Crises e Síndromes Epilépticas Período Neonatal

Dra. Magda Lahorgue Nunes

Professora Titular de Neurologia Escola de Medicina da PUCRS

Sem conflitos de interesse a declarar
Apoio CNPq – Edital PQ 303168/2021-8

Em consideração aos pais que cederam as imagens para esta aula favor não fotografar ou gravar a apresentação

CC Neonatal

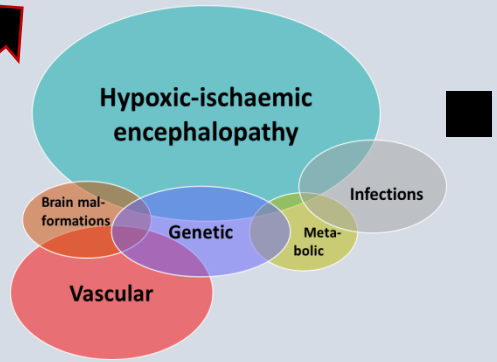
Incidência

Relativamente comum (1-3.5 :1000 nascimentos)

(Ronnen et al 1999; Berg et al 2012)

Evento agudo associado a varias etiologias

(Glass et al 2016, Cornet et al.2021)



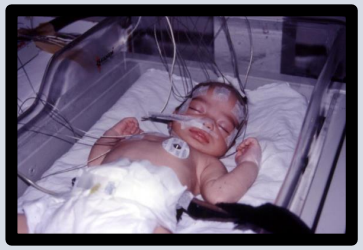
Desafios do diagnostico

Evento agudo x Epilepsia

(Shellhaas et al,2021; Zuberi et al.2022)

Dissociação eletro clinica

(Kellaway & Mizhari, 1987)



Influencia no prognóstico neurológico

(Shellhaas et al,2021)

Desafio terapêutico

(Painter et al 1999; Boylan et al 2003; WHO Guidelines on Neonatal Seizures 2011, Pressler & Mangum 2013)

CC Neonatal

Definição

- Evento agudo reativo associado a uma grande variedade de fatores etiológicos, decorrente de desequilíbrio entre sistema inibitório (GABA) e excitatório (Glutamato e aspartato).

Incidência

- Estudos em população de risco : 24.2/1000 recém nascidos – pacientes selecionados em UTINEO (Silva et al. 2004)
- Estudos de base populacional:
- 1.0 -3.5 / 1000 recém nascidos (Lanska et al. 1995, Saliba et al. 1999, Ronen et al. 1999)

- Geral USA
- 0.26/1000 nascidos a termo (Berry et al. 2017)

Considerações gerais

- Maioria das CC neonatais são eventos sintomáticos agudos (provocados)
- 10-15% das CC que iniciam no período neonatal podem ser a manifestação inicial de síndromes epilépticas
- Entretanto.... a maioria das CC sintomáticas agudas não evoluem para epilepsia pós neonatal

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Evento agudo associado a várias etiologias

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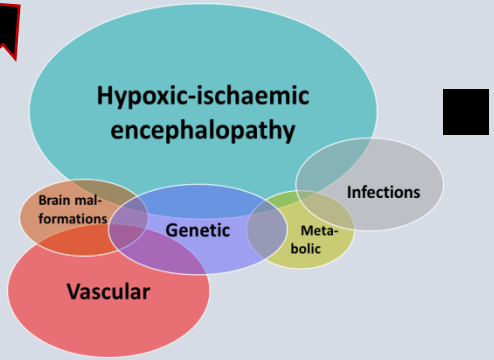

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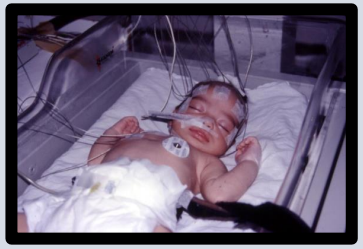

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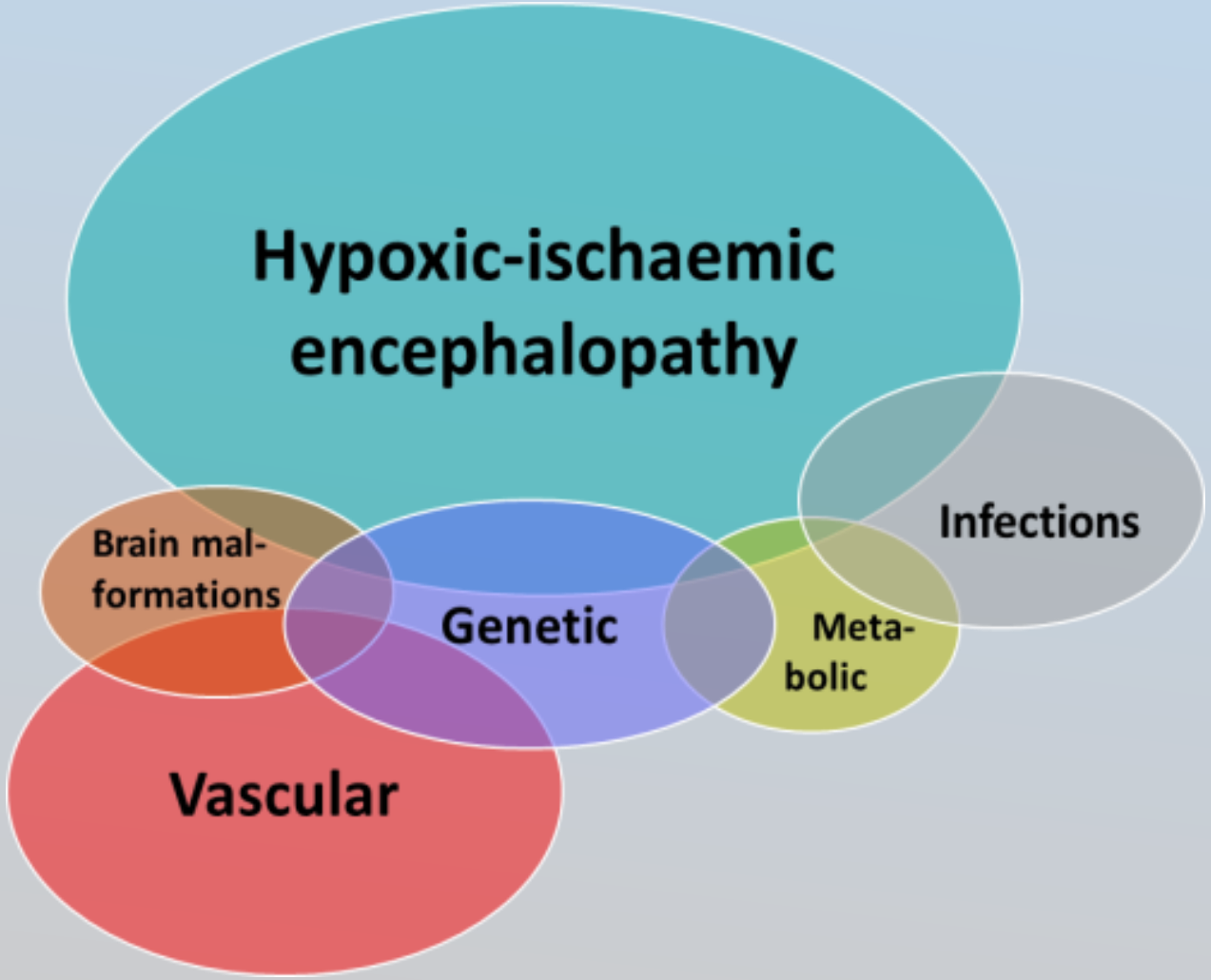
Prevalência das diferentes etiologias

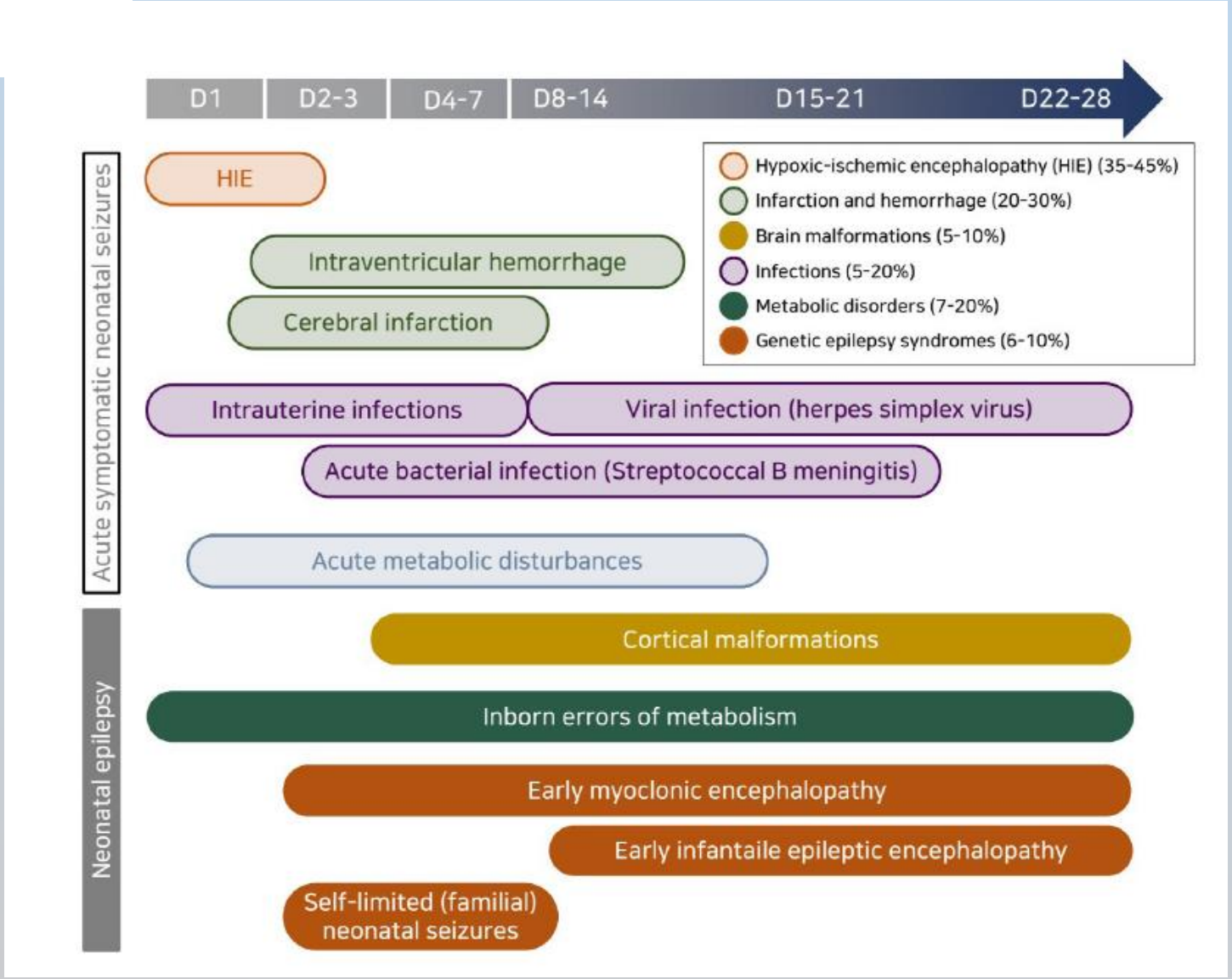


CEP Clin Exp Pediatr Vol. 65, No. 8, 387-397, 2022
https://doi.org/10.3345/cep.2021.01361

Rev

Neonatal seizures: diagnostic updates based on new definition and classification

Eun-Hee Kim, MD, PhD, Jeongmin Shin, MD, Byoung Kook Lee, MD



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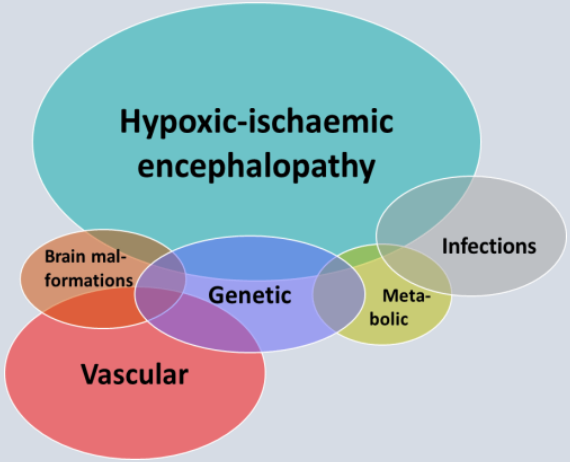

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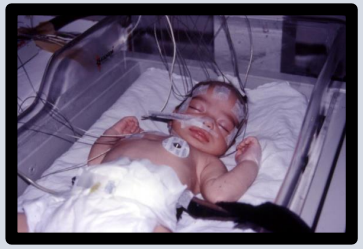

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Evento agudo x epilepsia: papel da etiologia

Evento agudo

Infecção

EHI

Vascular

Desconhecida

Epilepsia

Metabólica

Malformação SNC

Genética

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Seizures and paroxysmal events: symptoms pointing to the diagnosis of pyridoxine-dependent epilepsy and pyridoxine phosphate oxidase deficiency

BERNHARD SCHMITT[1] | MATTHIAS BAUMGARTNER[1] | PHILIPPA B MILLS[2] | PETER T CLAYTON[2] | CORNELIS JAKOBS[3] | ELMAR KELLER[4] | GABRIELE WOHLRAB[1]

Pyridox(am)ine-5-Phosphate Oxidase Deficiency Treatable Cause of Neonatal Epileptic Encephalopathy With Burst Suppression: Case Report and Review of the Literature

Journal of Child Neurology
2015, Vol. 30(9) 1218-1225

DOI: 10.1177/0883073814550829
jcn.sagepub.com
SAGE

Andrea Guerin, MD[1], Aly S. Aziz, MD[2], Carly Mutch, OT[3], Jillian Lewis, MD[4], Cristina Y. Go, MD[2], and Saadet Mercimek-Mahmutoglu, MD, PhD[1,5]

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 15 (2011) 74–77

ELSEVIER

Official Journal of the European Paediatric Neurology Society

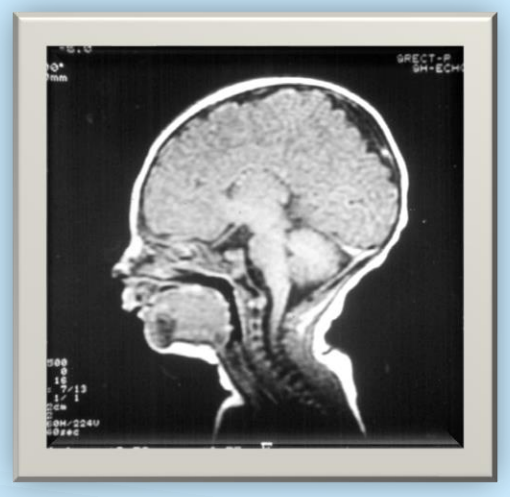
Case study

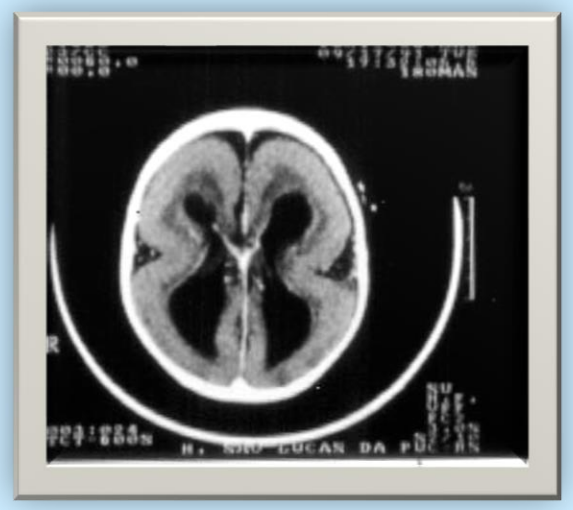
Novel mutations in pyridoxine-dependent epilepsy

