Epileptologischer Vogelflug

GNP Stuttgart 2024

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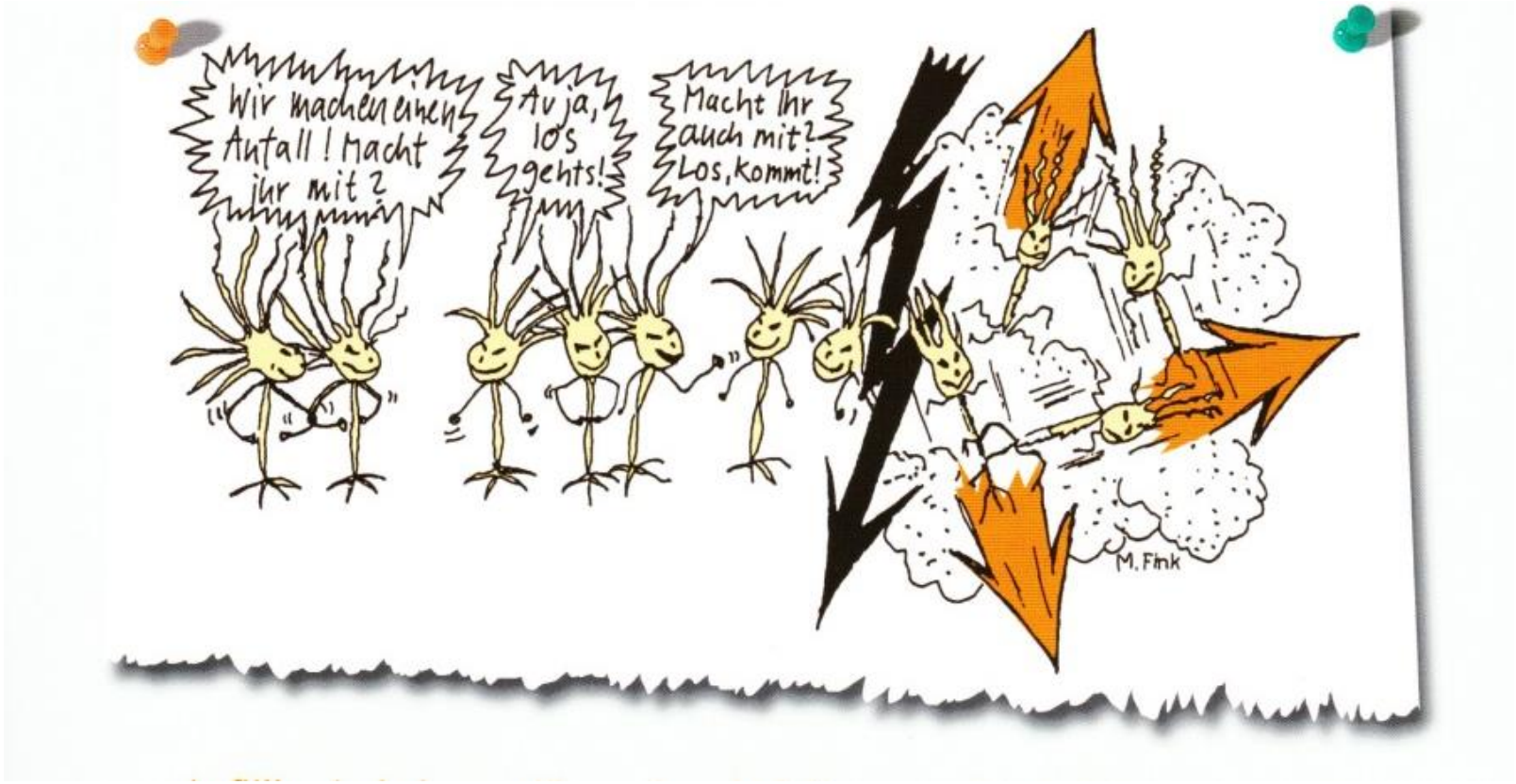
Disclosures

Consultant activities for Idorsia, Neurocrine, Epilog, Takeda, Biocodex

Advisory board activity for Idorsia, Eisai, Jazz Pharmaceuticals, UCB, Angelini, Neuraxpharm

The world of pediatric epileptology



Aus dem Famoses Schulungsbuch

Disease Progression in DEEs

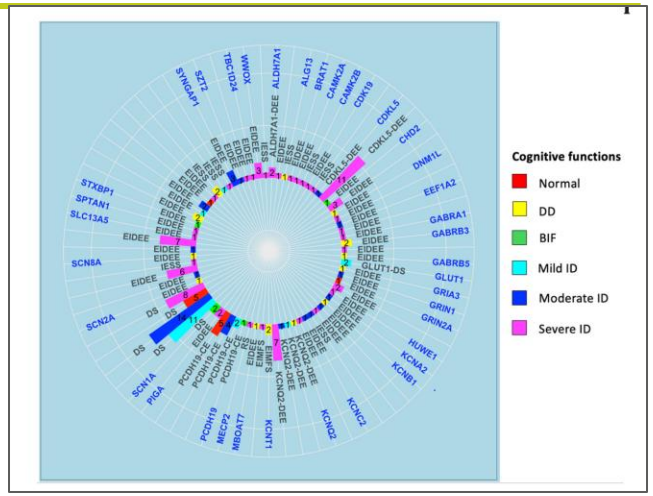
Received: 3 March 2024 | Revised: 29 August 2024 | Accepted: 29 August 2024
DOI: 10.1111/epi.18127

Epilepsia

RESEARCH ARTICLE

Unveiling the disease progression in developmental and epileptic encephalopathies: Insights from EEG and neuropsychology

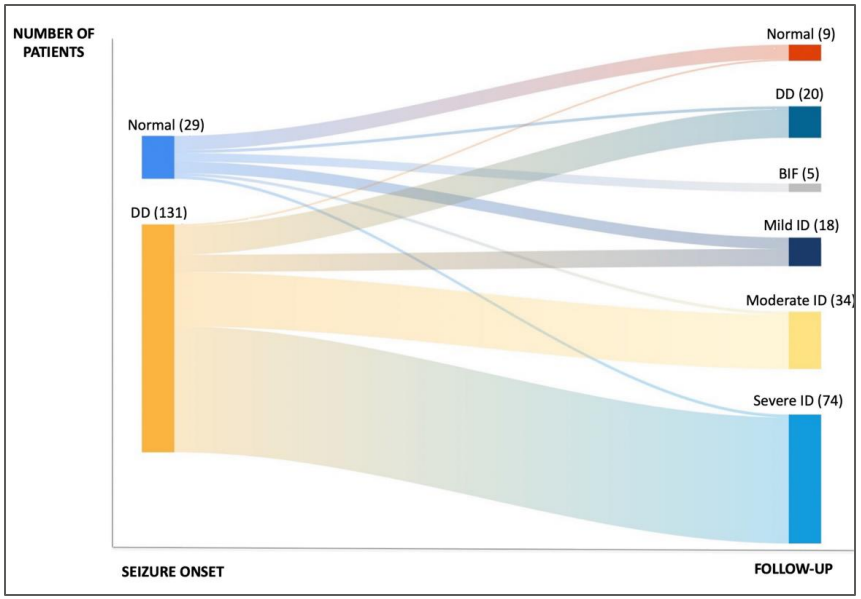
Paolo Surdi[1] | Marina Trivisano[2] | Angela De Dominicis[2] | Mattia Mercier[2] | Ludovica Maria Piscitello[2] | Giusy Carfì Pavia[2] | Costanza Calabrese[2] | Simona Cappelletti[2] | Cinzia Correale[2] | Luigi Mazzone[1] | Federico Vigevano[3] | Nicola Specchio[2]



