Il paziente con encefalopatia epilettica: il paradigma della s. di Dravet e della s. di Lennox-Gastaut

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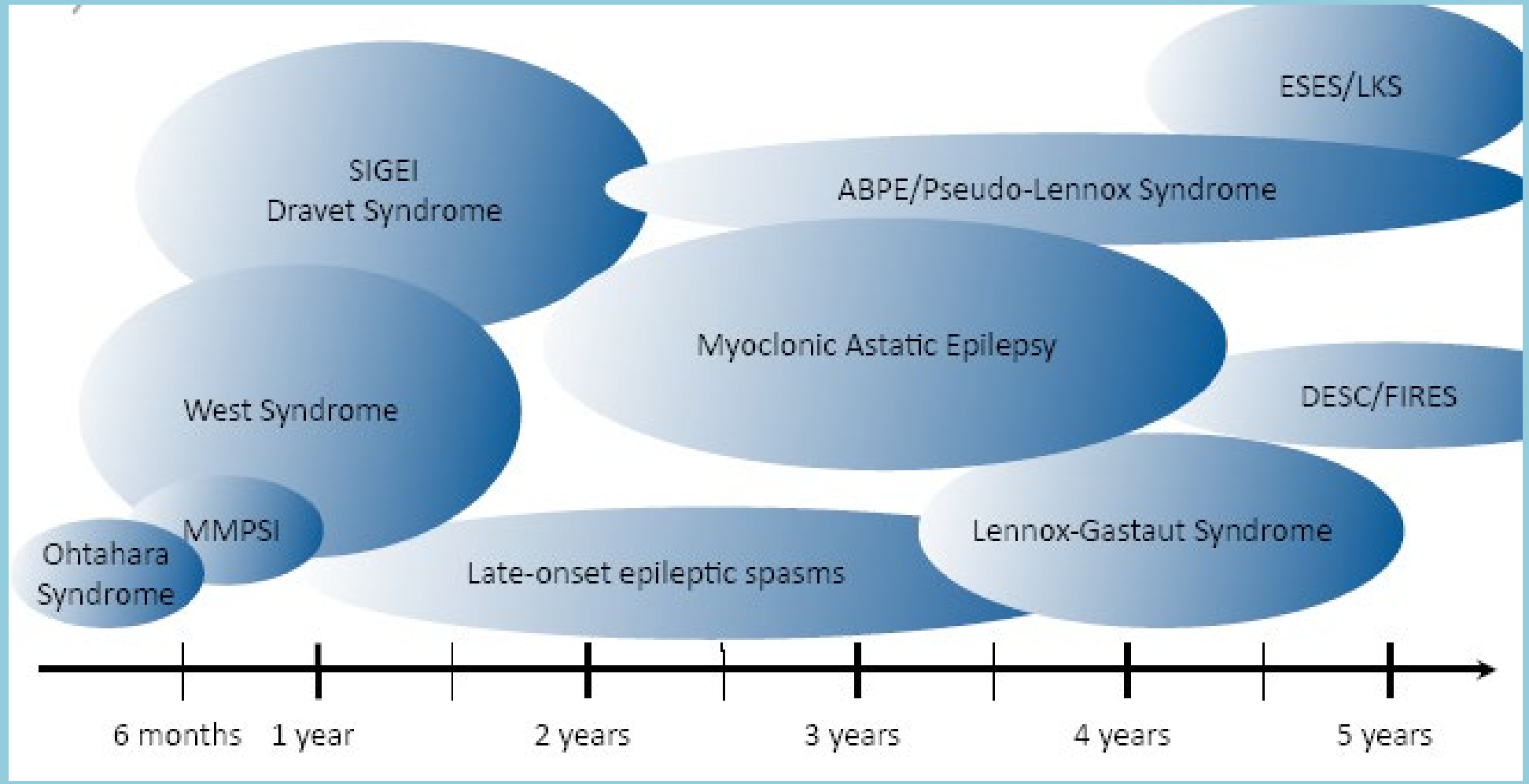
DINOGMI 2018-2022 | DIPARTIMENTO DI ECCELLENZA MIUR