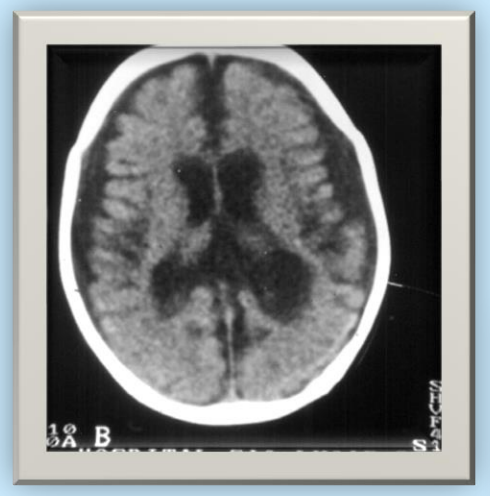
A. Millet[a], G.S. Salomons[c], F. Cneude[a,*], C. Corne[b], T. Debillon[a], C. Jakobs[c], E. Struys[c], S. Hamelin[d,e]

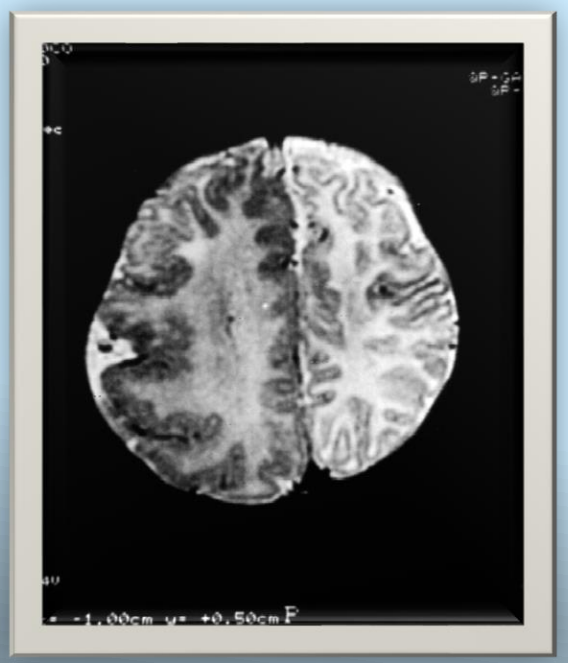
Mutações no gene PNPO ou ALDH7A

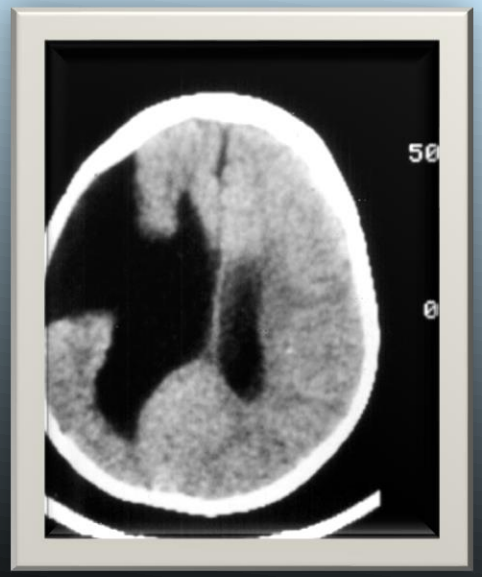
Malformações do desenvolvimento SNC

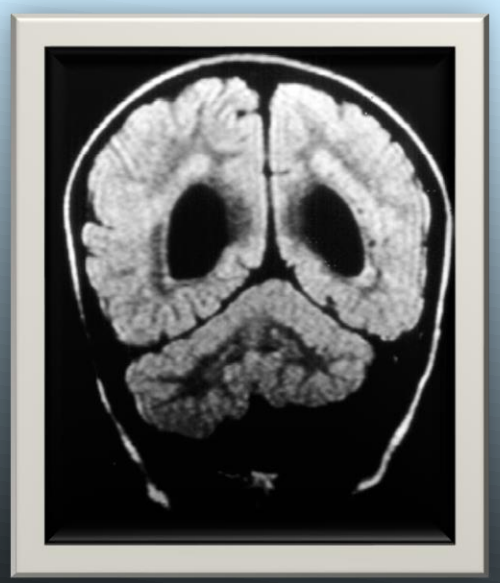


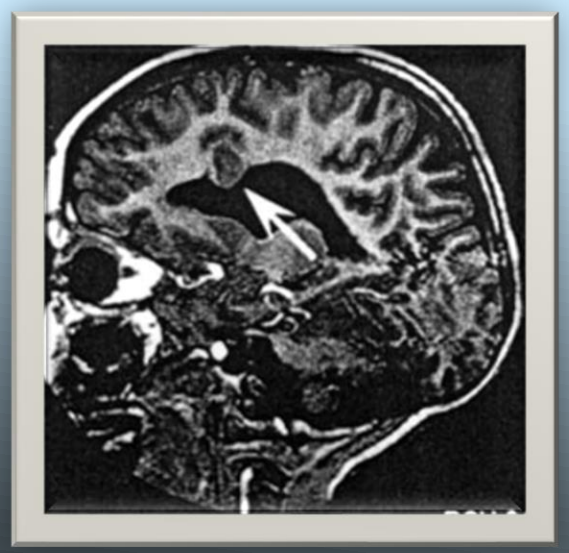






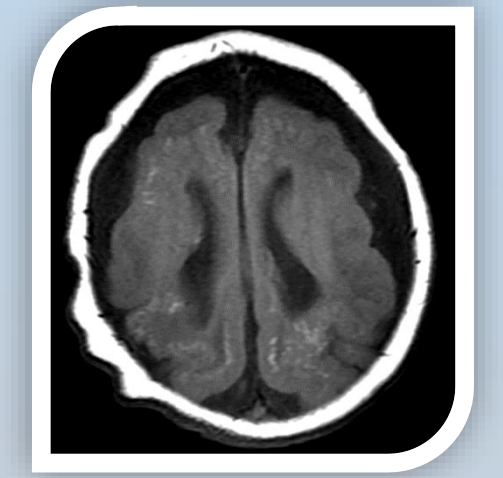




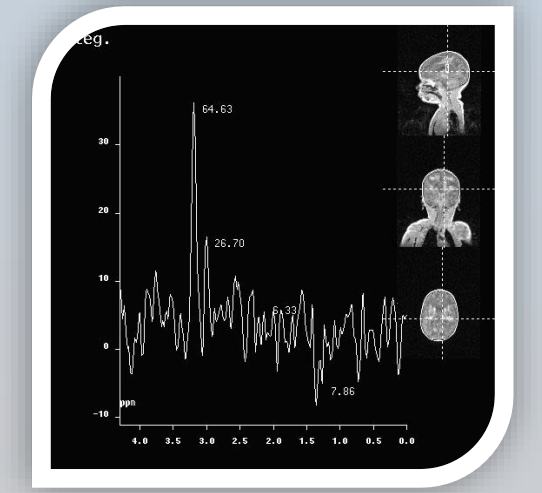


Algumas etiologias mesmo iniciando como evento agudo levam a maior risco de epilepsia pós neonatal

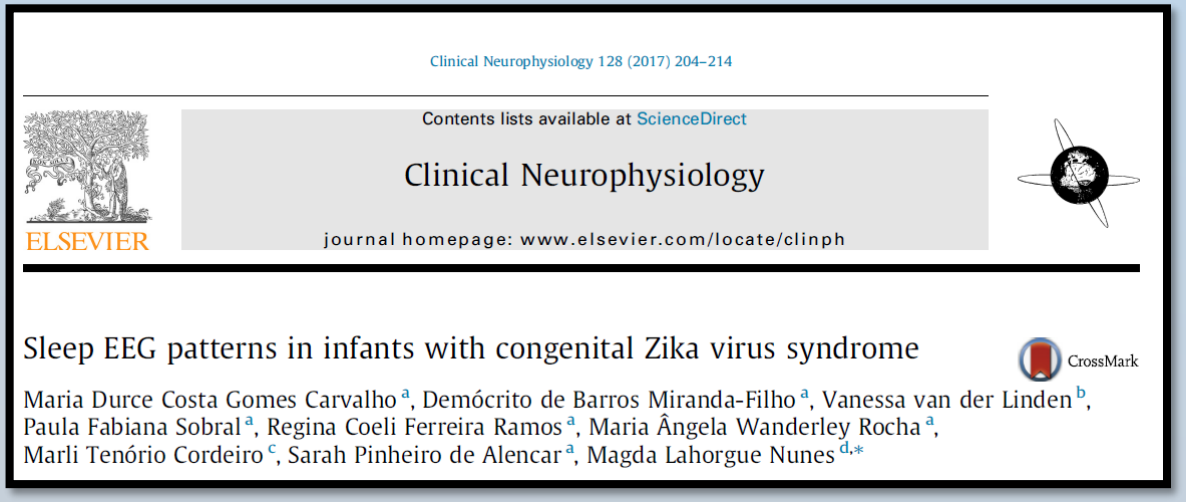
Infecção



EHI



Epilepsia após infecção congénita pelo virus Zika



Clinical Neurophysiology 128 (2017) 204–214

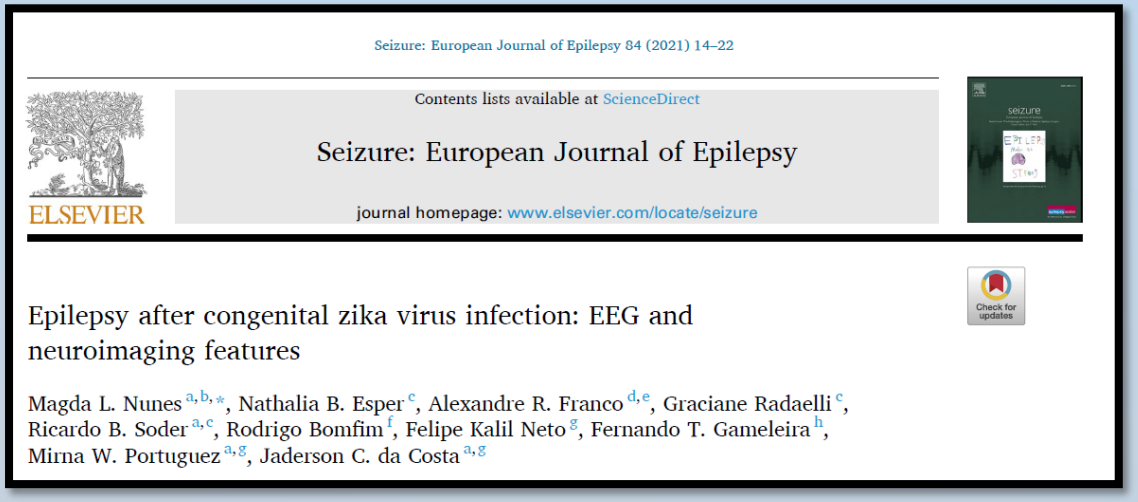
Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Sleep EEG patterns in infants with congenital Zika virus syndrome

Maria Durce Costa Gomes Carvalho [a], Demócrito de Barros Miranda-Filho [a], Vanessa van der Linden [b], Paula Fabiana Sobral [a], Regina Coeli Ferreira Ramos [a], Maria Ângela Wanderley Rocha [a], Marli Tenório Cordeiro [c], Sarah Pinheiro de Alencar [a], Magda Lahorgue Nunes [d,*]



Seizure: European Journal of Epilepsy 84 (2021) 14–22

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Epilepsy after congenital zika virus infection: EEG and neuroimaging features

Magda L. Nunes [a,b,*], Nathalia B. Esper [c], Alexandre R. Franco [d,e], Graciane Radaelli [c], Ricardo B. Soder [a,c], Rodrigo Bomfim [f], Felipe Kalil Neto [g], Fernando T. Gameleira [h], Mirna W. Portuguez [a,g], Jaderson C. da Costa [a,g]

Pernambuco cohort
N=37 infants
Mean age = 2.6 (1-5 months)
Abnormal background (59.5%):low voltage (n = 7), asymmetrical voltage between hemispheres (n = 6) and hypsarrhythmia with or without burst–suppression (n = 11)
Interictal EEG abnormalities (62%) : focal or multifocal spikes
Ictal EEG = 4 (10%)

Alagoas cohort
N=43 infants
Mean age F/U = 25.5 ± 6.01 months
Sz started < age 3 months = 35%
Active epilepsy = 41 **(95%)**
Ictal EEG = 22 (51%)

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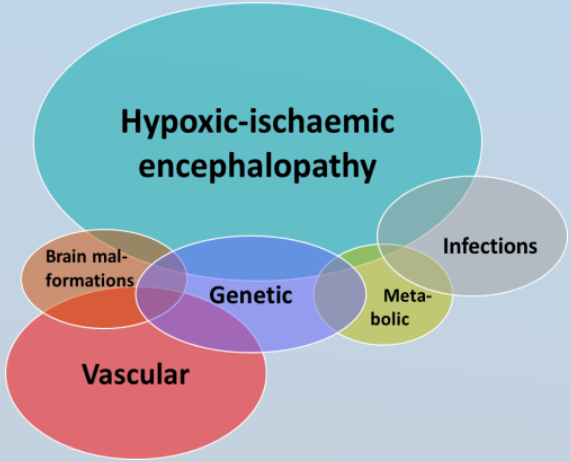

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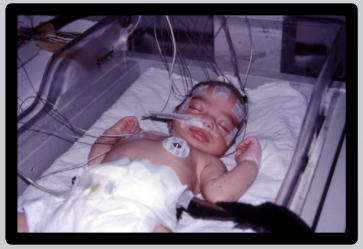