160 Patienten mit DEEs
Neurpsychologie
EEG

Key points

- Genetic developmental and epileptic encephalopathies (DEEs) are characterized by various seizure types, genetic heterogeneity, and cognitive impairment with variable clinical trajectories.
- Comparison of electroencephalography (EEG) data between seizure onset and last follow-up revealed a predominance of poorly organized and slow background activity at follow-up.
- Cognitive assessments indicated a high prevalence of cognitive impairment, with an increased rate of severe intellectual disability at the last follow-up, highlighting the possible progressive nature of DEEs.
- The presence of a high prevalence of drug-resistant seizures, status epilepticus, movement disorders, and behavioral problems underscores the need for further research to better understand the complexity underlying DEEs.



DEE vs EE-SWAS

91 Patienten

RESEARCH ARTICLE

Annals of Neurology, 24

Solving the Etiology of Developmental and Epileptic Encephalopathy with Spike–Wave Activation in Sleep (D/EE-SWAS)

Sindhu Viswanathan, MBChB,[1,2] Karen L. Oliver, PhD,[1,3,4] Brigid M. Regan, BSc(Hons),[1] Amy L. Schneider, MGenCouns,[1] Candace T. Myers, PhD,[5] Michele G. Mehaffey, MS,[5,6] Amy J. LaCroix, BS,[6] Jayne Antony, MD, PhD,[7] Richard Webster, MBBS, MSc,[7] Michael Cardamone, PhD, MBBS,[8] Gopinath M. Subramanian, MBBS, MD,[9] Annie T.G. Chiu, MBBS,[1] Eugenia Roza, PhD, MD,[10,11] Raluca I. Teleanu, PhD, MD,[10,11] Stephen Malone, MBBS, PhD,[12,13] Richard J. Leventer, MBBS, PhD,[14,15] Deepak Gill, MBBS,[7,16] Samuel F. Berkovic, MD, FRS,[1] Michael S. Hildebrand, PhD,[1,15] Beatrice S. Goad, BS,[14,15] Katherine B. Howell, PhD, MBBS (Hon), BMedSc,[14,15] Joseph D. Symonds, PhD,[17,18] Andreas Brunklaus, MD,[17,18] Lynette G. Sadleir, MBChB, MD,[19] Sameer M. Zuberi, MBChB, MD,[17,18] Heather C. Mefford, MD, PhD,[6,20] and Ingrid E. Scheffer, MBBS, PhD, FRS[1,14,15,21]

Objective: To understand the etiological landscape and phenotypic differences between 2 developmental and epileptic encephalopathy (DEE) syndromes: DEE with spike–wave activation in sleep (DEE-SWAS) and epileptic encephalopathy with spike–wave activation in sleep (EE-SWAS).

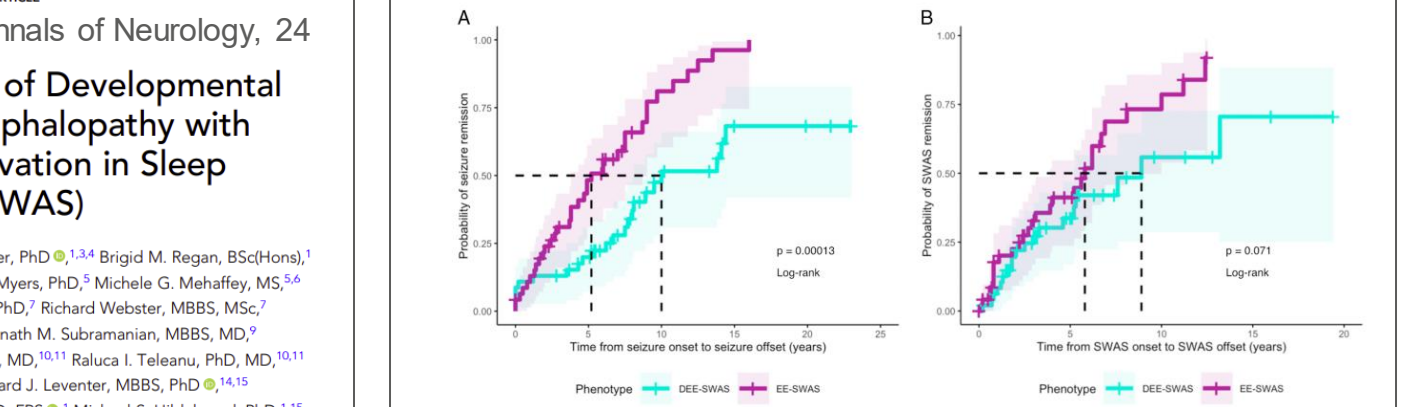


FIGURE 3: (A) Probability of time to seizure remission (n = 93). (B) Probability of time to SWAS remission (n = 101). Probability was calculated using the Kaplan–Meier method for survival analysis. The shaded color regions define the 95% confidence intervals. Colored vertical dashes along each survival curve denote the most recent age of individuals known to still be experiencing seizures (A) or SWAS (B) (censored observations). Median time to event (seizure or SWAS offset) for each group indicated by black dashed lines.

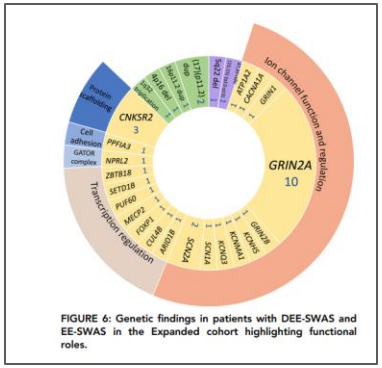


FIGURE 6: Genetic findings in patients with DEE-SWAS and EE-SWAS in the Expanded cohort highlighting functional roles.

