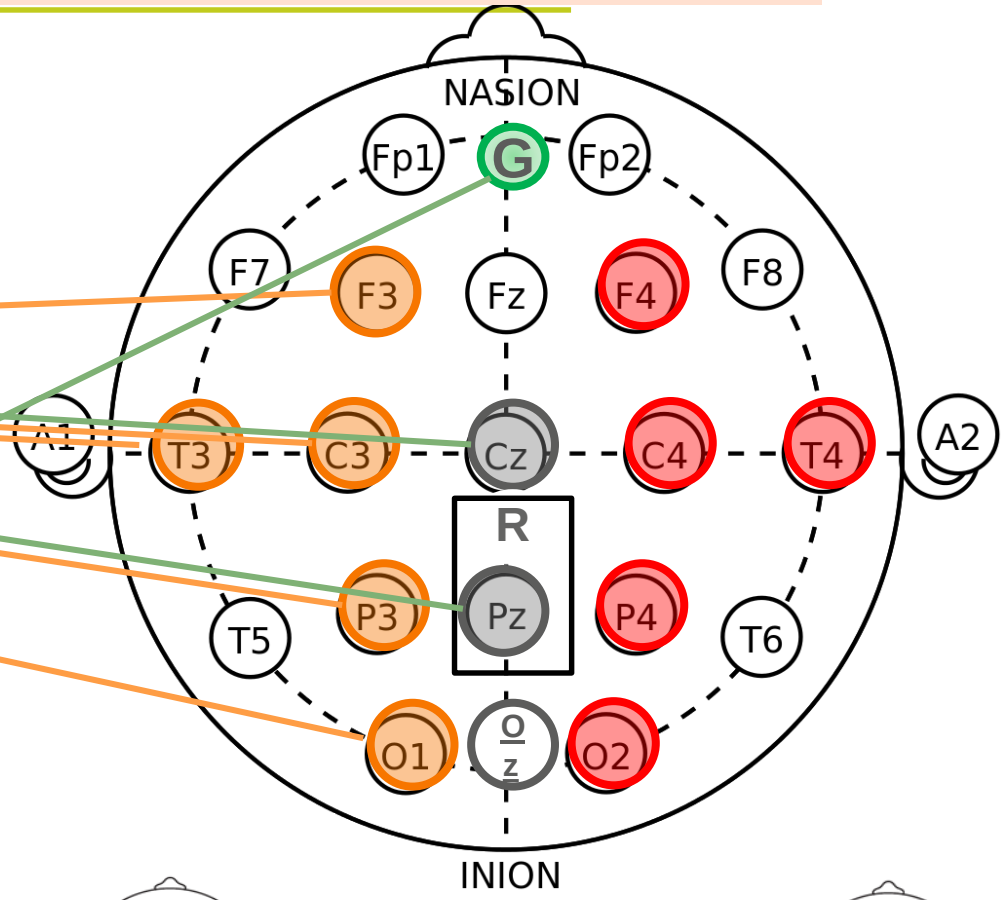
Janackova et al, 2016

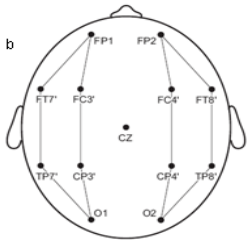


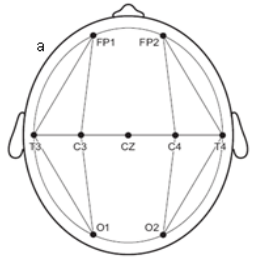
5. Full EEG in neonates

up to 3 months of age → 60-minute →1 cycle with AS and QS + wake







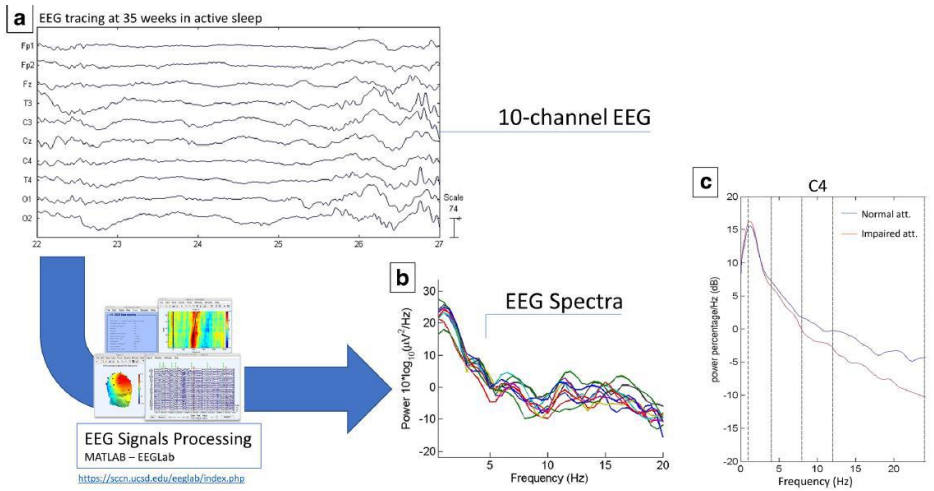


UK: Courtesy M. Alves, J. Kirkham and R. Pressler

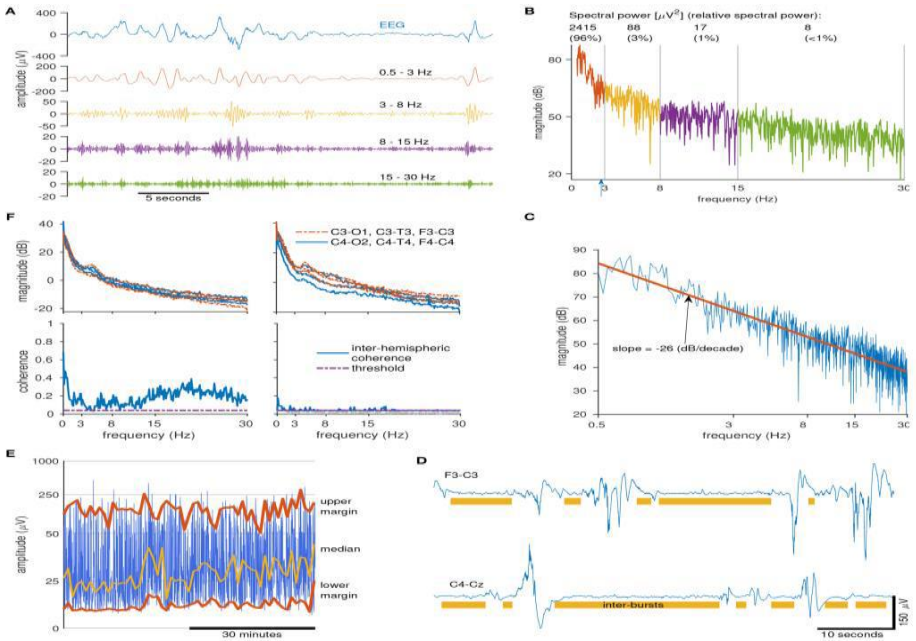
Dumermuth

American Epilepsy Society

5. Automatized seizure detection in continuous EEG



Cainelli et al Eur J Pediatr (2021) 180:909–918

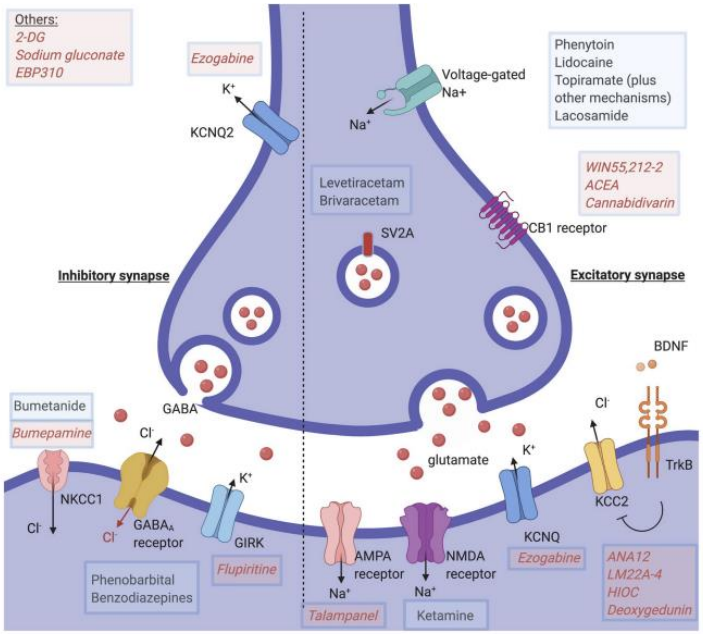


O'Toole & Boylan (2017) NEURAL: quantitative features for newbornEEG using Matlab, ArXive-prints

Alexandre.Datta@ukbb.ch

6. New recommendation for treatment

- In provoked/ symptomatic seizures → safe to discontinue ASM prior to discharge, especially if seizure free for 48-72h
- EEG at 3 months → not meaningfull for incidence epilepsy
  - 85% of children with abnormal EEG at 3 months did not develop epilepsy. Slaughter et al, 2013



Ziobro et la, 2021

6. New recommendation for treatment