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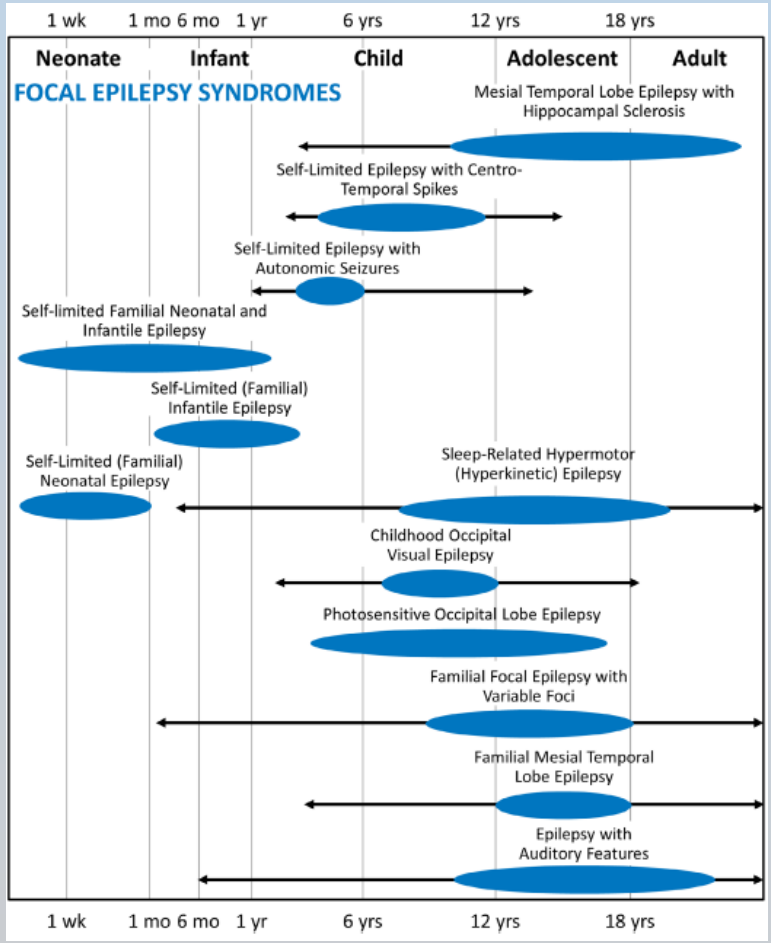
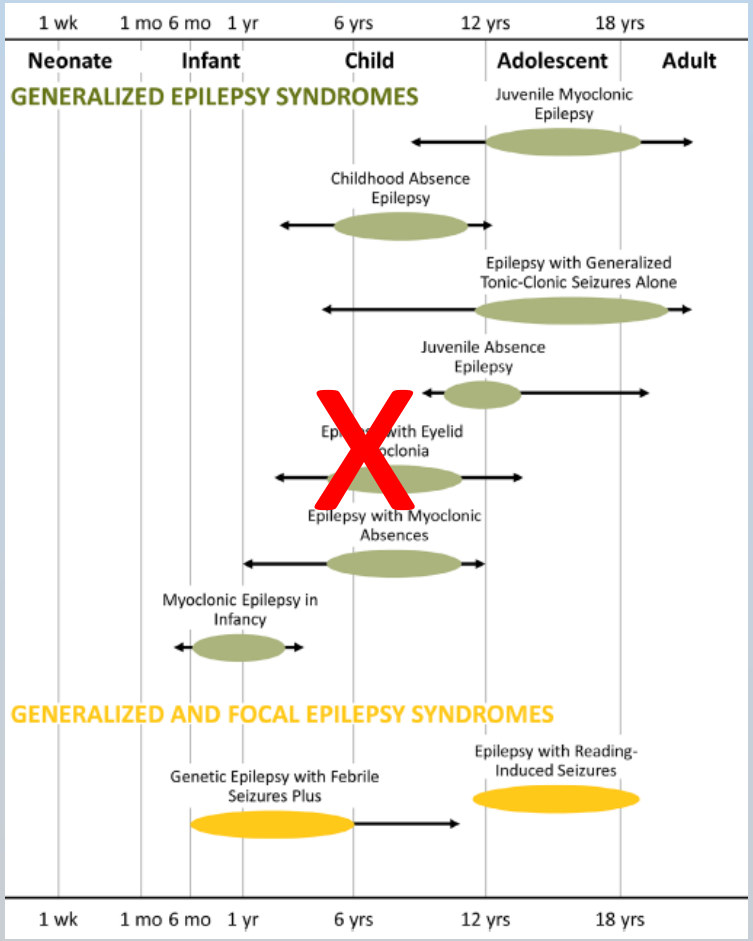
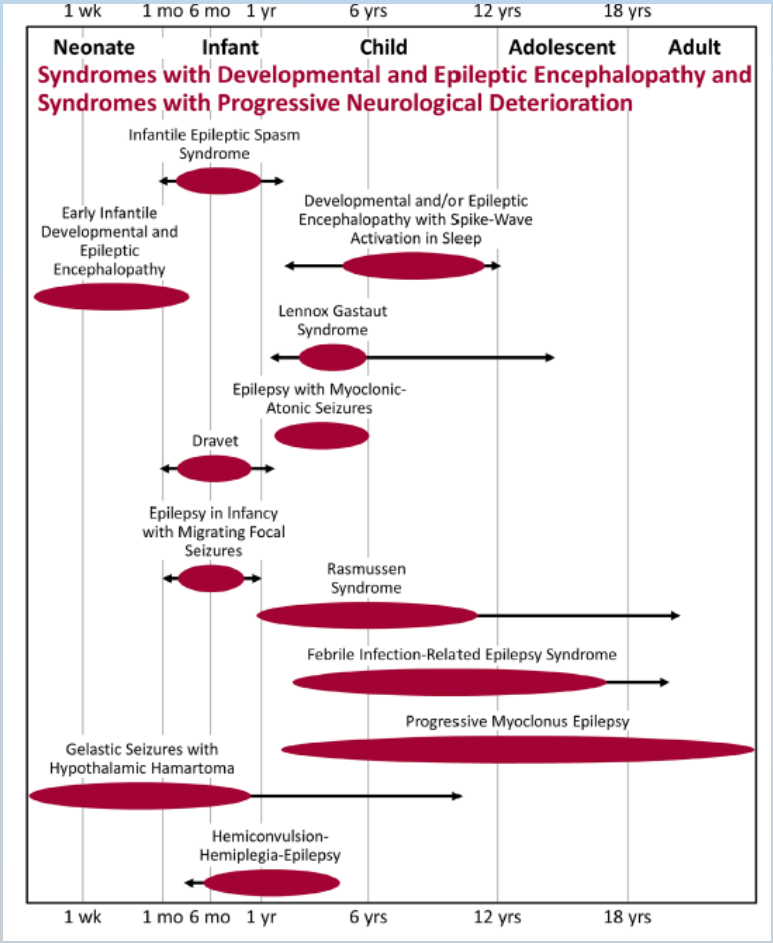
Síndromes epilépticas ao longo da vida



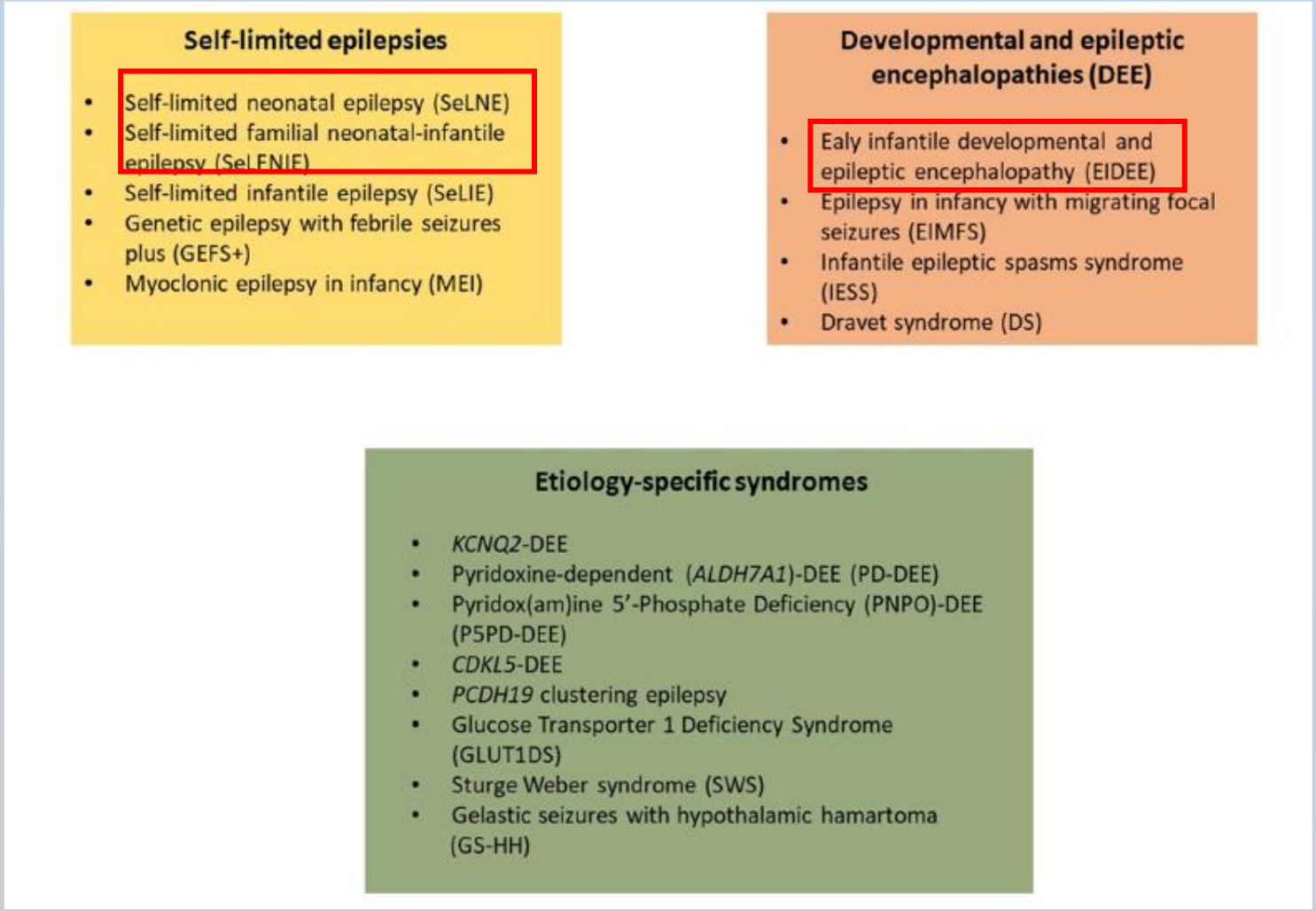




Wirrel et al. Epilepsia 2022- DOI: 10.1111/epi.17237

SPECIAL REPORT

ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions



Zuberi et al. Epilepsia 2022- DOI: 10.1111/epi.17239

Epilepsia neonatal (familial) auto-limitada

Self-Limited (Familial) Neonatal Epilepsy

- **Contexto clinico:** as crises iniciam em torno do 2-7o dia vida, (em prematuros na idade corrigida de 40 semanas), ambos sexos afetados de forma equivalente, hx da gestação e parto sem intercorrências, PC e EN ambos normais.
- **Epidemiologia :** incidência estimada de 5.3/ 100.00 nascidos vivos
- **Semiologia CC:** predomínio de clônica e tonica focal em face e membros, lateralização variável, podem progredir na forma sequencial incluindo mioclônica e autonômica (apnéia e/ou cianose frequentes) e automatismos. A crises tem duração de minutos e são amis longas que em eventos agudos . Ocorrem em salvas com neonato normal entre as crises
- **Evolução:** Remissão até 6 meses de vida (maioria até 6 semanas). DNPM normal, (raros relatos de atraso ou dificuldade aprendizagem) 1/3 pode ter outras CC (crise febril, salvas de crises focais, TCG isolada, rolandicas). Algumas variantes genéticas levam a miokimia (contração muscular continua com rigidez e torção) **EEG:** ritmo de base geralmente normal. Anormalidades epileptiformes focais podem ocorrer (regiões CT, FT). Padrão “theta pointu alternant” em torno de 50% . Eventual alentecimento focal ou generalizado r nos períodos com mais crises. Padrão ictal: atenuação do EEG (±20s) seguido por descargas de pontas (geralmente CT) bilateral e assíncrona. Topografia e lateralidade podem mudar a cada episodio.
- **Neuroimagem:** normal
- **Genética:** Herança autossômica dominante com penetrância variável. Mutações *de novo* do KCNQ2 and KCNQ3. Na familiar a historia de crises neonatais autolimitadas tem que ser positiva. Variações patogênicas do KCNQ2 é achado mais comum. KCNQ3 e SCN2A são menos frequentes.

Epilepsia neonatal- infantil (familial) autolimitada

Self-Limited (Familial) Neonatal-Infantile Epilepsy

- **Contexto clinico :** Síndrome autossômica dominante com inicio no período neonatal ou até 23 meses de vida (media 11 semanas). As crises iniciam a partir do 2º dia de vida. A hx familiar auxilia no diagnóstico, tratamento, investigação e prognostico.
- **Epidemiologia:** incidência desconhecida
- **Semiologia CC:** Inicialmente observa-se desvio ocular e da cabeça, seguido por crises clônicas e tônicas. Pode ocorrer apneia ou olhar fixo. Duração: entre 20s a 4 minutos. Podem ocorrer em salvas e serem recorrentes (horas/dias). A frequência das crises varia muito de individuo a individuo , em alguns casos não é necessário uso de FAC. Cessam em torno de 12-24 meses e geralmente não recorrem.
- **Evolução:** DNPM, EN e PC normais
- **EEG:** ritmo de base normal. No período de crises mais ativas pode ocorrer descargas focais em regiões posteriores ou alentecimento generalizado. EEG interictal pode ter descargas posteriores ou rolandicas.
- **Neuroimagem :** normal
- **Genética:** herança autossômica dominante com penetrância variável observada em vários membros da família. Variantes do SCN2A ou mais raramente KCNQ2 . Nos casos não familiares mutações *de novo*.

Encefalopatias epilépticas e/ou do desenvolvimento do período neonatal

- Encefalopatia mioclônica precoce

  (Aicardi & Goutiéres , 1978)

- Encefalopatia epiléptica infantil precoce

  (Ohtahara et al. 1976)

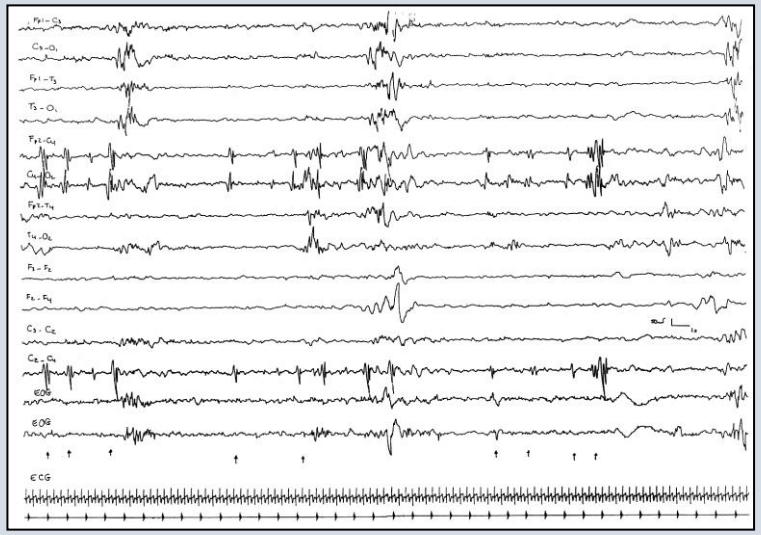
- Crises refratarias
- Múltiplas etiologias

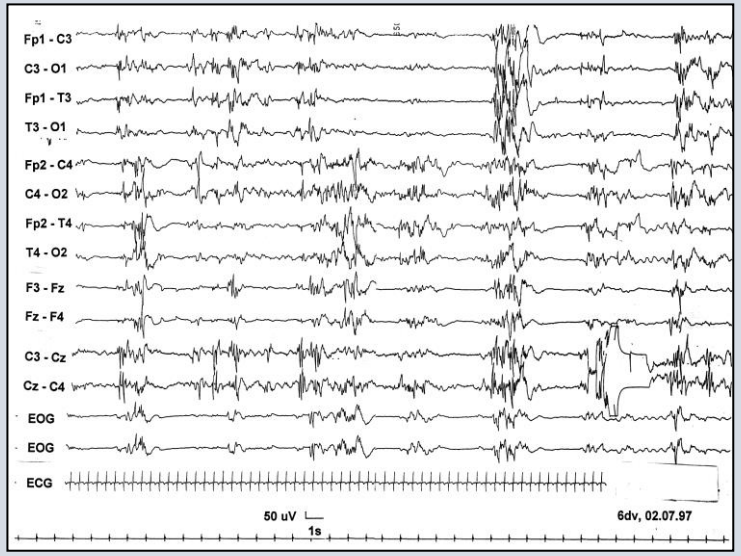
  EMP –mais associada a EIM

  EEIP – mais associada a disgenesia e EIH
- Semiologia

  EMP- mioclonias maciças ou fragmentarias e erráticas, crises motoras focais.