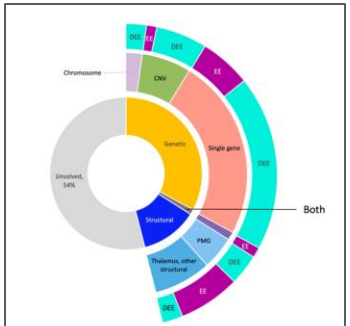


FIGURE 5: Solved cases in our Core cohort, n = 91, by etiology and epilepsy syndromes.

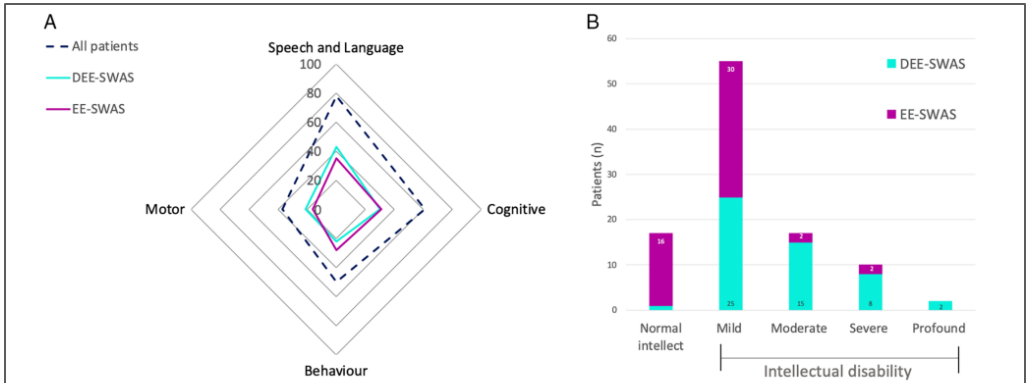


FIGURE 2: (A) Developmental regression by domain (speech and language, cognitive, behavior and motor) in individuals with DEE-SWAS and EE-SWAS. (B) Intellectual outcome in patients with DEE-SWAS and EE-SWAS.

Steroids or Clobazam in (D)EE-SWAS?

Corticosteroids versus clobazam for treatment of children with epileptic encephalopathy with spike-wave activation in sleep (RESCUE ESES): a multicentre randomised controlled trial

Marleen M L van Arnhem, Bart van den Munckhof*, Alexis Arzimanoglou, Emilio Perucca, Liisa Metsähonkala, Guido Rubboli, Marianne Søndergaard Khinchi, Anne de Saint-Martin, Kerstin A Klotz, Julia Jacobs, J Helen Cross, Irene Garcia Morales, Wim M Otte, Heleen C van Teeseling, Frans S S Leijten, Kees P J Braun, Floor E Jansen, on behalf of the RESCUE ESES study group†*

Lancet Neurology, 24

	Clobazam (n=21)		Corticosteroids (n=22)		RR (95% CI) or β (95% CI)	p value
	n (%)	Mean (SD) or median (IQR)	n (%)	Mean (SD) or median (IQR)		
Primary outcomes at 6 months						
IQ responder rate	0 (0%), n=18	..	5 (25%), n=20	..	RR 10·0 (1·2 to 1310·4)	0·025
Cognitive sum score responder rate	1 (5%)	..	1 (5%)	..	RR 1·0 (0·1–11·7)	0·97
Secondary outcomes at 6 months						
Delta IQ	18 (86%)	−0·7 (6·2)	20 (91%)	4·9 (9·3)	β 5·6 (0·3 to 10·8)	0·039
Delta cognitive sum score	21 (100%)	0·1 (0·43)	22 (100%)	0·3 (0·41)	β 0·2 (−0·1 to 0·4)	0·20
Delta SWI (%)	21 (100%)	0 (−12 to 4)	22 (100%)	−5 (−55 to 7)	NA	0·72*
Global daily functioning (VAS score)	16 (76%)	1·3 (1·0)	17 (77%)	1·3 (1·3)	β 0·0 (−0·8 to 0·8)	0·96
EEG responder†	4 (19%)	..	7 (32%)	..	RR 1·7 (0·5 to 3·5)	0·34
Sleep SWI <50%‡	3 (14%)	..	7 (32%)	.	RR 0·8 (0·3 to 1·1)	0·18
Occurrence of seizures‡	9 (43%)	..	8 (36%)	..	RR 0·8 (0·3 to 1·5)	0·66
Secondary outcomes at 18 months						
IQ responder rate	3 (21%), n=14	..	2 (12%), n=17	..	RR 0·5 (0·1 to 2·3)	0·47
Cognitive sum score responder rate	2 (10%), n=20	..	3 (15%), n=20	..	RR 1·5 (0·3 to 5·9)	0·63
Delta IQ	14 (67%)	−0·1 (12·0)	17 (77%)	1·2 (10·2)	β 1·2 (−6·9 to 9·4)	0·76
Delta cognitive sum score	20 (95%)	0·1 (0·9)	20 (91%)	0·2 (0·5)	β 0·1 (0·3 to 0·6)	0·60
Delta SWI (%)	21 (100%)	−3 (−55 to 4)	21 (95%)	−10 (−39 to 2)	NA	0·86*
Global daily functioning (VAS score)	14 (67%)	2·0 (1·8)	14 (64%)	1·8 (1·4)	β −0·2 (−1·5 to 1·1)	0·73
EEG responder†	6 (29%)	..	9 (43%), n=21	..	RR 1·5 (0·6 to 2·6)	0·34
Sleep SWI <50%‡	6 (29%)	..	7 (33%), n=21	..	RR 0·9 (0·5 to 1·2)	0·74
Occurrence of seizures‡	8 (38%)	..	8 (38%), n=21	..	RR 1·0 (0·4 to 1·8)	>0·99

IQ=intelligence quotient. SWI=spike-wave index. NA=not applicable. *p value derived from Wilcoxon rank-sum test because skewed variable could not be included in linear regression. †Defined as SWI decline by ≥25% compared to baseline. ‡Post-hoc analyses.