Developmental Epileptic Encephalopathies

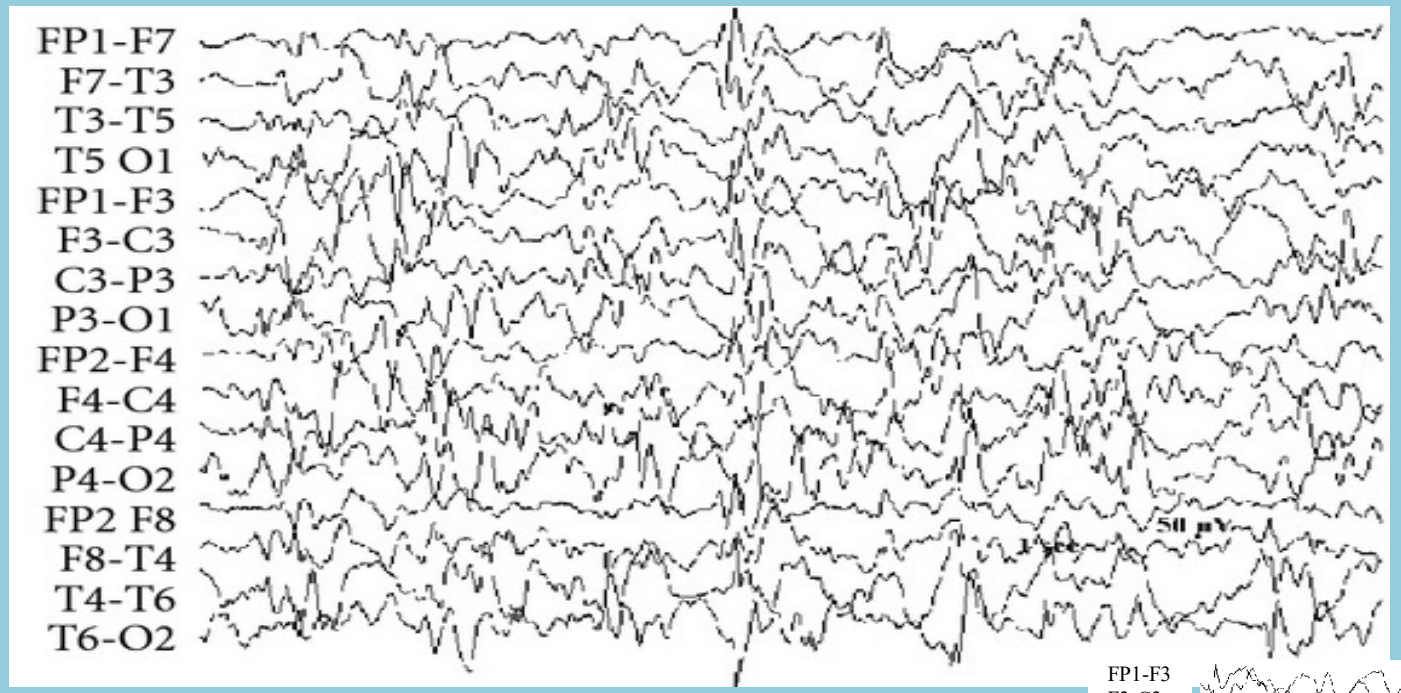


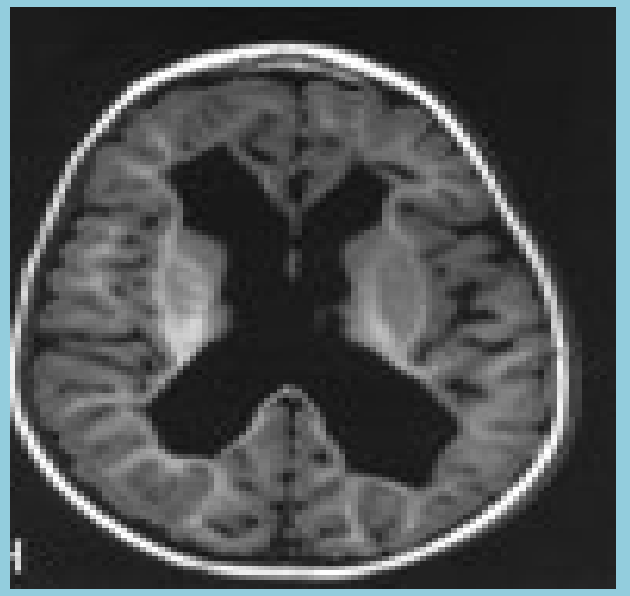
DEEs: Conceptual issues

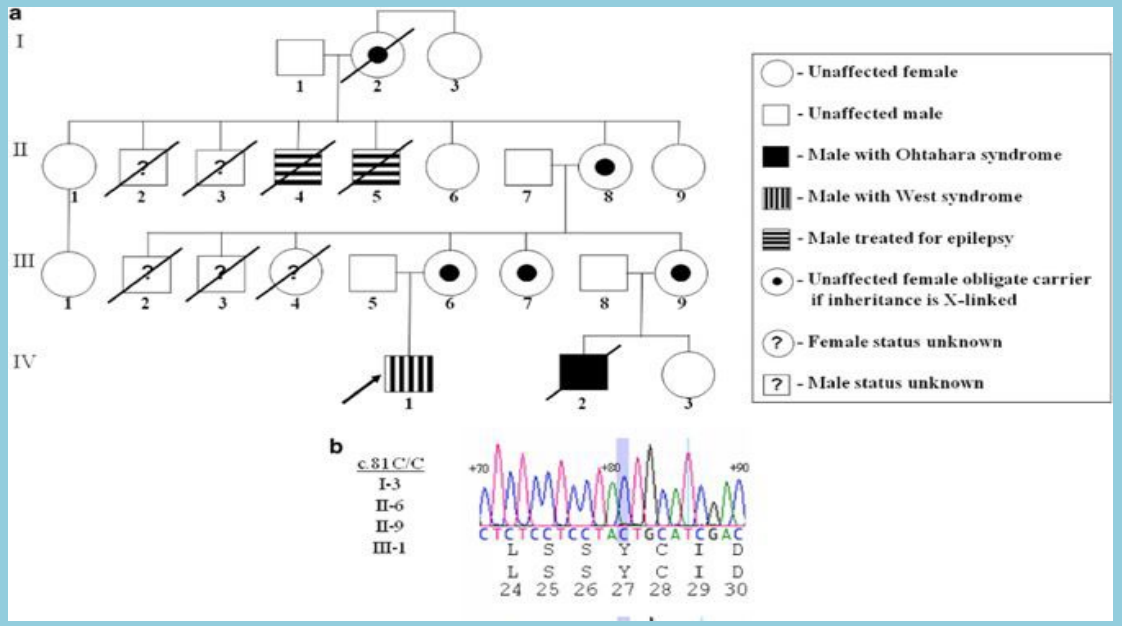
- ”Developmental epileptic encephalopathy” describes the process of cognitive impairment due to epileptic