  EEIP- crises tônicas focais isoladas ou em salvas
- Farmacorresistentes
- EEG com padrão de SS
- Elevada morbi-mortalidade





Encefalopatias epilépticas e/ou do Desenvolvimento (Early-Infantile Developmental and Epileptic Encephalopathy)

- **<u>Características</u>**
- Inicio antes do 3o mês de vida , crises frequentes fármaco- resistentes
- Etiologia: variável (Inclui dx prévio de Ohtahara e Epilpesia mioclônica precoce (EMP)
- Epidemiologia : 10/100.000 nascidos vivos
- Exame neurológico anormal (tônus, postura, movimentos) . Hx familiar , parto e nascimento: sp . PC varia com etiologia mas geralmente normal ao nascimento
- Semiologia das crises : tônica focal ou generalizada, mioclônica, clônica focal, crises sequenciais e espasmos epilépticos.
- EEG interictal anormal : padrão de surto-supressão , alentecimento difuso ou descargas multifocais
- Neuroimagem, testes metabólicos e/ou genéticos permitem definir etiologia (80%)
- Curso clinico/EEG: crises refratarias (exceto nas metabólicas/genéticas ou estruturais com alvo para terapia de precisão). Evoluem com frequência para West. Déficit intelectual profundo. O padrão SS evolui para hispssaritmia ou EEG multifocal. Podem apresentar transtornos paroxísticos não epilépticos associadamente (tremor, coreia, distonia). Diversas co-morbidades associadas (déficit cortical visual, déficit motor, problemas ortopédicos- comportamentais-deglutição, elevada morbimortalidade. Declínio moderado a profundo do DNPM evidenciado no seguimento

Fenótipo x genótipo :

- *KCNQ2*- DEE – crises sequenciais (componente Tonico predominando E EEG SS
- *SCN2A*-DEE – crises sequenciais (tônica, autonômica).
- *SCN8A-DEE – crises focais*
- *STXBP1-DEE- crises tonicas assimétricas ou sequenciais* .
- *CDKL5*-DEE – crise tônicas (espasmo tônico hipermotor)
- *KCNT1*-DEE – crises tônica focais ou autonômicas .
- *UBA5*-DEE - crises mioclônicas

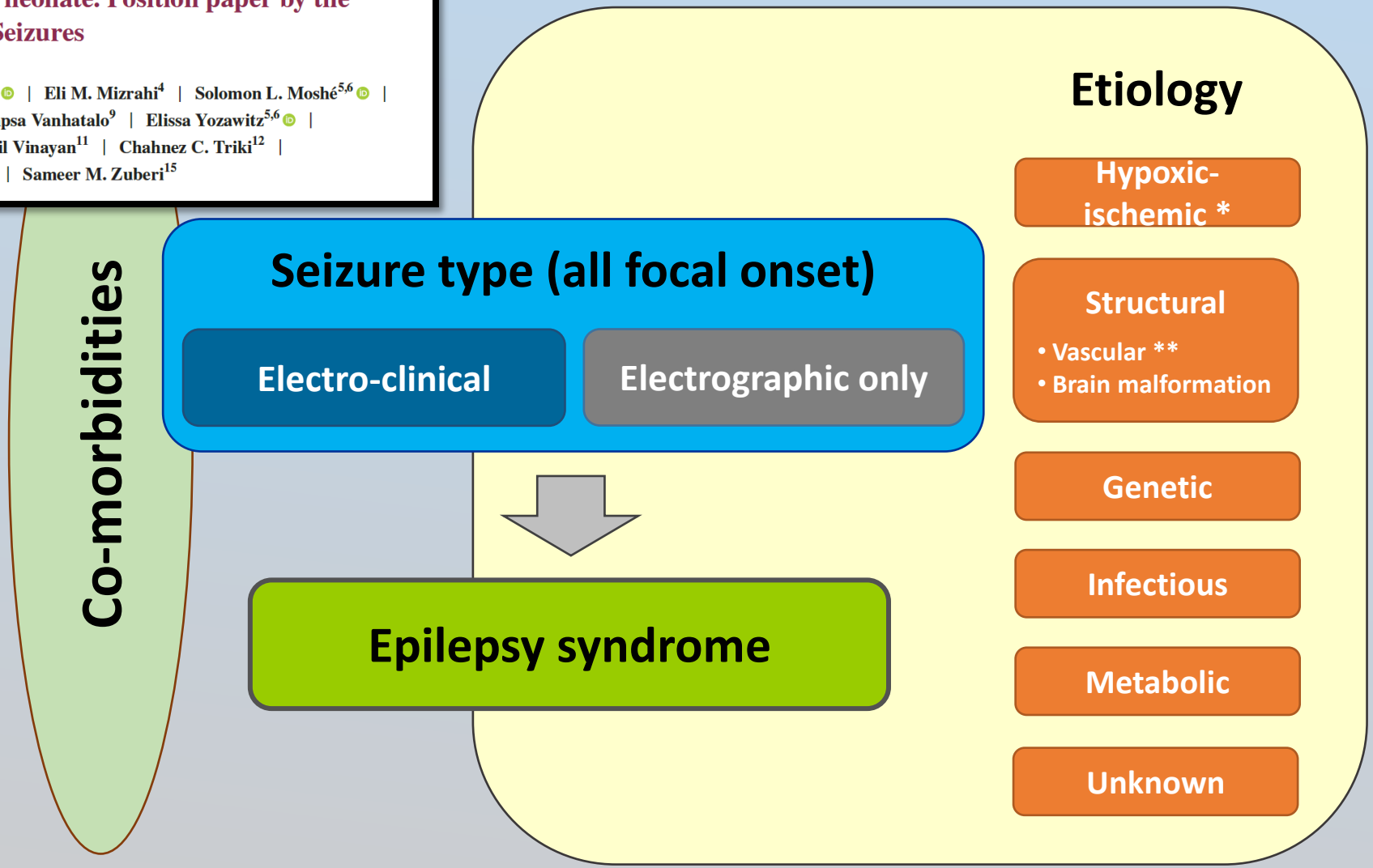
Received: 8 August 2020 | Revised: 23 December 2020 | Accepted: 23 December 2020
DOI: 10.1111/epi.16815

Epilepsia®

SPECIAL REPORT

The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures

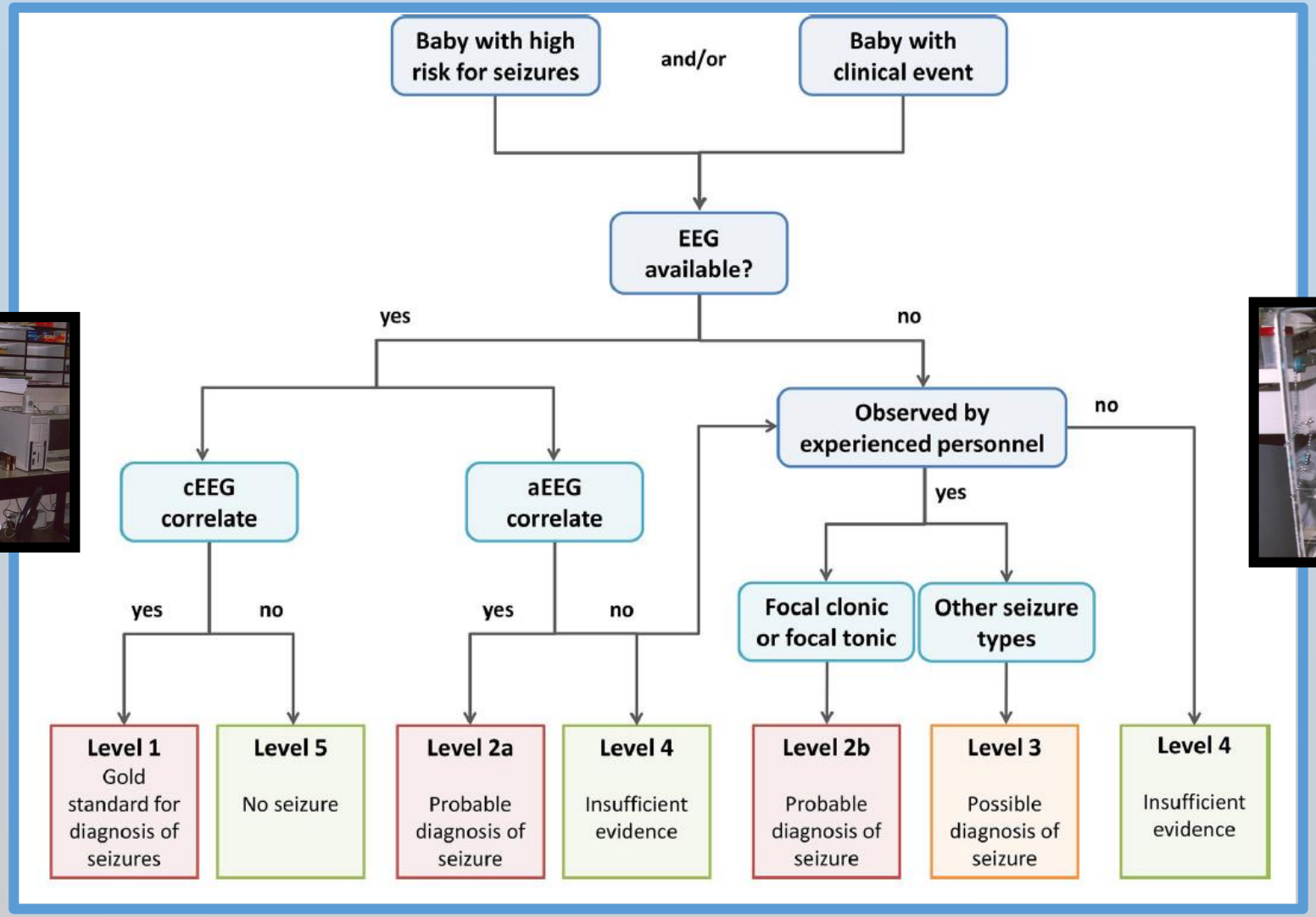
Ronit M. Pressler[1,2] | Maria Roberta Cilio[3] | Eli M. Mizrahi[4] | Solomon L. Moshé[5,6] | Magda L. Nunes[7] | Perrine Plouin[8] | Sampsa Vanhatalo[9] | Elissa Yozawitz[5,6] | Linda S. de Vries[10] | Kollencheri Puthenveettil Vinayan[11] | Chahnez C. Triki[12] | Jo M. Wilmshurst[13] | Hitoshi Yamatomo[14] | Sameer M. Zuberi[15]

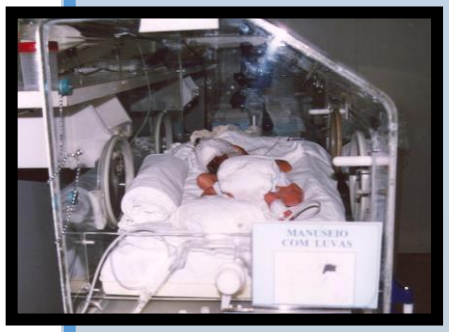


* Including perinatal hypoxic-ischaemic encephalopathy and other hypoxic events in the neonatal period

** Including acute ischemic stroke, haemorrhage (intraventricular, subarachnoid, intraparenchymal) and other vascular induced ischemia (such as periventricular leukomalacia)

Porque a semiologia é importante?





Algorithm developed by the Brighton collaboration (adapted from Pelegrin et al 2019)

Received: 8 August 2020 | Revised: 23 December 2020 | Accepted: 23 December 2020

DOI: 10.1111/epi.16815

Epilepsia

SPECIAL REPORT

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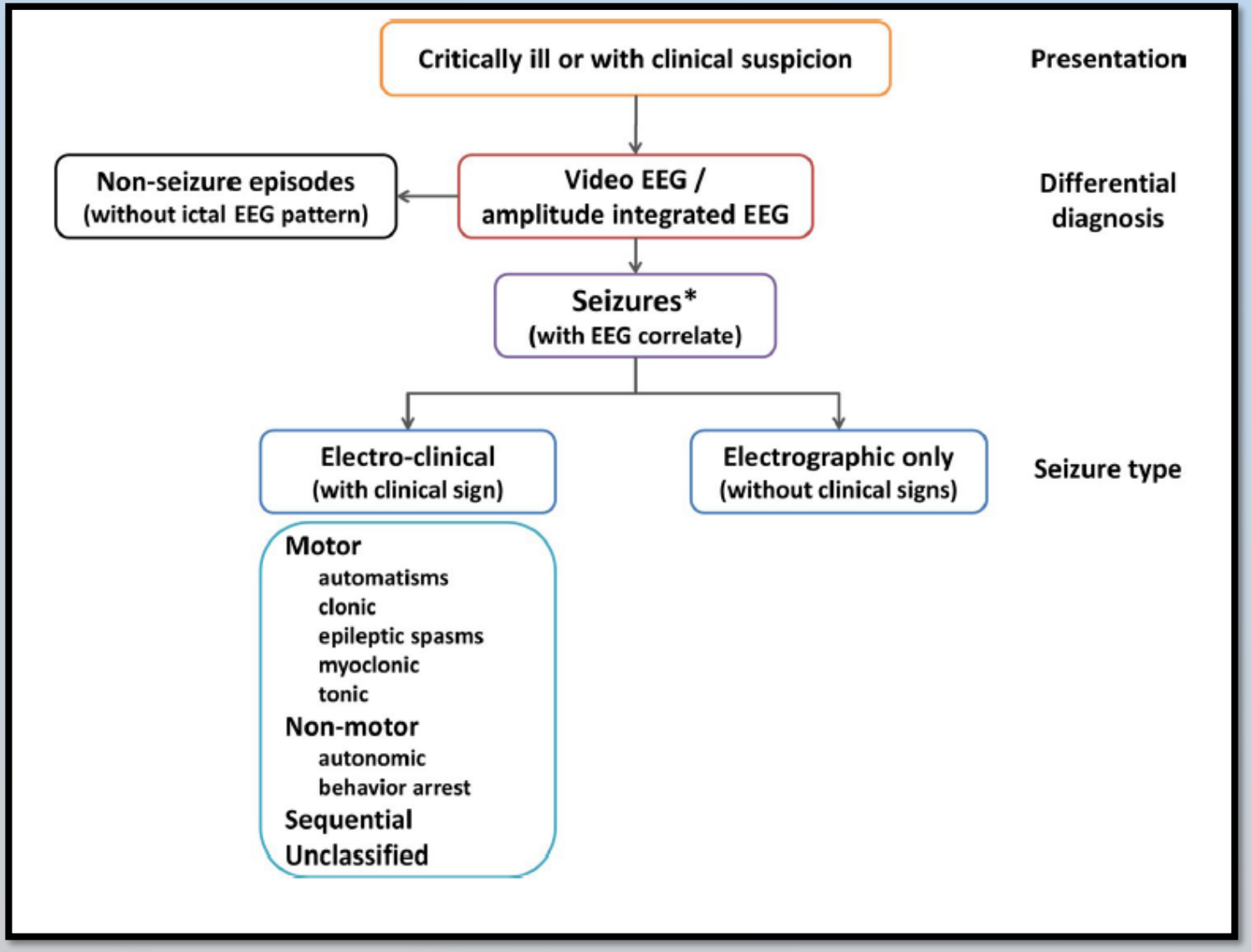

Integração com a classificação ILAE -2017

Tables

Type	Description [7,39]	Special considerations for neonates
Automatisms	A more or less coordinated motor activity usually occurring when cognition is impaired. This often resembles a voluntary movement and may consist of an inappropriate continuation of preictal motor activity	Typically, oral and usually in association with other features. Normal and abnormal behavior in term and preterm infants may mimic ictal automatisms. [9,86]
Clonic	Jerking, either symmetric or asymmetric, that is regularly repetitive and involves the same muscle groups	Seizure type which is more reliably diagnosed clinically compared to other seizure types. [9,12]
Epileptic spasms	A sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles that is usually more sustained than a myoclonic movement but not as sustained as a tonic seizure. Limited forms may occur: Grimacing, head nodding, or subtle eye movements. May occur in clusters.	Rare. May be difficult to differentiate from myoclonic seizures without EMG channel. [50,87-89]
Myoclonic	A sudden, brief (<100 msec) involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).	Clinically difficult to differentiate from non-epileptic myoclonus. [50,89-92]
Sequential seizure	This term is used in the instruction manual for the ILAE 2017 operational classification of seizure types for events with a sequence of signs, symptoms, and EEG changes at different times. [39]	No predominant feature can be determined, instead the seizure presents with a variety of clinical signs. Several features typically occur in a sequence, often with changing lateralization within or between seizures [93].
Tonic	A sustained increase in muscle contraction lasting a few seconds to minutes.	Usually focal, unilateral or bilateral asymmetric. Generalized tonic posturing is often not of epileptic origin [9,87].
Autonomic	A distinct alteration of autonomic nervous system function involving cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, and thermoregulatory functions.	May involve respiration (apnea). Typically seen with other seizure manifestations. EEG confirmation mandatory [9,94].
Behavioral arrest	Arrest (pause) of activities, freezing, immobilization, as in behavior arrest seizure.	May be followed by apnea, other autonomic manifestations and motor seizures. [95]
Unclassified seizure type	Due to inadequate information or unusual clinical features with inability to place in other categories.	