Table 2: Primary and secondary outcomes

	Clobazam (n=23)	Corticosteroids (n=22)
Sex		
Male	15 (65%)	15 (68%)
Female	8 (35%)	7 (32%)
Age at inclusion, years	6·1 (1·8)	7·4 (2·5)
Age at onset of seizures, years	3·2 (2·3)	5·4 (2·8)
Age at EE-SWAS diagnosis, years	5·9 (1·8)	7·2 (2·4)
Complicated perinatal history	9 (39%)	13 (59%)
Febrile seizures	5 (22%)	2 (9%)
Afebrile seizures	20 (87%)	15 (68%)
Seizure type at inclusion*		
Generalised	8 (35%)	4 (18%)
Focal	15 (65%)	11 (50%)
No seizures	3 (13%)	7 (32%)
Previously treated with at least one antiseizure medications	18 (78%)	15 (86%)
Aetiology of EE-SWAS		
Unknown	9 (39%)	10 (45%)
Established structural or genetic	14 (61%)	12 (55%)
MRI abnormalities*		
Thalamic injury	3 (13%)	2 (9%)
Infarction	1 (4%)	1 (5%)
Malformation of cortical development	1 (4%)	1 (5%)
Other†	8 (35%)	5 (23%)
Non-specific	2 (9%)	2 (9%)
None	11 (48%)	12 (56%)
Metabolic abnormality	0	0
Genetic abnormality‡	5 (22%)	1 (5%)
Psychomotor development before EE-SWAS onset		
Normal (EE-SWAS)	9 (39%)	9 (41%)
Mildly delayed (developmental EE-SWAS)	5 (22%)	8 (36%)
Moderately delayed (developmental EE-SWAS)	5 (22%)	3 (14%)
Severely delayed (developmental EE-SWAS)	4 (17%)	2 (9%)
Behavioural disorder before EE-SWAS onset	4 (17%)	6 (27%)
EE-SWAS clinical or EEG semiology		
Typical EE-SWAS	18 (78%)	14 (64%)
Atypical EE-SWAS	5 (22%)	8 (36%)
Sleep spike-wave index percentage at baseline EEG	90 (82–95)	87 (82–93)
Physiological sleep phenomena present at baseline EEG	16 (73%), n=22	13 (72%), n=18
Total IQ at baseline neuropsychological assessment	76 (21)	76 (21)
Cognitive sum score at baseline	−2·0 (1·4)	−1·5 (1·4)

Data are n (%), mean (SD), or median (IQR). EE-SWAS=epileptic encephalopathy with spike-wave activation in sleep. IQ=intelligence quotient. *Patients can be reported in more than one category, thus percentages will not always add up to 100%. †Including periventricular leukomalacia, porencephalic cyst, haemorrhages, sinus thrombosis, white matter abnormalities, dilated ventricles, and arteriovenous malformation. ‡Including *TRPM3*, *WAC*, *16p11.2* microdeletion, *CBS*, *ATP1A3*, and *SETD2* mutations.

Table 1: Baseline demographic and clinical characteristics

Interpretation The trial was terminated prematurely, and the target sample size was not met, so our findings must be interpreted with caution. Our data indicated an improvement in IQ outcomes with corticosteroids compared with clobazam treatment, but no difference was seen in cognitive sum score. Our findings strengthen those from previous uncontrolled studies that support the early use of corticosteroids for children with EE-SWAS.

Epilepsy surgery

https://doi.org/10.1093/brain/awae121 BRAIN 2024: 147; 2791–2802 | 2791

BRAIN
ORIGINAL ARTICLE

Long-term neuropsychological trajectories in children with epilepsy: does surgery halt decline?

Maria H. Eriksson,[1,2,3] Freya Prentice,[1,2] Rory J. Piper,[1,4] Konrad Wagstyl,[5] Sophie Adler,[1] Aswin Chari,[1,4] John Booth,[6] Friederike Moeller,[7] Krishna Das,[3,7] Christin Eltze,[7] Gerald Cooray,[7,8] Ana Perez Caballero,[9] Lara Menzies,[10] Amy McTague,[1,10] Sara Shavel-Jessop,[1,2] Martin M. Tisdall,[1,4] J. Helen Cross,[1,3,4,11] Patricia Martin Sanfilippo[1,2] and Torsten Baldeweg[1,2,4]

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Epilepsia Open®
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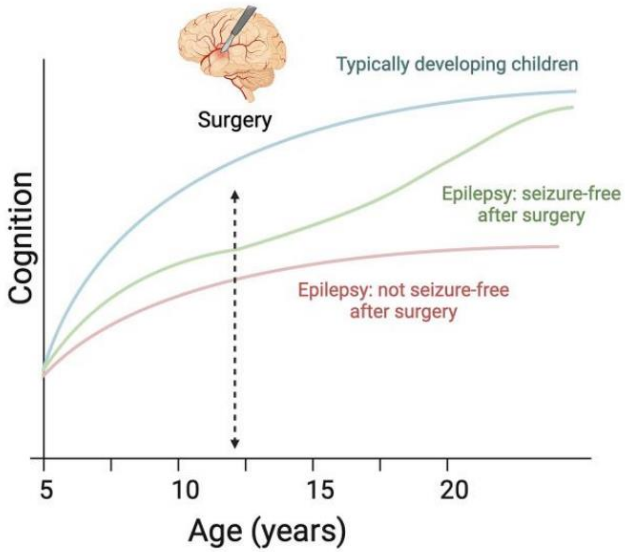
ORIGINAL ARTICLE

Epilepsy surgery below the age of 5 years: Are we still in time to preserve developmental and intellectual functions?

Simona Cappelletti[1] | Cinzia Correale[1] | Mattia Mercier[1] | Giusy Carfi Pavia[1] | Chiara Falamesca[1] | Alessandro De Benedictis[2] | Carlo Efisio Marras[2] | Chiara Quintavalle[1] | Concetta Luisi[1] | Chiara Pepi[1] | Daniela Chiarello[1] | Federico Vigevano[3] | Luca De Palma[1] | Nicola Specchio[1,4]



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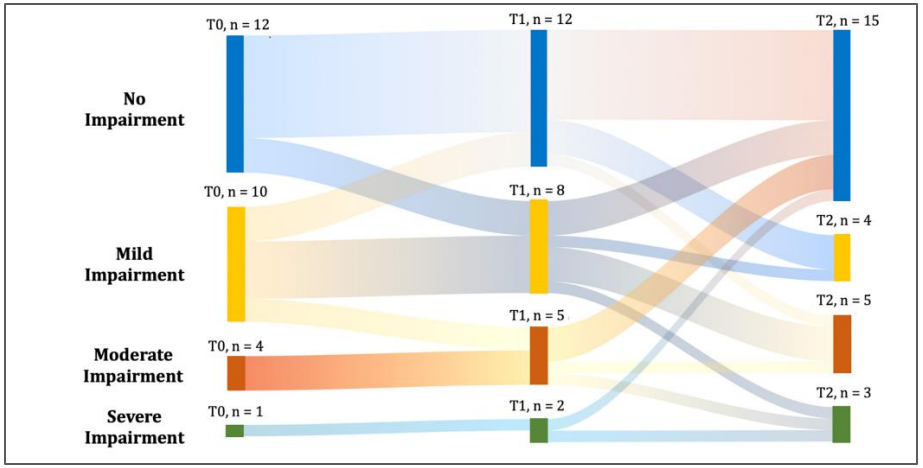