- Phenobarbital 43% response rate, Phenytoin as second line 57% . Painter et al, 1999

- Lidocaine: seizure response 70%, higher response rate than Midazolam as second line, synergism with Midazolam, better in higher GA, stroke and hypothermia. Cardiac toxicity! Weeke et al, 2016

- NEMO study: Bumetamide; stopped for ototoxicity (Bumetamide, 2009).
- Bumetamide: Soul et al, 2021: good tolerability and efficacy, await phase 3 trial. Soul et al, 2021
- Bumetamide and Midazolam: in rat model Bumetamide no efficacy increase to Pheno. Johne et al, 2021

- NEOLEV: Phenobarbital respose rate 80%, Levetiracetam 28%, but Phenobarbital more side effects
  → Pheno possible deleterious effect on development. Sharpe et al, 2021

Farwell et al, 1990; Camfield et al, 1979

6. Treatment recommendations

To be ruled out at first:
Hypoglycemia
Hypocalcaemia
Hypomagnesemia
Hypo/Hypernatraemia
Hypokaliaemia

First choice	Second choice	Third choice	Dosage	
time →			loading dosage	maintenance
Phenobarbital i.v.			20-30 mg/kg, in 2 dosages	5 mg/kg/d
	Levetiracetam i.v.		20-40 mg/kg	40 mg/kg/d
	Phenytoin i.v.		20 mg/kg	5 mg/kg/d
	Lidocan i.v.		2 mg/kg over 10 min, then 6mg/kg/h over 6 h, 4 mg/kg/h over 12 h, 2 mg/kg/h ober 12 h	
		Benzodiazepines i.v.	MDZ: Bolus: 0.15 mg/kg, then 0.1-0.4 mg/kg/h. Bolus: CZP: 0.1 mg/kg, then 0.01 mg/kg	
		Topiramate p.o.		1-5 (-25mg/kg) mg/kg/d

Algorythm for treatable neonatal seizures in Co-factor deficiencies	Dosage: synchronous to the antiepileptic treatment	
time →	loading dosage	maintenance dose
Pyridoxin	100 mg i.v. 3-5 days	30 mg/kg/d
Pyridoxal Phosphate		30 mg/kg/d
Folinic acid		3-5 mg/kg/d
Biotin		20 mg/kg/d

Other potentially early infantile metabolic epilepsies	
Glucose transporter 1 deficiency	ketogenic diet
Serine deficiency syndromes	Serine
Creatine deficiency syndromes	Creatine
Phenylketonuria	Diet
Molybdaen Co factor deficieny	cyclic pyranopterin before onset of seizures

Datta AN, Kroell J, Rational antiepileptic treatment in childhood NeuroPsychopharmacotherapy, edited by Peter Riederer, Gerd Laux, Benoit Mulsant, Weidong Le and Toshiharu Nagatsu, 2020