Seizure type	Descriptors
Automatisms	Unilateral Bilateral asymmetric Bilateral symmetric
Clonic seizures	Focal Multifocal Bilateral
Epileptic spasms	Unilateral Bilateral asymmetric Bilateral symmetric
Myoclonic seizures	Focal Multifocal Bilateral asymmetric Bilateral symmetric
Tonic seizures	Focal Bilateral asymmetric Bilateral symmetric

Received: 3 June 2022 | Accepted: 13 September 2022

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Epileptic Disorders

ORIGINAL ARTICLE

Application of the International League Against Epilepsy Neonatal Seizure Framework to an international panel of medical personnel

Elissa G. Yozawitz[1] | Maria R. Cilio[2] | Eli M. Mizrahi[3] | Jee-Young Moon[4] | Solomon L. Moshé[1,5] | Magda L. Nunes[6] | Perrine Plouin[7] | Sampsa Vanhatalo[8] | Sameer Zuberi[9] | Ronit M. Pressler[10]

Abstract

Objective: The International League Against Epilepsy (ILAE) Neonatal Seizure Framework was tested by medical personnel.

Methods: Attendees at the 2016 ILAE European Congress on Epileptology in Prague, the International Video-EEG Course in Pediatric Epilepsies in Madrid 2017, and a local meeting in Utrecht 2018, were introduced to the proposed ILAE neonatal classification system with teaching videos covering the seven types of clinical seizures in the proposed neonatal classification system. Five test digital video recordings of electroencephalography (EEG)-confirmed motor neonatal seizures were then shown and classified by the rater based on their knowledge of the proposed ILAE Neonatal Seizure Framework. A multi-rater Kappa statistic was used to assess the agreement between observers and the true diagnosis.

Results: The responses of 194 raters were obtained. There was no single predominant classification system that was currently used by the raters. Using the ILAE framework, 78%–93% of raters correctly identified the clinical seizure type for each neonate; the overall inter-rater agreement (Kappa statistic) was 0.67. The clonic motor seizure type was most frequently accurately identified (93% of the time; $\kappa = 0.870$). EEG technicians correctly identified all presented motor seizure types more frequently than any other group (accuracy = 0.9).

Significance: The ILAE Neonatal Seizure Framework was judged by most raters to be better than other systems for the classification of clinical seizures. Among all seizure types presented, clonic seizures appeared to be the easiest to accurately identify. Average accuracy across the five seizure types was 84.5%. These data suggest that the ILAE neonatal seizure classification may be used by all health-care professionals to correctly identify the predominant clinical seizure type.

Received: 6 October 2018 | Revised: 11 December 2018 | Accepted: 11 December 2018
DOI: 10.1002/epi4.12298

CRITICAL REVIEW AND INVITED COMMENTARY

Epilepsia Open® Open Access

Neonatal seizures: Is there a relationship between ictal electroclinical features and etiology? A critical appraisal based on a systematic literature review

Magda L. Nunes[1] | Elissa G. Yozawitz[2] | Sameer Zuberi[3] | Eli M. Mizrahi[4] | Maria Roberta Cilio[5] | Solomon L. Moshé[6] | Perrine Plouin[7] | Sampsa Vanhatalo[8] | Ronit M. Pressler[9] | Task Force on Neonatal Seizures, ILAE Commission on Classification & Terminology

8507 artigos na busca

57 articles included

(with full description of methodology and correlation of seizure semiology and ictal EEG)

Dados referentes a 151 neonatos

Etiologia x EEG

Vascular e EEG focal ($p < 0.001$)

Def. Vitamina e EEG multifocal ($p=0.003$)

Genética e EEG com SS ($p<0.001$)

TABLE 2 General characteristics of the 151 included neonates

Sex[a] (n = 125)	Male 37.7%	Female 45.0%	Missing 17.2%
Gestational age[a] (n = 114)	Term 62.9%	Preterm 12.6%	Missing 24.5%
			N (%)
Etiology (n = 151)			
Hypoxic-ischemic encephalopathy			6 (4.0)
Cortical malformations			3 (2.0)
CNS infections			4 (2.6)
Metabolic disorders			
Electrolyte imbalance			3 (2.0)
Inborn errors of metabolism			3 (2.0)
Vitamin-related disorders			11 (7.3)
Withdrawal seizures			2 (1.3)
Genetics			
Channelopathies			67 (44.4)
Chromosomal disorders			3 (2.0)
Other gene disorders			7 (4.6)
Vascular			
Stroke			25 (16.6)
Hemorrhage			8 (5.3)
Undetermined/unknown			9 (6.0)
Seizure type (n = 151)			
Sequential			62 (41.1)
Clonic			36 (23.8)
Tonic			26 (17.2)
Autonomic			14 (9.3)
Myoclonic			9 (6.0)
Spasms			3 (2.0)
Automatisms			1 (0.7)
EEG (n = 151)[b]			
Focal			56 (37.1)
Burst-suppression			48 (31.8)
Multifocal			46 (30.5)
Generalized			1 (0.7)

[a]Information not available for all newborns.
[b]Information related to ictal EEG except in some cases of burst-suppression (BS). Burst-suppression was described as an ictal pattern in 2 neonates and as an inter-ictal in 8; in the remining cases, it was not clearly defined as an ictal or interictal pattern/background abnormality.

Received: 6 October 2018 | Revised: 11 December 2018 | Accepted: 11 December 2018
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CRITICAL REVIEW AND INVITED COMMENTARY

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Seizure semiology/EEG	Focal	Multifocal	Generalized	Burst-suppression
Clonic (n = 36)	22 (61.1%)	8 (22.2%)	1 (2.8%)	5 (13.9%)
Tonic (n = 26)	3 (11.5%)	8 (30.8%)	0 (0.0%)	15 (57.7%)
Myoclonic (n = 9)	2 (22.2%)	0 (0.0%)	0 (0.0%)	7 (77.8%)***
Automatisms (n = 1)	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Spasms (n = 3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (100%)*
Sequential (n = 62)	16 (25.8%)	28 (45.2%)	0 (0.0%)	18 (29.0%)**
Autonomic (n = 14)	12 (85.7%)	2 (14.3%)	0 (0.0%)	0 (0.0%)

Burst-suppression was described as an ictal pattern* in one neonate with myoclonic seizures and in one with spasms; as an interictal pattern** in 4 with myoclonic and four with sequential seizures; for the others it was not clearly defined as ictal or interictal pattern/background abnormality.

TABLE 3 Seizures etiology × semiology

	Clonic	Tonic	Myoclonic	Automatisms	Spasms	Sequential	Autonomic
Etiology/seizure classification, n (%)							
HIE (n = 6)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (16.7%)	3 (50.0%)
Cortical malformations (n = 3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)	1 (33.3%)
CNS infection (n = 4)	3 (75.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)
Metabolic disorders							
Electrolyte imbalance (n = 3)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (33.3%)
Inborn errors of metabolism (n = 3)	0 (0.0%)	0 (0.0%)	3 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vitamin-related disorders (n = 11)	2 (18.2%)	0 (0.0%)	2 (18.2%)	0 (0.0%)	0 (0.0%)	7 (63.6%)	0 (0.0%)
Withdrawal (n = 2)	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Genetic disorders							
Channelopathy (n = 67)	5 (7.5%)	26 (38.8%)	3 (4.5%)	0 (0.0%)	0 (0.0%)	33 (49.3%)	0 (0.0%)
Chromosomal disorder (n = 3)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (33.3%)
Other gene disorders (n = 7)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	3 (42.9%)	0 (0.0%)
Vascular disorders							
Stroke (n = 25)	18 (72.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (20.0%)	2 (8.0%)
Hemorrhage (n = 8)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)	4 (50.0%)
Unknown Undetermined/ (n = 9)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	6 (66.7%)	2 (22.2%)

CNS, central nervous system.

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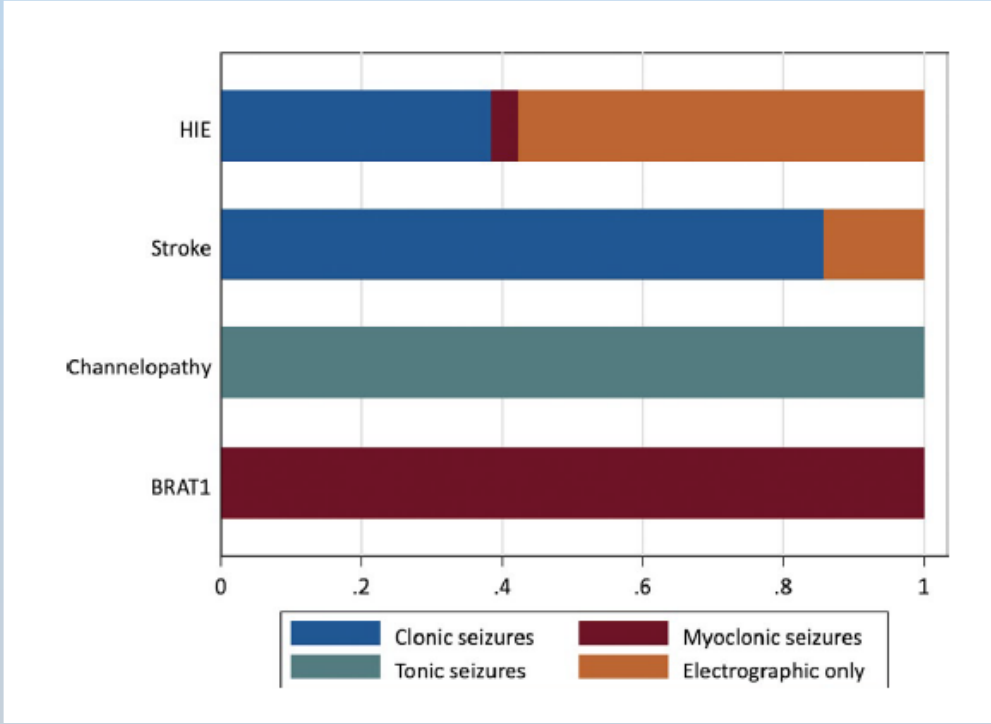
Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Neonatal presentation of genetic epilepsies: Early differentiation from acute provoked seizures

Marie-Coralie Cornet[1] | Valeria Morabito[2] | Damien Lederer[3] | Hannah C. Glass[1,4] | Susana Ferrao Santos[5] | Adam L. Numis[4] | Donna M. Ferriero[1,4] | Tristan T. Sands[6] | Maria Roberta Cilio[2]



População: 20 RN com epilepsias genéticas x 40 com CC Neo sintomática aguda
Semiologia CC tem relação com etiologia.
Nas epilepsias genéticas predominam as crises tônicas (associadas a apneia e dessaturação) e/ou sequenciais
Nas CC agudas provocadas predominam as clônicas e/ou eletrográficas

CC Neonatal

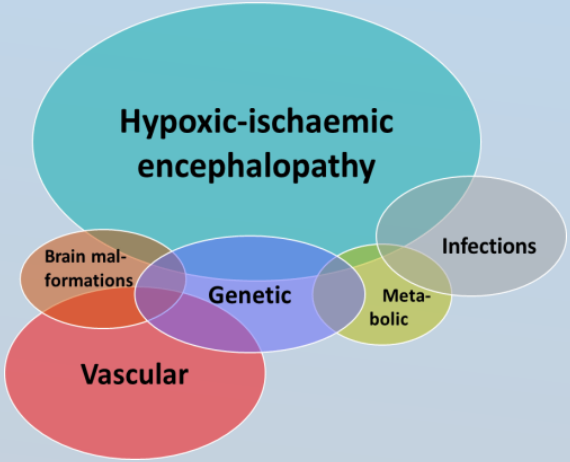
Incidência

Relativamente comum (1-3.5 :1000 nascimentos)

(Ronnen et al 1999; Berg et al 2012)

Evento agudo associado a varias etiologias

(Glass et al 2016, Cornet et al.2021)



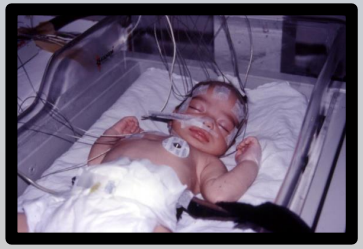
Desafios do diagnostico

Evento agudo x Epilepsia

(Shellhaas et al,2021; Zuberi et al.2022)

Dissociação eletro clinica

(Kellaway & Mizhari, 1987)



Influencia no prognóstico neurológico

(Shellhaas et al,2021)

Desafio terapêutico

(Painter et al 1999; Boylan et al 2003; WHO Guidelines on Neonatal Seizures 2011, Pressler & Mangum 2013)