27 Patienten
2 Gruppen: lange Epilepsiedauer vor OP: Time is brain!
Kürzerer Epilepsiedauer vor OP: Verbesserung Kognition
Längere Epilepsiedauer vor OP: Verschlechterung möglich

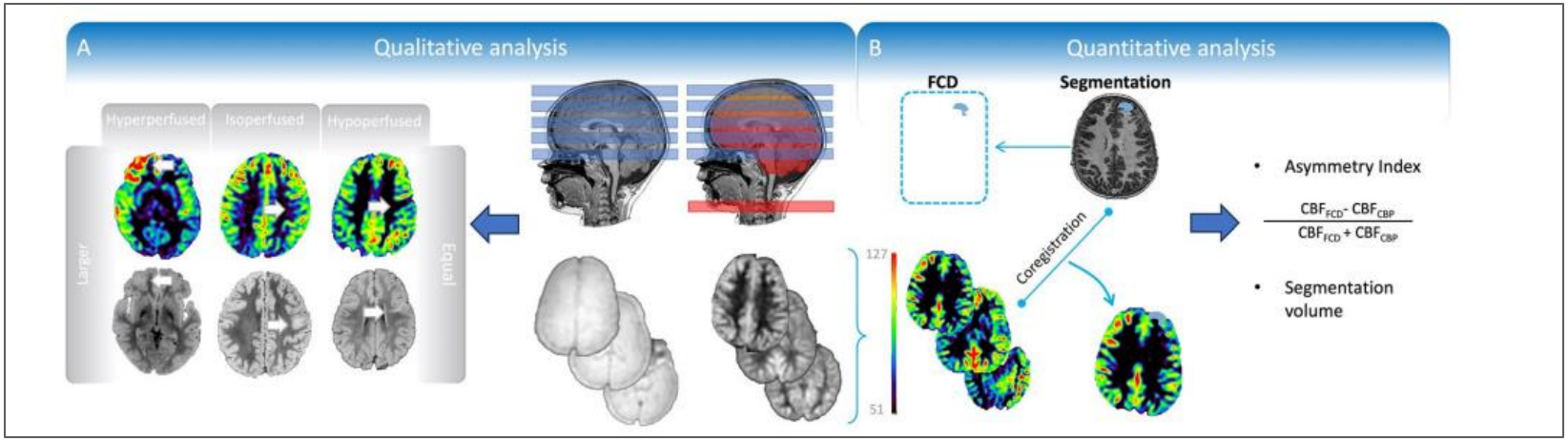
Spin labelig perfusion, EEG activity, lesion size

OPEN

Lesion volume and spike frequency on EEG impact perfusion values in focal cortical dysplasia: a pediatric arterial spin labeling study

Antonio Giulio Gennari[1,2], Giulio Bicciato[1,3], Santo Pietro Lo Biundo[1], Raimund Kottke[4], Ilona Stefanos-Yakoub[1], Dorottya Cserpan[1], Ruth O'Gorman Tuura[2,5,6,7] & Georgia Ramantani[1,5,6,7]✉

Sci Rep. 2024 Mar



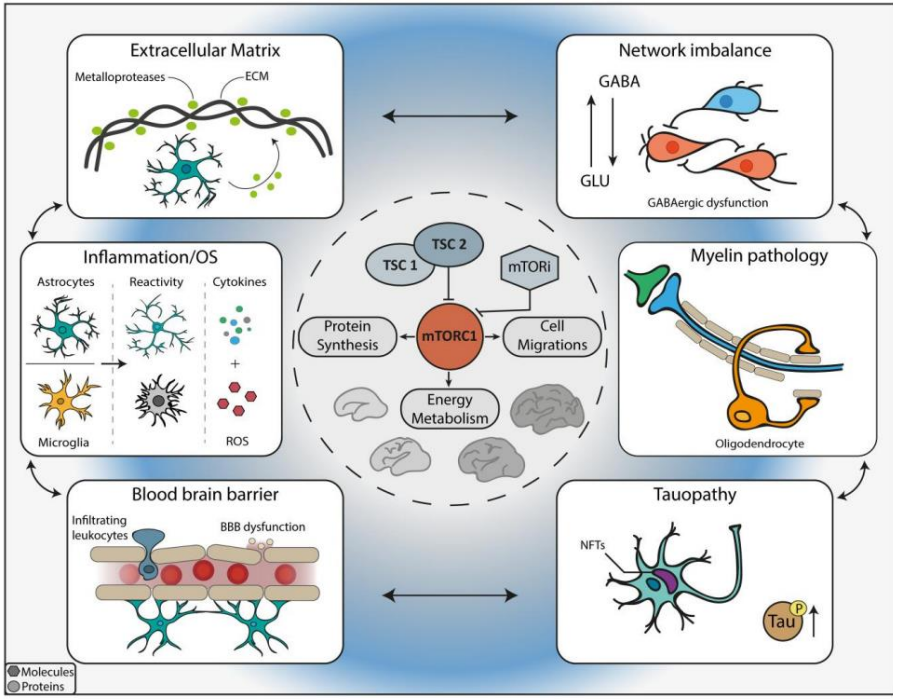
Epileptogenesis TSC

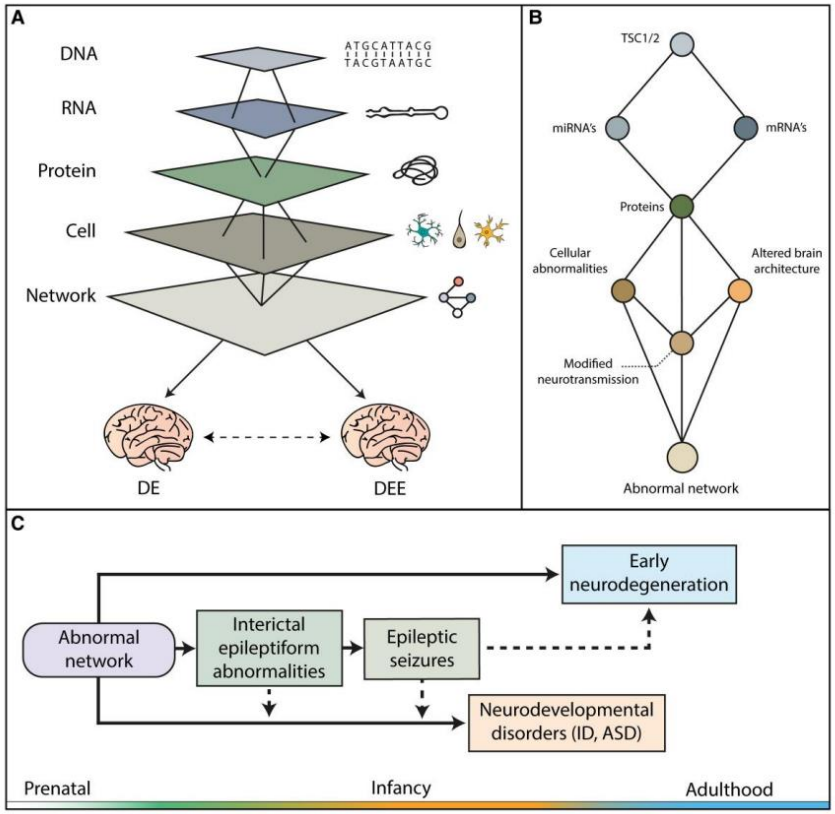
https://doi.org/10.1093/brain/awad048 BRAIN 2023: 146; 2694–2710 | 2694