activity which occurs across a range of epilepsy syndromes, and to a variable extent over time.

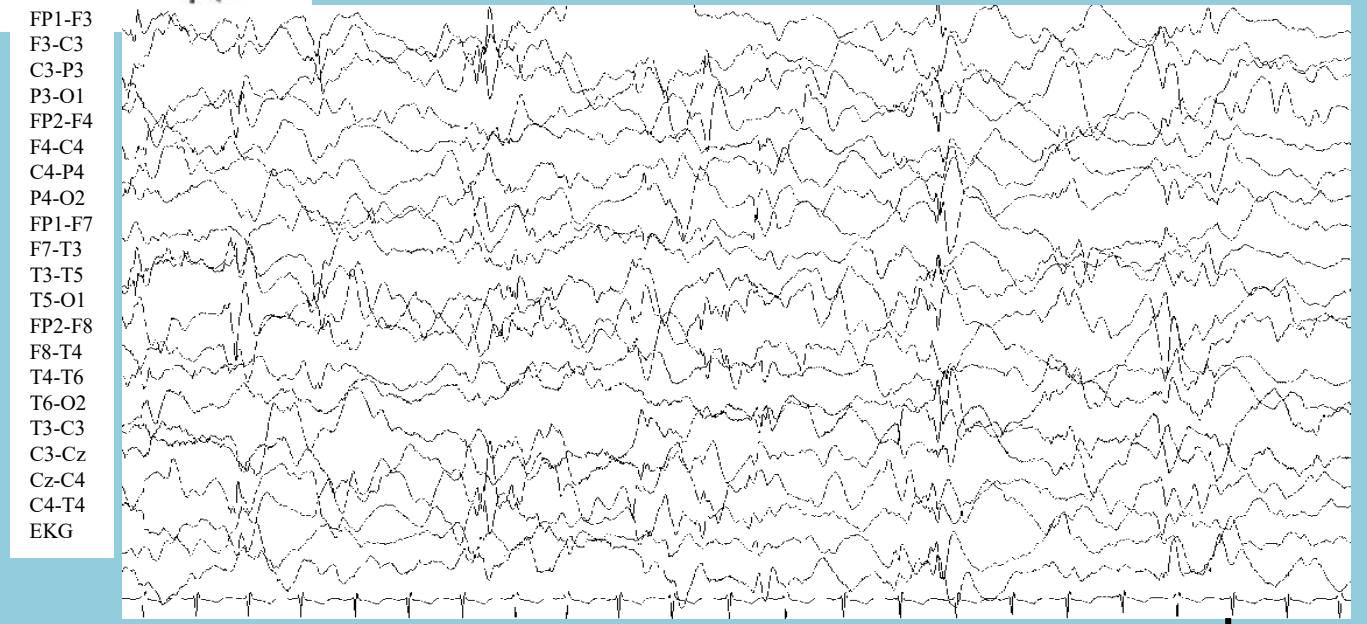
- The epileptic encephalopathy is the **potentially reversible state** that a patient with epilepsy can be in, but it does not represent the overall diagnosis.