Classificação das Crises Convulsivas Neonatais

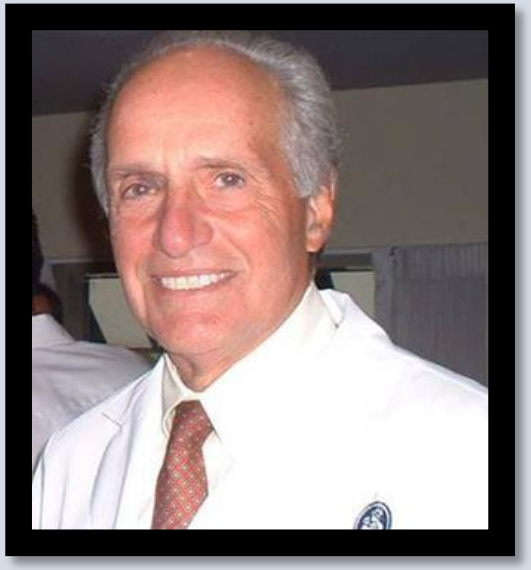
- Classificação clínica (Volpe, 1977)

o Crise tônica

o Crise clônica

o Mioclônica

o Sutil

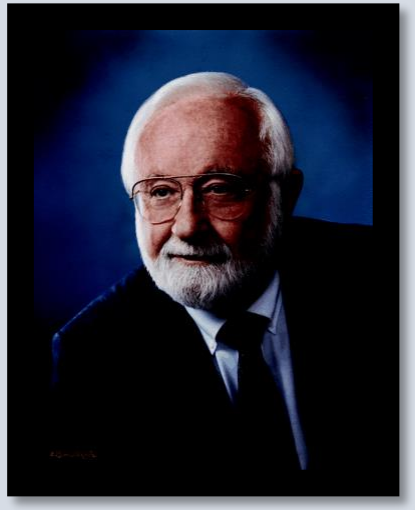


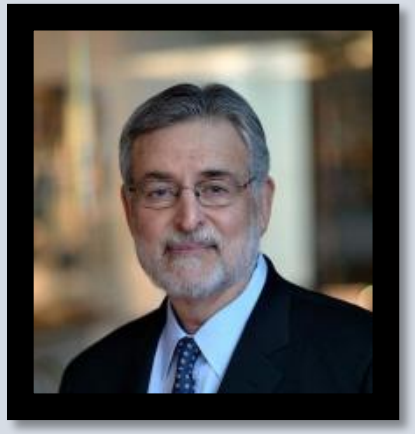
- Classificação por vídeo – EEG (Kellaway e Mizrahi, 1987)

oCrise clínica com confirmação EEG

oCrise clínica sem correspondente no EEG

oCrise eletrográfica sem manifestação clínica

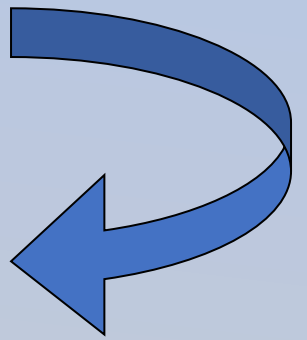




Dissociação eletro-clínica

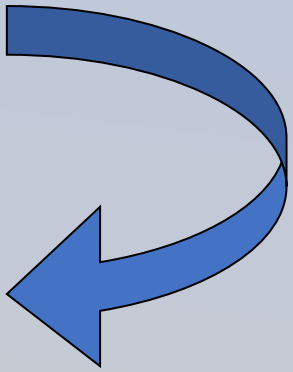
- Crises eletrográficas sem manifestação clínica

  - Áreas silentes do córtex
  - Lesões periféricas
  - Bloqueio farmacológico



- Crises clínicas sem manifestação eletrográfica

  - Lesão cortical grave (atividade deprimida)
  - Crises "subcorticais" (fenômenos de liberação)



Crise eletrográfica sem manifestação clinica

Crise eletro clinica, motora e não motora, sequencial

CC Neonatal

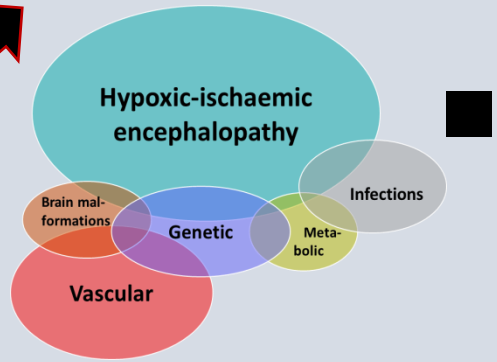
Incidência

Relativamente comum (1-3.5 :1000 nascimentos)

(Ronnen et al 1999; Berg et al 2012)

Evento agudo associado a varias etiologias

(Glass et al 2016, Cornet et al.2021)



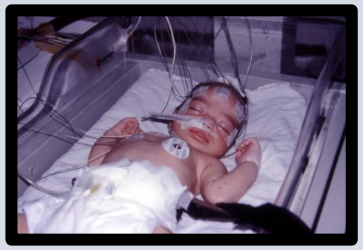
Desafios do diagnostico

Evento agudo x Epilepsia

(Shellhaas et al,2021; Zuberi et al.2022)

Dissociação eletro clinica

(Kellaway & Mizhari, 1987)



Influencia no prognóstico neurológico

(Shellhaas et al,2021)

Desafio terapêutico

(Painter et al 1999; Boylan et al 2003; WHO Guidelines on Neonatal Seizures 2011, Pressler & Mangum 2013)

Current Pediatric Reviews, 2006, 2, 315-321

Outcome of Newborns with Neonatal Seizures: Risk Factors and Predictors

Magda Lahorgue Nunes* and Jaderson Costa da Costa

Division of Neurology, Hospital São Lucas from PUCRS Medical School, Brazil

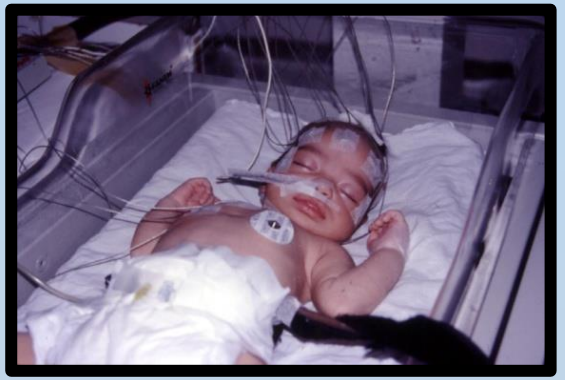
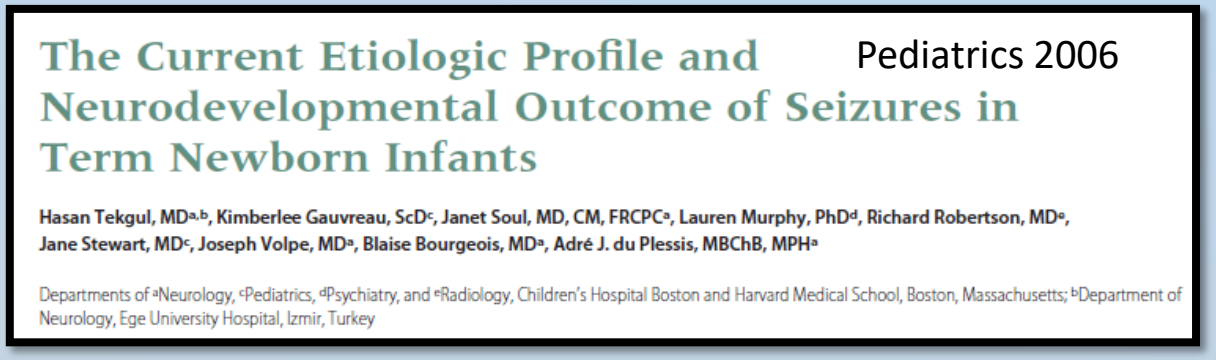


Table IV– Incidence of epilepsy after neonatal seizures

Reference	n	Inclusion Period	Mean FU (years)	Epilepsy (%)
Toet et al. 2005	206	1992-2002	5	9.4
Da Silva et al. 2004	158	1987-1997	4	33.8
Brunquell et al. 2002	77	1992-1998	3.5	21
Doose et al.2000	76	-	2	55*
Watanabe et al. 1999	75	1970-1995	3	100**
Gherpelli et al.	23		1	30***
Legido et al. 1991	40	1982-1985	2.5	56
Bergman et al. 1983	131	1976-1979	1-5	20
Holden et al. 1982	277	-	7	20
Kuromori et al 1976	130	-	3	18.2
Nunes et al (data in preparation)	101	1999-2003	2.5	21.3

Obs: n= number of newborns included, Mean FU = mean duration of follow up, epilepsy = percentage that developed epilepsy. *The authors considered together the outcome epilepsy and febrile seizures. ** Inclusion criteria were confirmed neonatal epileptic syndromes. * Seizure recurrence.**

Media=34.9%

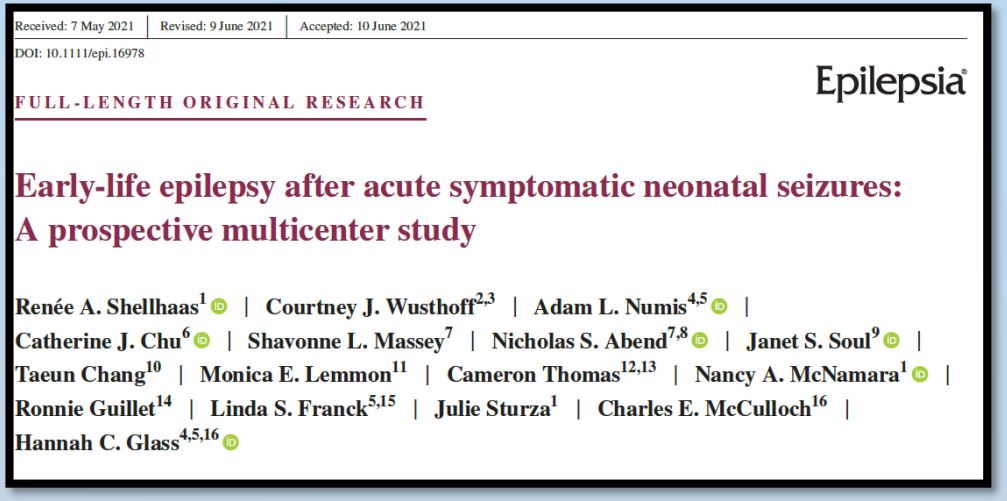


The Current Etiologic Profile and Neurodevelopmental Outcome of Seizures in Term Newborn Infants

Pediatrics 2006

Hasan Tekgul, MD[a,b], Kimberlee Gauvreau, ScD[c], Janet Soul, MD, CM, FRCPC[a], Lauren Murphy, PhD[d], Richard Robertson, MD[e], Jane Stewart, MD[c], Joseph Volpe, MD[a], Blaise Bourgeois, MD[a], Adré J. du Plessis, MBChB, MPH[a]

Departments of [a]Neurology, [c]Pediatrics, [d]Psychiatry, and [e]Radiology, Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts; [b]Department of Neurology, Ege University Hospital, Izmir, Turkey



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DOI: 10.1111/epi.16978

Epilepsia®

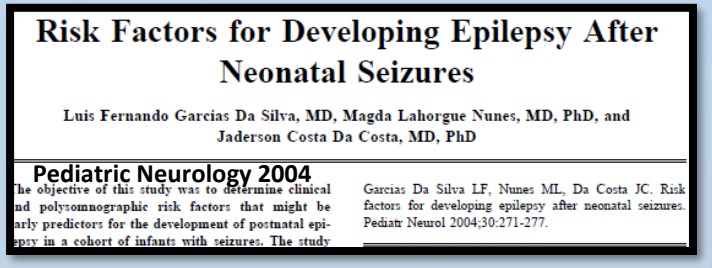
FULL-LENGTH ORIGINAL RESEARCH

Early-life epilepsy after acute symptomatic neonatal seizures: A prospective multicenter study

Renée A. Shellhaas[1] | Courtney J. Wusthoff[2,3] | Adam L. Numis[4,5] | Catherine J. Chu[6] | Shavonne L. Massey[7] | Nicholas S. Abend[7,8] | Janet S. Soul[9] | Taeun Chang[10] | Monica E. Lemmon[11] | Cameron Thomas[12,13] | Nancy A. McNamara[1] | Ronnie Guillet[14] | Linda S. Franck[5,15] | Julie Sturza[1] | Charles E. McCulloch[16] | Hannah C. Glass[4,5,16]

- Retrospective design
- Seizure diagnosis based on NICU staff observation (Volpe classification) , confirmed by Neurologist
- N=100 term newborns (89 were followed)
- Etiology : 40% global and 18% focal hypoxia-ischemia
- Unfavorable outcome= 28%
- Neonatal mortality = 7%
- Seizures after NICU discharge = **21%**

- Prospective design
- Seizure diagnosis: EEG confirmed
- N=282 term and preterm neonates (*Neonatal Seizure Registry* US)
- Post neonatal epilepsy after acute symptomatic seizures=**13%.**
- 1/3 with refractory epilepsy
- Risk for neurodevelopment delay increases 3x after seizures
- Duration of electrographic only seizures (in days) is a risk factor for epilepsy



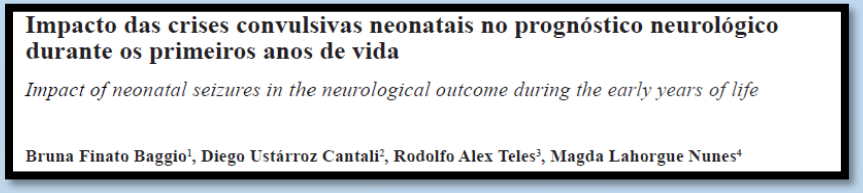
Risk Factors for Developing Epilepsy After Neonatal Seizures

Luis Fernando Garcias Da Silva, MD, Magda Lahorgue Nunes, MD, PhD, and Jaderson Costa Da Costa, MD, PhD

Pediatric Neurology 2004

The objective of this study was to determine clinical and polysomnographic risk factors that might be early predictors for the development of postnatal epilepsy in a cohort of infants with seizures. The study

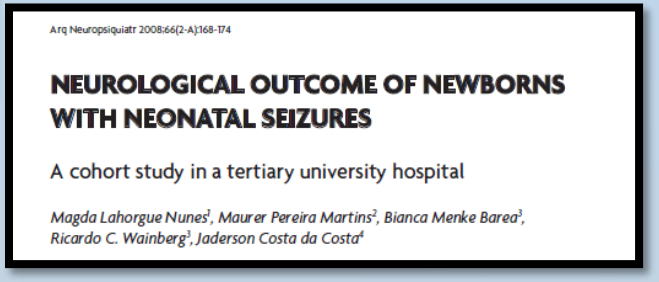
Garcias Da Silva LF, Nunes ML, Da Costa JC. Risk factors for developing epilepsy after neonatal seizures. Pediatr Neurol 2004;30:271-277.