BRAIN
REVIEW ARTICLE

Epileptogenesis in tuberous sclerosis complex-related developmental and epileptic encephalopathy

Eleonora Aronica,[1,2] Nicola Specchio,[3] Mark J. Luinenburg[1] and Paolo Curatolo[4]





Epilepsy and Comorbidities

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DOI: 10.1111/epi.17115

Epilepsia

CRITICAL REVIEW

The epilepsy–autism spectrum disorder phenotype in the era of molecular genetics and precision therapy

Nicola Specchio[1] | Valentina Di Micco[2] | Marina Trivisano[1] | Alessandro Ferretti[1] | Paolo Curatolo[2]

RESEARCH ARTICLE

Movement Disorders in Patients With Genetic Developmental and Epileptic Encephalopathies

Sterre van der Veen, MD,* Gabrielle T.W. Tse, MD,* Alessandro Ferretti, MD, Giacomo Garone, MD, Bart Post, MD, PhD, Nicola Specchio, MD, PhD, Victor S.C. Fung, MBBS, PhD, Marina Trivisano, MD, PhD, and Ingrid E. Scheffer, MBBS, PhD

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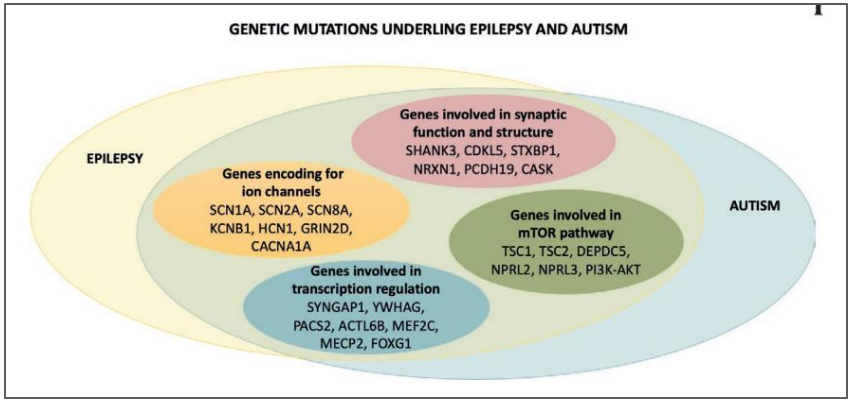
Neurology® 2023;101:e1884-e1892. doi:10.1212/WNL.0000000000207808

Neurology 23



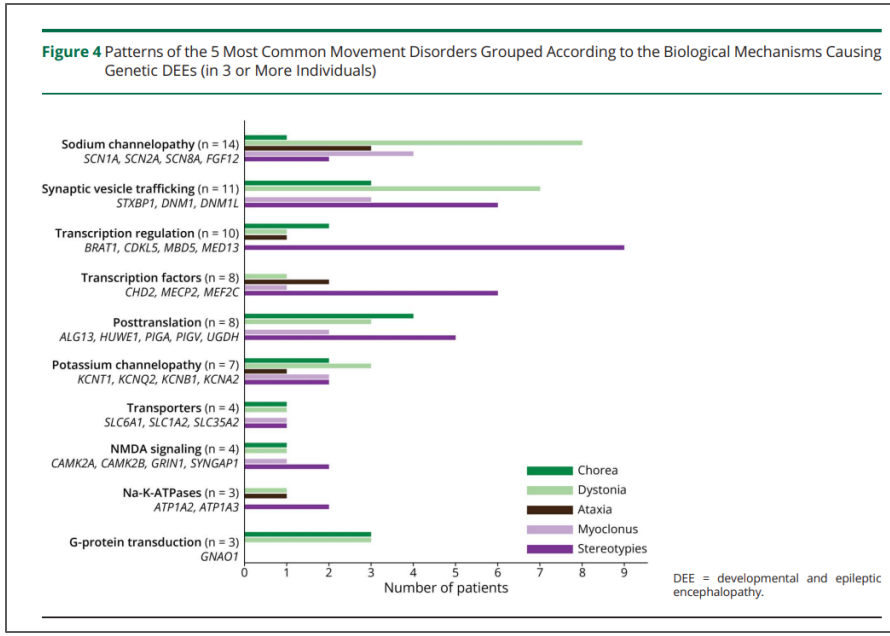


Figure 4 Patterns of the 5 Most Common Movement Disorders Grouped According to the Biological Mechanisms Causing Genetic DEEs (in 3 or More Individuals)

DEE = developmental and epileptic encephalopathy.

Fenfluramine bei Dravet, Lennox und anderen DEEs

Received: 12 April 2023 | Revised: 2 August 2023 | Accepted: 3 August 2023
DOI: 10.1111/epi.17737
Epilepsia™
RESEARCH ARTICLE

Fenfluramine in the treatment of Dravet syndrome: Results of a third randomized, placebo-controlled clinical trial

Joseph Sullivan[1] | Lieven Lagae[2] | J. Helen Cross[3] | Orrin Devinsky[4] | Renzo Guerrini[5] | Kelly G. Knupp[6] | Linda Laux[7] | Marina Nikanorova[8] | Tilman Polster[9] | Dinesh Talwar[10] | Berten Ceulemans[11] | Rima Nabbout[12] | Gail M. Farfel[13] | Bradley S. Galer[13] | Arnold R. Gammaitoni[13] | Michael Lock[14] | Anupam Agarwal[13] | Ingrid E. Scheffer[15] | on behalf of the FAiRE DS Study Group

3. Phase 3 Studie, 12 Wochen, 169 K., 65% Reduktion Anfälle

Received: 15 February 2024 | Revised: 20 May 2024 | Accepted: 4 June 2024
DOI: 10.1002/epi4.12998
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CRITICAL REVIEW

Practical considerations for the use of fenfluramine to manage patients with Dravet syndrome or Lennox–Gastaut syndrome in clinical practice