- Deterioration is independent from epilepsy, even if epilepsy can aggravate the clinical picture and epileptic activity may contribute to cognitive and behavioral impairment that can worsen over time (“epileptogenic” encephalopathy’’).





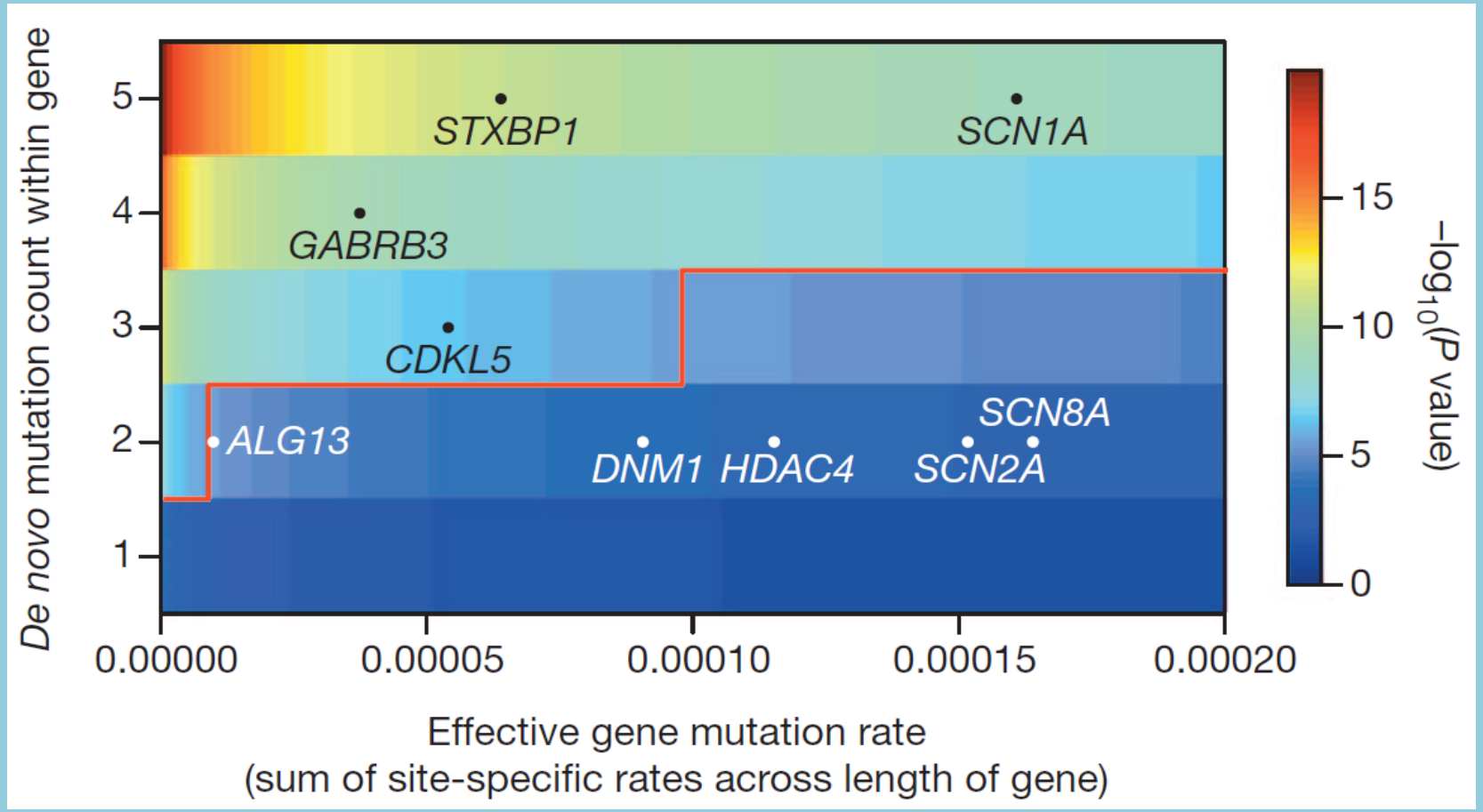




European Journal of Human Genetics 2010

De novo mutations in epileptic encephalopathies

Epi4K Consortium* & Epilepsy Phenome/Genome Project*



Epileptic encephalopathies

0-3 months	• Ohtahara syndrome (*STXBP1, KCNQ2, SCN2A*)
	  • Neonatal onset, tonic seizures, burst suppression on EEG
	• Epilepsy of Infancy with Migrating Focal Seizures (*KCNT1, SCN2A*)
	  • Refractory focal seizures, migrate from one region to another