Impacto das crises convulsivas neonatais no prognóstico neurológico durante os primeiros anos de vida

Impact of neonatal seizures in the neurological outcome during the early years of life

Bruna Finato Baggio[1], Diego Ustárroz Cantali[2], Rodolfo Alex Teles[3], Magda Lahorgue Nunes[4]

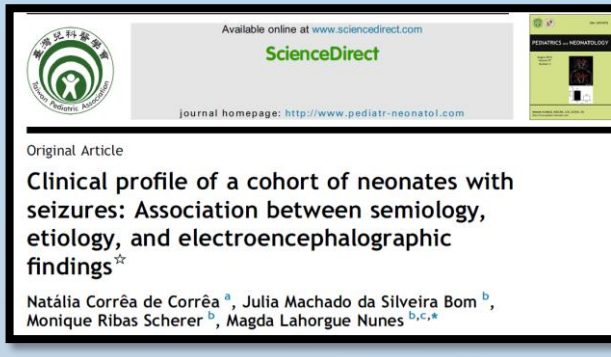


Arq Neuropsiquiatr 2008;66(2-A):168-174

NEUROLOGICAL OUTCOME OF NEWBORNS WITH NEONATAL SEIZURES

A cohort study in a tertiary university hospital

Magda Lahorgue Nunes[1], Maurer Pereira Martins[2], Bianca Menke Bared[3], Ricardo C. Wainberg[3], Jaderson Costa da Costa[4]



Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com

Original Article

Clinical profile of a cohort of neonates with seizures: Association between semiology, etiology, and electroencephalographic findings☆

Natália Corrêa de Corrêa [a], Julia Machado da Silveira Bom [b], Monique Ribas Scherer [b], Magda Lahorgue Nunes [b,c,*]

	1987-1997	1999-2003	2004-2009*	2010-2017**
Number patients	127	101	22	97
Sex (%)	56 male	58 male	54.6 male	54.6 male
Term/preterm	65.4/34.6 %	71.4/29.6 %	72.7/27.3 %	60.8/39.2 %
Incidence (per 1000 live births)	24.2/1000	27.6/1000	11.2/1000	-
Mortality (neonatal)	15%	25%	9.2%	19.6%
Post Neonatal Epilepsy	33.8%	29.6%	45.5%	No follow up but 70.6% discharged with ASM

OBS:* Crises confirmadas por vídeo-EEG, **39 com EEG ictal

CC Neonatal

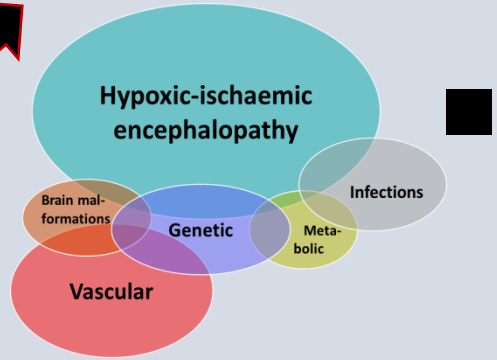
Incidência

Relativamente comum (1-3.5 :1000 nascimentos)

(Ronnen et al 1999; Berg et al 2012)

Evento agudo associado a varias etiologias

(Glass et al 2016, Cornet et al.2021)



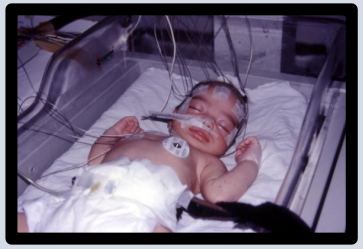
Desafios do diagnostico

Evento agudo x Epilepsia

(Shellhaas et al,2021; Zuberi et al.2022)

Dissociação eletro clinica

(Kellaway & Mizhari, 1987)



Influencia no prognóstico neurológico

(Shellhaas et al,2021)

Desafio terapêutico

(Painter et al 1999; Boylan et al 2003; WHO Guidelines on Neonatal Seizures 2011, Pressler & Mangum 2013)

Pediatric Neurology 128 (2022) 67–74

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

Treatment of Neonatal Seizures: Comparison of Treatment Pathways From 11 Neonatal Intensive Care Units

Jennifer C. Keene, MD, MS, MBA [a, 1, *], Lindsey A. Morgan, MD [a], Nicholas S. Abend, MD, MSCE [b], Sara V. Bates, MD [c], Sarah L. Parsons Hwang, MD, PhD [d], Taeun Chang, MD [e], Catherine J. Chu, Shavonne L. Massey, MD, MSCE [b], Bet, Craig A. Press, MD, PhD [k], Janet S. Sou, Cameron Thomas, MD, MS [n, o], Niranj

Variance in ASM Dosing in 11 Pathways

Medication Category	Medication	Initial Bolus Dosing	Repeat Bolus Dosing	Target Serum Levels	Maintenance
Rescue therapy	Lorazepam	Range: 0.05-0.1 mg/kg IV Most common: 0.1 mg/kg IV (6)	Range: None Most common: 0.1 mg/kg IV (2)		
	Midazolam	0.1 mg/kg IV (1) 0.25-0.5 mg/kg buccal (1)			
First-line therapy	Phenobarbital	Range: 20-30 mg/kg IV Most common: 20 mg/kg IV (10)	Range: 5-20 mg/kg IV Most common: 20 mg/kg IV (5)	Goal level 1-2 hours after final loading dose: Range: 15-60 mcg/mL Most common: 40-50 mcg/mL (3)	Range: 3-5 mg/kg/day Most common: 5 mg/kg/day (6)
Second- and third-line therapy	Fosphenytoin	20 mg PE/kg IV (11)	Range: 5-10 mg PE/kg IV Most common: 10 mg PE/kg IV (5)	Goal level 1-2 hours after final loading dose: Range: 10-25 mcg/mL Most common: 10-20 mcg/mL (2)	Range: 5-10 mg PE/kg/day IV Most common: 8-10 mg PE//kg/day IV (2)
	Levetiracetam	Range: 40-60 mg/kg IV Most common: 40 or 60 mg/kg IV (4 each)	Range: 20-60 mg/kg IV Most common: 20 mg/kg IV (2)	Not used	Range: 30-120 mg/kg/day IV/PO Most common: 40 mg/kg/day IV/PO (3)
	Topiramate	Range: 2-10 mg/kg PO Most common: N/A. 2-3 or 10 mg/kg PO (1 each)	10 mg/kg PO repeated once in 24 hrs (1)	Not used	Range: 2-4 mg/kg/day PO Most common: 3 mg/kg/day PO, uptitrated QOD (2)
Pyridoxine related[l]	Pyridoxine	100 mg IV (7)	Range: 100 mg IV repeated 2 to 5 doses Most common: 100 mg IV repeated Q 5 min up to 500 mg IV (3)	Not used	Range: 15-30 mg/kg/day IV/PO Most common: 30 mg/kg/day IV/PO (3)
Continuous infusion	Midazolam	Range: 0.05-0.2 mg/kg Most common: 0.2 mg/kg/dose IV (3)	Range: 0.1-0.2 mg/kg/dose IV Most common: None - All pathways differ from each other	Not used	Range: 50 mcg/kg/hr to 1000 mcg/kg/hr Most common: 50 mcg/kg/hr increased by 40-60 mcg/kg/hr to 1000 mcg/kg/hr(2) Infusion titration based on weight, normo vs hypothermia
	Lidocaine	2 mg/kg/IV (2)			

Received: 16 April 2023 | Revised: 9 August 2023 | Accepted: 10 August 2023
DOI: 10.1111/epi.17745

Epilepsia™

SPECIAL REPORT

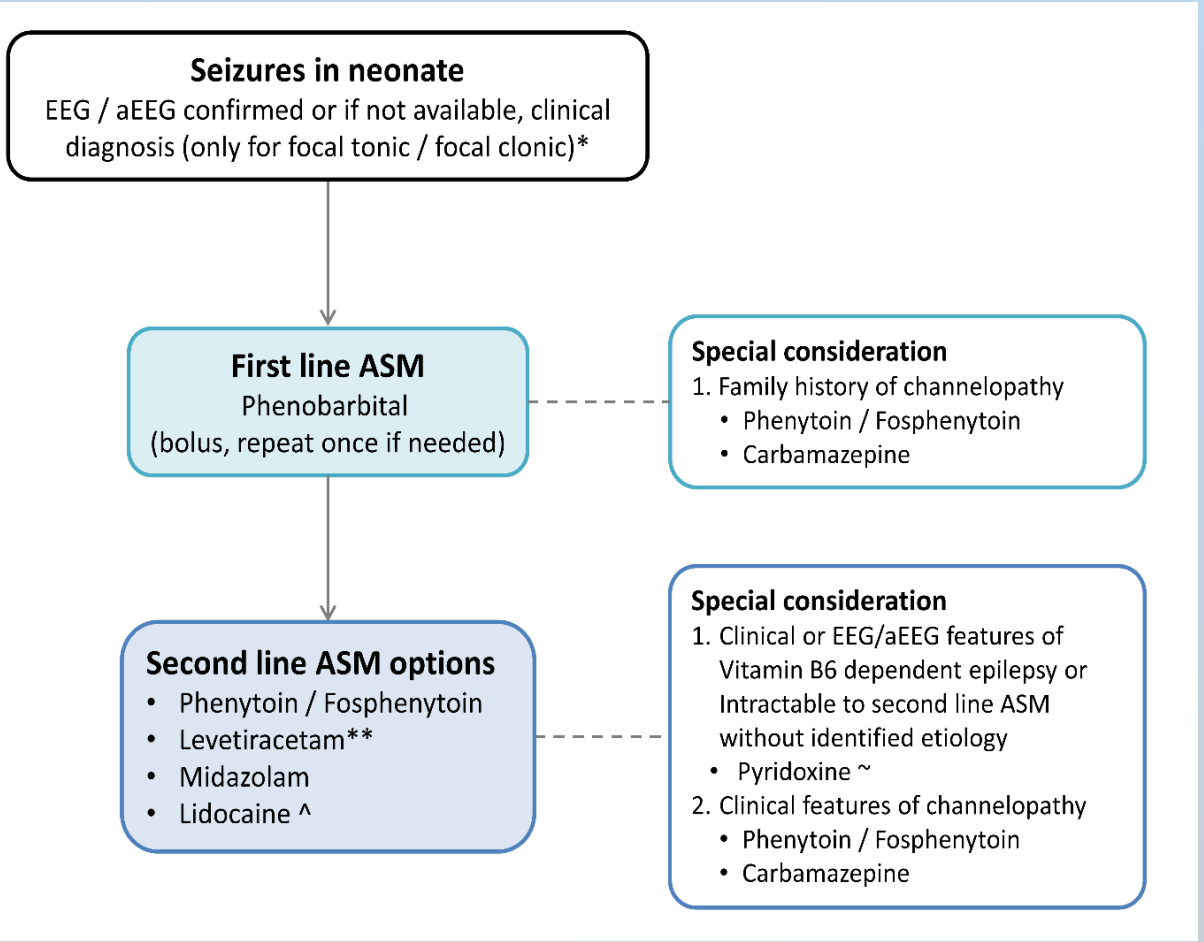
Treatment of seizures in the neonate: Guidelines and consensus-based recommendations—Special report from the ILAE Task Force on Neonatal Seizures

Ronit M. Pressler[1,2] | Nicholas S. Abend[3] | Stéphan Auvin[4] | Geraldine Boylan[5,6] | Francesco Brigo[7,8] | Maria Roberta Cilio[9] | Linda S. De Vries[10] | Maurizio Elia[11] | Alberto Espeche[12] | Cecil D. Hahn[13] | Terrie Inder[14] | Nathalie Jette[15] | Angelina Kakooza-Mwesige[16] | Silke Mader[17] | Eli M. Mizrahi[18] | Solomon L. Moshé[19,20] | Lakshmi Nagarajan[21] | Iris Noyman[22,23] | Magda L. Nunes[24] | Pauline Samia[25,26] | Eilon Shany[27] | Renée A. Shellhaas[28] | Ann Subota[15] | Chahnez Charfi Triki[29] | Tammy Tsuchida[30] | Kollencheri Puthenveettil Vinayan[31] | Jo M. Wilmshurst[32] | Elissa G. Yozawitz[19] | Hans Hartmann[33]

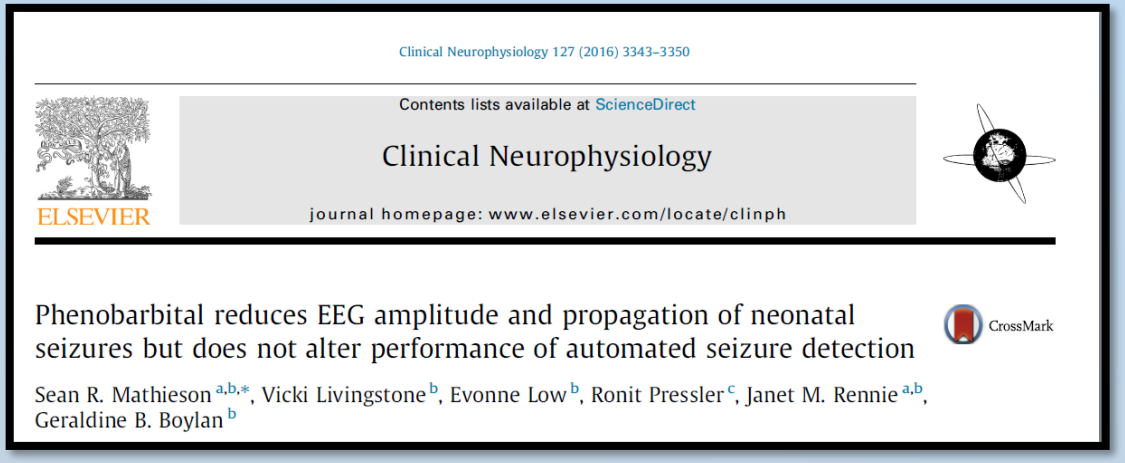
Consensus-based recommendations:

A standardized treatment pathway for the management of neonatal seizures should be available in each center.

Level of agreement: **High**



Lembrar....



Clinical Neurophysiology 127 (2016) 3343–3350

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Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Phenobarbital reduces EEG amplitude and propagation of neonatal seizures but does not alter performance of automated seizure detection

Sean R. Mathieson [a,b,*], Vicki Livingstone [b], Evonne Low [b], Ronit Pressler [c], Janet M. Rennie [a,b], Geraldine B. Boylan [b]

- Reduz a amplitude e a propagação das crises.
- Promove a dissociação eletroclínica com a perda do componente clinico!

Medication	Dosage	Common Side effects	Remarks
Phenobarbital	Loading dose: 20 mg/kg iv, repeated once as needed Maintenance: 3-6 mg/kg/day iv or oral	Respiratory depression Depressed consciousness Hypotension	Prolonged half-life first week of life and preterm (43-217 hr), thus maintenance may not be needed. Renal and hepatic excretion can be affected in HIE
Phenytoin/ Fosphenytoin	Loading dose: 15-20 mg/kg PE over 20 min Maintenance: 4-8 mg/kg/day in 2 divided doses Target level 10-20 mcg/ml Administer over 10 min	Infusion site irritation Arrhythmia	Phenytoin poor oral bioavailability Fosphenytoin preferred over phenytoin Levels likely higher in infants receiving therapeutic hypothermia and hence maintenance dose can be determined based on level .Cardiac monitoring required
Carbamazepine	Loading dose: 10 mg/kg orally Maintenance: 10-20 mg/kg/day in 2 divided doses	Transient somnolence	Usually well tolerated but limited information regarding dosage and side effects for the neonatal population.
Levetiracetam	Loading dose: 20-60 mg/kg/day iv Maintenance: 40-60 mg/kg/day in 3 divided doses Optimal dosing & target level not known	Mild sedation Irritability	Limited information regarding dosing side effect for the neonatal population
Lidocaine	Loading dose 2 mg/kg iv over 10 min Maintenance: 7 mg/kg/hr for 4 hr, reduce to 3,5 mg/kg/h for 12 hr, reduce to 1,75 mg/kg/h for 12 hr, then stop. Adapt dose for birth weight, PMA and therapeutic hypothermia	Cardiac (arrhythmias; atrioventricular block; cardiac arrest) Hypotension Methemoglobinemia	Not to be given to a patient with congenital heart disease and on proarrhythmic drugs like phenytoin Cardiac monitoring required
Midazolam	Loading dose 0.05 0.15mg/kg Maintenance: 1 mcg /kg/minute (60mcg/kg/h), continuous infusion titrated upward in steps to effect (maximal 5mcg/kg/minute)	Respiratory depression Depressed consciousness Hypotension	Developing brain may have an excitatory response to benzodiazepines rather than the preferred inhibition hence potentially can make seizure worse
Pyridoxine-HCL	Loading 100 mg iv or orally Maintenance 30 mg/kg/day iv or orally in 2 dosages for at least 3 days	Respiratory depression if effective. Prolonged treatment with high dosages may cause peripheral neuropathy	Ventilatory support should be available for trial. Max dosage 300 mg/kg/day
Pyridoxal-5-phosphate	30 mg/kg/day in 2 dosages orally for at least 3 days	Respiratory depression if effective. Hepatotoxic in prolonged treatment.	Not licensed as medical product, but most promising approach in PNPO deficient patients.