Elaine C. Wirrell[1] | Lieven Lagae[2] | Ingrid E. Scheffer[3] | J. Helen Cross[4,5] | Nicola Specchio[6] | Adam Strzelczyk[7]

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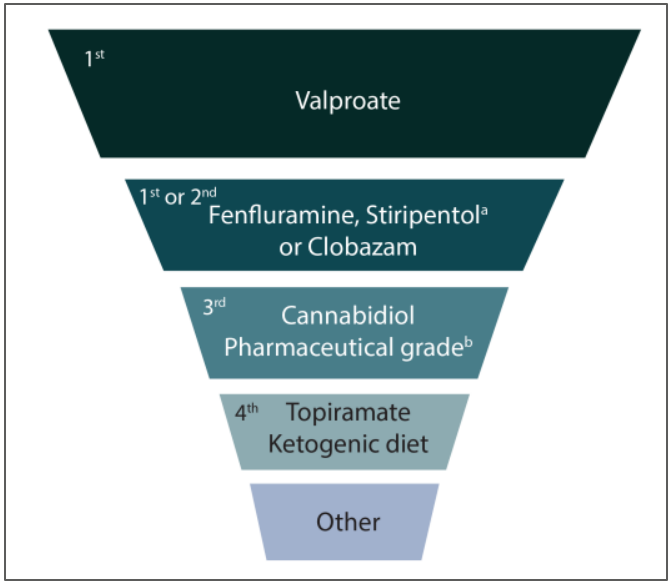
DOI: 10.1111/epi.18020
Epilepsia
CRITICAL REVIEW

Comprehensive scoping review of fenfluramine's role in managing generalized tonic–clonic seizures in developmental and epileptic encephalopathies

Antonio Gil-Nagel[1] | J. Helen Cross[2] | Orrin Devinsky[3] | Berten Ceulemans[4] | Lieven Lagae[5] | Kelly Knupp[6] | An-Sofie Schoonjans[4] | Philippe Ryvlin[7] | Elizabeth A. Thiele[8] | Shikha Polega[9] | Amélie Lothe[10] | Rima Nabbout[11]



CBD und Stiripentol

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DOI: 10.1002/epi4.12956

Epilepsia Open®
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CRITICAL REVIEW

Consensus panel recommendations for the optimization of EPIDIOLEX® treatment for seizures associated with Lennox–Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex

Robert T. Wechsler[1] | David E. Burdette[2] | Barry E. Gidal[3] | Ann Hyslop[4] | Patricia E. McGoldrick[5] | Elizabeth A. Thiele[6] | James Valeriano[7]

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Epilepsia Open®
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CRITICAL REVIEW

Efficacy and safety of stiripentol in the prevention and cessation of status epilepticus: A systematic review

Nicola Specchio[1] | Stéphane Auvin[2,3,4] | Adam Strzelczyk[5] | Francesco Brigo[6] | Vicente Villanueva[7] | Eugen Trinka[8,9,10]

BOX 1 Recommendations for the optimization of Epidiolex for seizures associated with LGS, DS, and TSC

Overcoming barriers to Epidiolex initiation

1. Identifying patients with LGS
   - History of multiple drug-resistant seizures
   - Some degree of cognitive impairment
   - EEG SSW activity
   - Review patient history and utilize REST-LGS for identification of potential LGS
2. Identifying patients with DS
   - Reference: 2022 International Consensus on Diagnosis and Management of DS[22]
   - Genetic testing recommended as SOC*
3. Identifying patients with TSC
   - Reference: 2021 Updated International TSC Diagnostic Criteria[13]
   - Conduct detailed skin examination
4. Differentiating Epidiolex from non-FDA-approved CBD products
   - Inform patients and their families that Epidiolex is approved and evaluated in RCTs
5. Setting expectations for therapeutic effect and safety/tolerability of Epidiolex
   - Proven efficacy in seizure reduction and anecdotal behavior/mood improvement

Epidiolex dosing for seizures associated with LGS, DS, and TSC

6. Initiation, titration, and maintenance of Epidiolex
   - Inform patients that response to Epidiolex is individualized
   - Determine initial target dose and titration rate based on patient baseline variables, prior response to ASMs, and therapeutic goals
7. Food effects
   - Epidiolex should be taken with or without food consistently, preferably with food, particularly high-fat food
   - Epidiolex can be taken while on dietary therapies
8. Managing AEs associated with Epidiolex
   - 8a. Gastrointestinal AEs
     - No proactive changes to bowel regimen needed
     - Diarrhea mitigation: slower dose titration; diet/concomitant medication adjustments; Epidiolex dose reduction if other efforts fail
   - 8b. Liver function AEs
     - Monitor liver function: pre-Epidiolex initiation, and 1, 3, and 6 mos post-initiation
     - Periodic LFTs thereafter or as clinically indicated
   - 8c. Sedation AEs
     - Initiate sedating medications at lower dose with slow titration when added to Epidiolex
     - Administer either a higher evening dose of Epidiolex or CLB (or both), or a single evening dose of Epidiolex QD if daytime sedation is a concern
9. Managing Epidiolex and concomitant medications
   - 9a. Epidiolex and CLB
     - If tolerated, maintain CLB without immediate dose adjustment when adding Epidiolex
     - If patients experience sedation, reduce CLB dose when adding Epidiolex
     - Consider low-dose CLB in patients who do not obtain optimal benefit from Epidiolex
   - 9b. Epidiolex and VPA
     - When adding Epidiolex to VPA or vice versa, monitor LFTs upon drug initiation and at 1, 3, and 6 mos after initiation
     - If LFTs are persistently elevated or patient is symptomatic while on VPA, and if patient failed VPA, gradually decrease or eliminate VPA; reduce Epidiolex dose if elevated LFTs not resolved
     - If VPA is added to Epidiolex, the same safety monitoring is recommended
   - 9c. Epidiolex and oral mTOR inhibitors
     - Epidiolex added to oral mTOR inhibitor: monitor mTOR inhibitor levels, reduce dosage
     - Oral mTOR inhibitor added to Epidiolex: initiate mTOR inhibitor at lower dose, titrate slowly, and monitor mTOR inhibitor levels
     - When discontinuing Epidiolex, consider increasing mTOR inhibitor dose
   - 9d. Epidiolex and other concomitant medications
     - Consider potential DDIs between Epidiolex and other concomitant medications
     - Consider increasing Epidiolex dosage up to 2-fold when coadministered with a strong CYP3A4 and/or CYP2C19 inducer
     - Reduce dosage of substrates of UGT1A9, UGT2B7, CYP1A2, CYP2C8, and CYP2C9 if patients experience AEs during coadministration with Epidiolex
10. Determining whether the optimal dose is reached
    - Increase Epidiolex dose as tolerated; consider response to maximum tolerated dose as effectiveness measure
    - Add other ASMs if Epidiolex is not optimally effective at maximum tolerated dose; medications should not be added when titrating Epidiolex
11. Assessing outcomes
    - Assess outcomes during each patient encounter
    - Primary efficacy outcome: reduction in seizure burden
    - Secondary efficacy outcomes: use of rescue medications, emergency room visits, and days missed from school/work
    - Effects on total medication regimen, mood, and behavior should also be assessed
12. Discontinuation of Epidiolex
    - Gradually taper patients off Epidiolex
    - If the situation is emergent or patient is having intolerable AEs, discontinue Epidiolex without tapering
    - Concomitant medications may need adjustment when discontinuing Epidiolex due to PK/PD interactions