6. Treatment recommendations

Epileptic Disease	Gene	Treatment
BFNE, BFNIE	SCN2A	CBZ, OXC, PHT, LTG
BFNE, BFNIE	SCN8A	CBZ, OXC, PHT, LTG
BFNE	KCNQ2	CBZ, OXC, PHT, LTG
BFNE	KCNQ3	CBZ, OXC, PHT, LTG
BFNIE	PRTT2	CBZ, OXC, PHT, LTG
DEE, epilepsy in infancy with migrating focal s.	SCN2A	CBZ, OXC, PHT, LTG
DEE, epilepsy in infancy with migrating focal s.	SCN8A	CBZ, OXC, PHT, LTG
DEE	KCNQ2, KCNQ3	CBZ, OXC, PHT, LTG
DEE, epilepsy in infancy with migrating focal s.	KCNT1	Quinidine (gain.of f.)
DEE, epilepsy in infancy with migrating focal s.	KCNT2	Quinidine (gain.of f.)
Pyridoxine-dependent epilepsy	ALDH7A1, ALDH7A	Pyridoxine
Pyridoxal-5 phospate dependent epilepsy	PNPO	Pyridoxal-5 phosphate
Folinic acid-responsive seizures	FOLR1	Folinic acid
Cerebral creatine deficiency syndrome 1	SLC6A8	Creatine + L-arginine and L-glycine
Cerebral creatine deficiency syndrome 2	GAMT	Creatine
Cerebral creatine deficiency syndrome 3	AGAT	Creatine
CAD deficiency, pyrimidine synthesis deficiency	CAD	Uridine monophosphate
Molybdenum cofactor deficiency	MOCS1	Cyclic pyranopterin monophosphate

Sands TT et al., 2016
Dilena R et al 2017
Numis AL et al, 2014.
Pisano T et al. 2015.
Chou IC et al, 2014.

DEE: Developmental and epileptic encephalopathy

GEFS+: Generalized eplepsy with febrile seizures +

BFNE: selflimiting (benign) neonatal epilepsy

BFNIE: selflimiting (benign) neonatal infantile epilepsy

DEE: Developmental and epileptic encephalopathy

Alexandre.Datta@ukbb.ch

Datta AN, Kroell J, Rational antiepileptic treatment in childhood NeuroPsychopharmacotherapy, edited by Peter Riederer, Gerd Laux, Benoit Mulsant, Weidong Le and Toshiharu Nagatsu, 2020

7. Outcome

- 84% have neurodevelopmental impairment; not limited to pharmacoresistant epilepsies
- Number of postnatal days with seizures → impact on development
- Neurological sequelae in 30%
- EEG: severe background or 3 or more days of seizures
- MRI: Basal ganglia or brain stem injury
- Abnormal tone on neurological examination at discharge

} >50% risk to develop spasms

- Mortality: Decreased from 40 to 20%.

- Permanent impairment in cognition incl. learning, memory and seizure susceptibility may result from seizure induced changes in neuronal connectivity and receptor expression

Shellhaas et al, 2021; Silverstein et al, 2007; Ramantani et al, 2019; Ben-Ari & Holmes, 2005; Brooks-Kayal, 2005

8. Conclusions

- Subtle nature of seizures in neonates: Overdiagnosis and under-recognition at the same time!
- Seizure incidence at neonatal age high: 85% are symptomatic seizures. Epilepsy only 15%.
- Seizures at term age: full EEG 1rst day of cooling, aEEG 72 h at least, then full EEG and MR scan; continuous full EEG would be ideal.
- Seizures at preterm age rather overestimated, full EEG before treating with ASM.
- Uncoupling due to immaturity and ASM (Phenobarbital): check with EEG!

8. Conclusions

- Background activity, regain of normal background activity, sleep wake cycling and MR scan important prognostic factors in terms, EEG around term in pretems.
- EEG should last 1 h in order to capture also sleep.
- Rule out treatable metabolic epilepsies, simutaneoulsy Phenobarbital before Levetiracetam, Phenytoin, Lidocain. Some mutations specific treatments for neonatal epilepsy syndromes.
- Seizures need to be treated because of neurodevelopmental impairment independent from the seizure origin.

Thank you very much

alexandre.datta@ukbb.ch