CLINICAL AND LABORATORY OBSERVATIONS www.jpeds.com • THE JOURNAL OF PEDIATRICS 2017

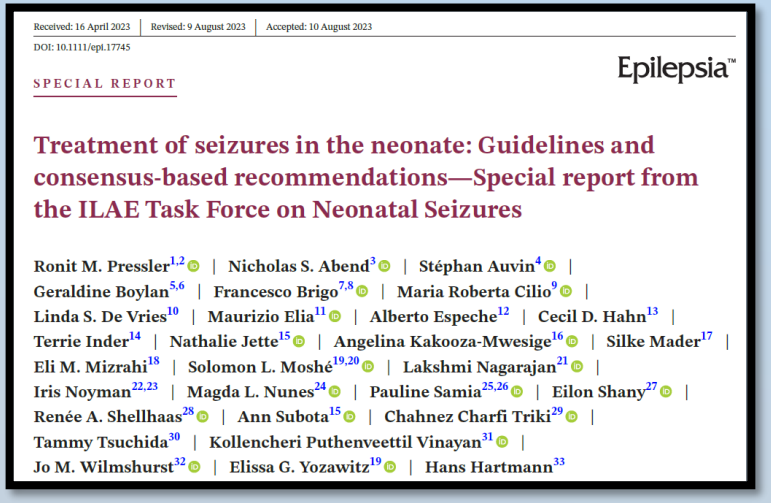
Treatment Duration After Acute Symptomatic Seizures in Neonates: A Multicenter Cohort Study

Renée A. Shellhaas, MD, MS[1], Taeun Chang, MD[2], Courtney J. Wusthoff, MD, MS[3], Janet S. Soul, MD[4], Shavonne L. Massey, MD[5], Catherine J. Chu, MD, MS[6], M. Roberta Cilio, MD, PhD[7], Sonia L. Bonifacio, MD, MS[3], Nicholas S. Abend, MD, MSCE[5], Tammy N. Tsuchida, MD, PhD[2], and Hannah C. Glass, MDCM, MS[7,8], on behalf of the Neonatal Seizure Registry Study Group*

Table II. Variables associated with medications continuation at the time of discharge to home among the 317 survivors of acute symptomatic seizures

			Univariable analyses*			Multivariable analyses†		
	n	Discharged with AED	RR	95% CI	*P*	OR	95% CI	*P*
EEG confirmed seizures								
Yes	266	206 (77%)	1.5	(1.2-2.0)	.0001	2.3	(0.97-5.4)	.06
No	51	26 (51%)						
Status epilepticus								
Yes	48	42 (88%)	1.2	(1.1-1.4)	.015	2.1	(0.6-7.3)	.2
No	269	190 (71%)						
Seizures refractory to initial loading dose								
Yes	196	160 (82%)	1.3	(1.1-1.5)	.0003	1.6	(0.8-3.2)	.2
No/unknown	115	71 (62%)						
Abnormal examination at discharge								
Yes	150	123 (82%)	1.3	(1.1-1.4)	.0008	2.0	(0.99-4.1)	.053
No	167	109 (67%)						

- Estudo envolvendo 7 centros norte americanos
- A maioria tem alta com FAC apesar de não haver indicação precisa



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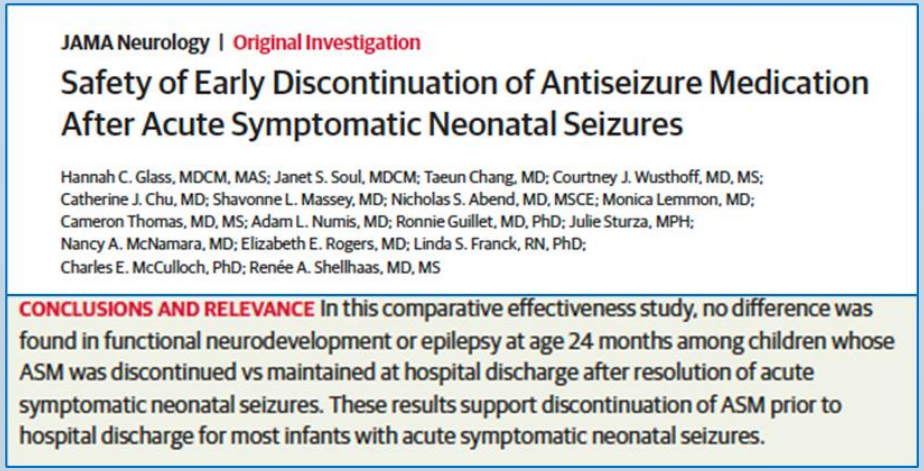


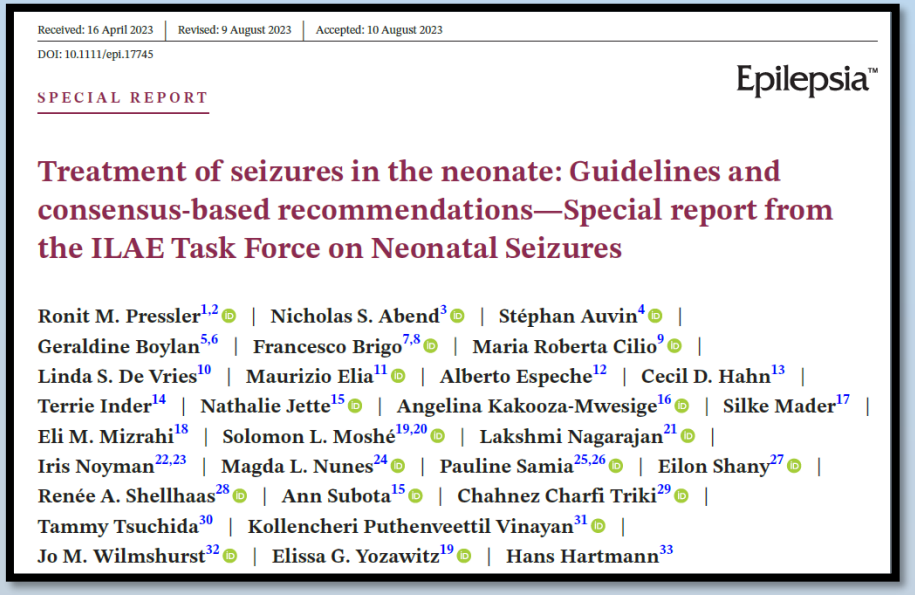
JAMA Neurology | Original Investigation

Safety of Early Discontinuation of Antiseizure Medication After Acute Symptomatic Neonatal Seizures

Hannah C. Glass, MDCM, MAS; Janet S. Soul, MDCM; Taeun Chang, MD; Courtney J. Wusthoff, MD, MS; Catherine J. Chu, MD; Shavonne L. Massey, MD; Nicholas S. Abend, MD, MSCE; Monica Lemmon, MD; Cameron Thomas, MD, MS; Adam L. Numis, MD; Ronnie Guillet, MD, PhD; Julie Sturza, MPH; Nancy A. McNamara, MD; Elizabeth E. Rogers, MD; Linda S. Franck, RN, PhD; Charles E. McCulloch, PhD; Renée A. Shellhaas, MD, MS

CONCLUSIONS AND RELEVANCE In this comparative effectiveness study, no difference was found in functional neurodevelopment or epilepsy at age 24 months among children whose ASM was discontinued vs maintained at hospital discharge after resolution of acute symptomatic neonatal seizures. These results support discontinuation of ASM prior to hospital discharge for most infants with acute symptomatic neonatal seizures.

- **Quando parar o FAC**
- **Recomendação baseada em consenso:**
- No caso de crises agudas sintomáticas (eletro clinicas ou eletrográficas) quando controladas, não havendo evidencia de SE , os FAC devem ser suspensos antes da alta hospitalar, independente de achados do EEG ou RM.
- *Nível de concordância: alto*



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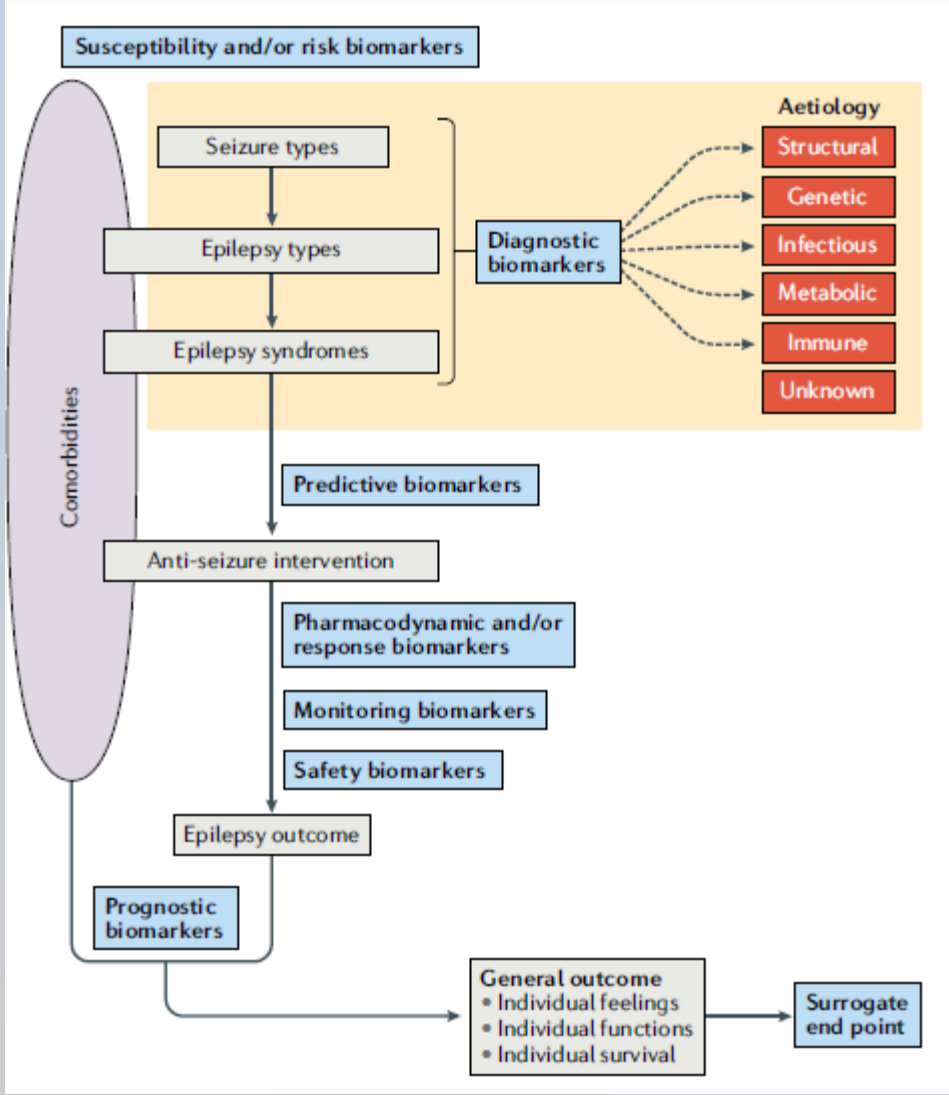
Resumo das considerações

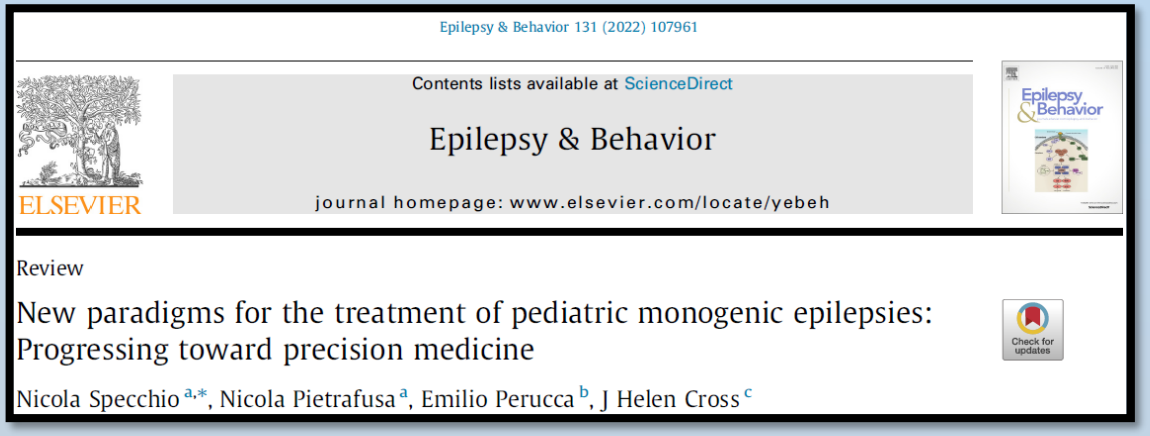
- Fenobarbital deve ser o FAC de escolha de 1a linha (baseado em evidencias)
- Para 2a linha de tratamento considerar: levetiracetam, fenitoína , midazolam, lidocaína
  - Considerações especificas em casos de canalopatias (carbamazepina) ou neonatos com cardiopatias (levetiracetam)
- Tratamento profilático após o período neonatal não é recomendado
- Hipotermia terapêutica reduz frequência de descargas (*seizure burden*) (baseado em evidencias)
- Tratar as crises neonatais (incluindo as somente eletrográficas) com o objetivo de reduzir as descargas (*seizure burden*) está associado a melhora do prognóstico.
- Teste de piridoxina ou piridoxal fosfato deve ser considerado em casos refratários.

E o que tem de novidades...
Medicina de Precisão : Uso de biomarcadores



Terapias :
Substitutivas para um alvo especifico
Modificação de sinalização de vias
Modificação da função de canis iônicos

Rima Nabbout & Mathieu Kuchenbuch, Nature Reviews- Neurology ,2020



Epilepsy & Behavior 131 (2022) 107961

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journal homepage: www.elsevier.com/locate/yebeh

Review

New paradigms for the treatment of pediatric monogenic epilepsies: Progressing toward precision medicine

Nicola Specchio [a,*], Nicola Pietrafusa [a], Emilio Perucca [b], J Helen Cross [c]

- Escolha racional do FAC tendo como alvo o(s) mecanismo(s) fisiopatológico(s). Ex: Mutações *SCN8A, SCN2A* ou *KCNQ2* resultante de ganho de função do canal de sódio respondem a bloqueadores.
- Desenvolvimento de terapias alvo baseada em novas moléculas. Ex: reposição enzimática para lipofuccinose ceróide neuronal, moléculas que modulem especificamente ganho x perda de função de canais iônicos.
- Uso de dietas ou alimentos que possam corrigir os defeitos metabólicos. Ex:dieta cetogênica, reposição de piridoxina, reposição de piridoxal-5-fosfato.
- Utilização de fármacos previamente aprovados para outras indicações clinicas. Ex: Everolimus para mutações m- Tor, quinidina para KCNT1, Memantina para GRIN2D.

Obrigada pela atenção!

mlnunes@pucrs.br