**SCN1A* variants are not required for diagnosis.
Abbreviations: AE, adverse event; ASM, antiseizure medication; CBD, cannabidiol; CLB, clobazam; DDI, drug–drug in-

Cenobamate in pediatric patients

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Brief Communication

Adjunctive use of cenobamate for pediatric refractory focal-onset epilepsy: A single-center retrospective study

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21 Kinder

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BRIEF RESEARCH REPORT
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Real-World Experience Treating Pediatric Epilepsy Patients With Cenobamate

Konstantin L. Makridis [1,2,3,4], Thomas Bast [5], Christine Prager [1,2,3], Tatjana Kovacevic-Preradovic [6], Petra Bittigau [1,2,3], Thomas Mayer [6], Eva Breuer [7] and Angela M. Kaindl [1,2,3,4*]

Anfallsreduktion um 50% bei 60-70%
NW: Somnolenz, Ataxie, Vertigo

226 Patienten, 20% Kinder

Pharmacoresistance

Received: 16 May 2023 | Revised: 8 August 2023 | Accepted: 16 August 2023

DOI: 10.1111/epi.17751

Epilepsia™

SPECIAL REPORT

Revisiting the concept of drug-resistant epilepsy: A TASK1 report of the ILAE/AES Joint Translational Task Force

Stéphane Auvin[1,2,3] | Aristea S. Galanopoulou[4] | Solomon L. Moshé[4,5] | Heidrun Potschka[6] | Luisa Rocha[7] | Matthew C. Walker[8] | on behalf of the TASK1 workgroup on drug-resistant epilepsy of the ILAE/AES Joint Translational Task Force

Genetic therapies ready for the clinic? Current developments

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Are Genetic Therapies for Epilepsy Ready for the Clinic?

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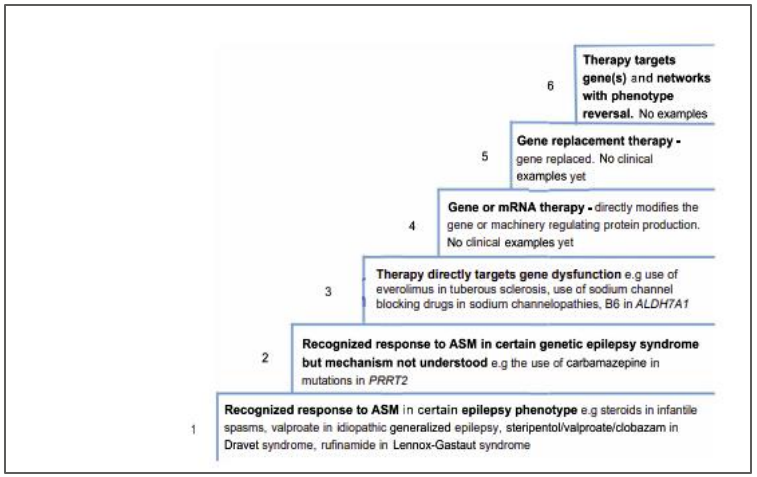

Byrne et al, 2021

Table 1. Current Genetic Therapies for Epilepsy Preclinically Tested.

	Strategy	Disease targeted	Vector delivered	Clinical trial	Citations
Causes	Gene supplementation	Dravet syndrome	HC-AdV-CAG-SCN1A/pAAV9-pGad1-NaVβ1-myc	–	1,2
		CDKL5 deficiency disorder	AAV-PHP.B-CBh-hCDKL5_1	–	3
	Gene modulation	Dravet syndrome	AAV9-PhP.eB-TetOn/mdlx-dCas9A-Scn1a/AAV9-PhP.eB-flox-VGAT-dCAS9A-Scn1a/AAV9-RE(GABA)-eTF(Scn1a)	ENDEAVOR (NCT05419492)	4-6
	Antisense oligonucleotides	Dravet syndrome	ASO-Scn1a nonproductive splicing event	MONARCH (NCT04740476)	7,8
		SCN2A DEE	ASO-Scn2a	–	9
		SCN8A encephalopathy	ASO-Scn8a	–	10
		Epilepsy of infancy with migrating focal seizures	ASO-Kcnt1	–	11
		Lafora disease	ASO-*Gys1*	–	12
		Angelman syndrome	ASO-Ube3a-ATS	GTX-102 (NCT04259281)	13,14
	RNA interference	Lennozx-Gastaut syndrome	scAAV9-miDnm1a	–	15
Symptoms	Neuropeptides	TLE	scAAV2-CBA-pDyn (predynorphin)	–	16,17
		TLE	rAAV1/2-CBA-NPY/AAV1-CAG-NPY-hY2	–	18,19
		TLE	AAV2-FIB-GAL (Galanin)	–	20
	Exogenous proteins	TLE and neocortical focal epilepsy	AAV5-CamkIIα-HA-hM4D(Gi)/AAV2/5-hCAMKII-hM4D(Gi)/AAV2/7-CamKIIα-hM4D(Gi)/AAV2.1-hSyn-hM4Di	–	21-23
		TLE, neocortical focal epilepsy and cortical injury	LV-Camk2a-NpHR/rAAV5-Camk2a-eNpHR/CamKII/PV-cre x floxed-STOP ChR	–	24-28
		Neocortical focalepilepsy	Lentivirus CAMK2A-eGluCL	–	29
	Endogenous channels	TLE	AAV9 CamKII-dCAS9A-Kcna1	–	30
		TLE and neocortical focal epilepsy	Lenti/AAV9 CAMK2A-EKC(KCNA1)	NCT04601974	31,32
		TLE	AAV9-cfos-EKC (KCNA1)	–	33
		Episodic ataxia type 1 with epilepsy	ASO-Scn8a	–	34
		Dravet syndrome	ASO-Scn8a	–	10
		KCNQ2 DEE	ASO-Scn8a	–	34
		TLE	AAV10-shRNA-Scn8a	–	35

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