4 months – 2 years	• West syndrome (*CDKL5, STXBP1, ARX, DNM1*)
	  • Infantile spasms with hypsarrhythmia on EEG
	• Dravet syndrome (*SCN1A*)
	  • Prolonged febrile/afebrile sz, focal (hemiclonic), regression

1-8 years	• Lennox-Gastaut syndrome (*CDKL5, DNM1*)
	  • Refractory seizures (tonic), generalized slow-spike wave on EEG
	• Myoclonic-atonic epilepsy/Doose syndrome (*SLC2A1, SLC6A1*)
	  • Febrile seizures, myoclonic-atonic seizures, regression

2-10 years	• Landau-Kleffner syndrome (*GRIN2A*)
	  • Acquired aphasia, previously normal devt, +/- seizures
	  • Electrical status epilepticus during slow wave sleep

Current Pediatrics Reports 2017, Volume 5, pp 24–29

Dravet Syndrome is an early-onset treatment-resistant epilepsy syndrome[1]

- Normal birth and neonatal history[1]
- First seizure: typically clonic, generalised or unilateral and in first year of life[1,2]
- Additional seizures: 2 weeks to 2 months after first seizure[2]
- The prevalence of DS is <1 in 40,000 worldwide and 1 in 28,000 in the UK[3]
- Patients suffer from multiple seizure types, including prolonged convulsive seizures which can evolve to SE[2]

1. ILAE. Available from: https://www.epilepsydiagnosis.org/syndrome/dravet-overview.html (Accessed 23 January 2019); 2. Dravet C. *Epilepsia.* 2011;52(Suppl. 2):S3–9; 3. Orphanet. Dravet syndrome. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=33069&lng=EN (Accessed 24 January 2019)

AED, anti-epileptic drug; DS, Dravet syndrome; IDEAL, International Dravet syndrome Epilepsy Action League; SE, status epilepticus; SUDEP, sudden unexpected death in epilepsy

5° HORIZONS FOR DRAVET SYNDROME INTERNATIONAL SYMPOSIUM

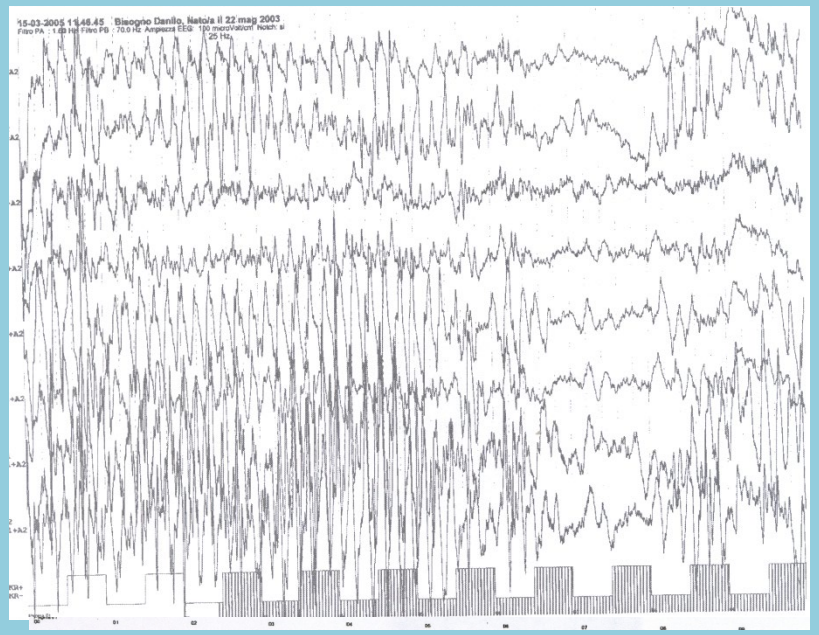
"40 Year Dravet Syndrome" Diagnosis and management of Dravet syndrome From unmet medical needs to best practices

Febrile and afebrile, generalized and unilateral, clonic or tonic-clonic seizures, that occur in the first year of life; later associated with myoclonus, atypical absences, and focal seizures

All seizure types are resistant to antiseizure drugs

Developmental delay becomes evident within the 2nd year, followed by cognitive impairment and personality disorders

Prevalence: 1:15-40,000 live births



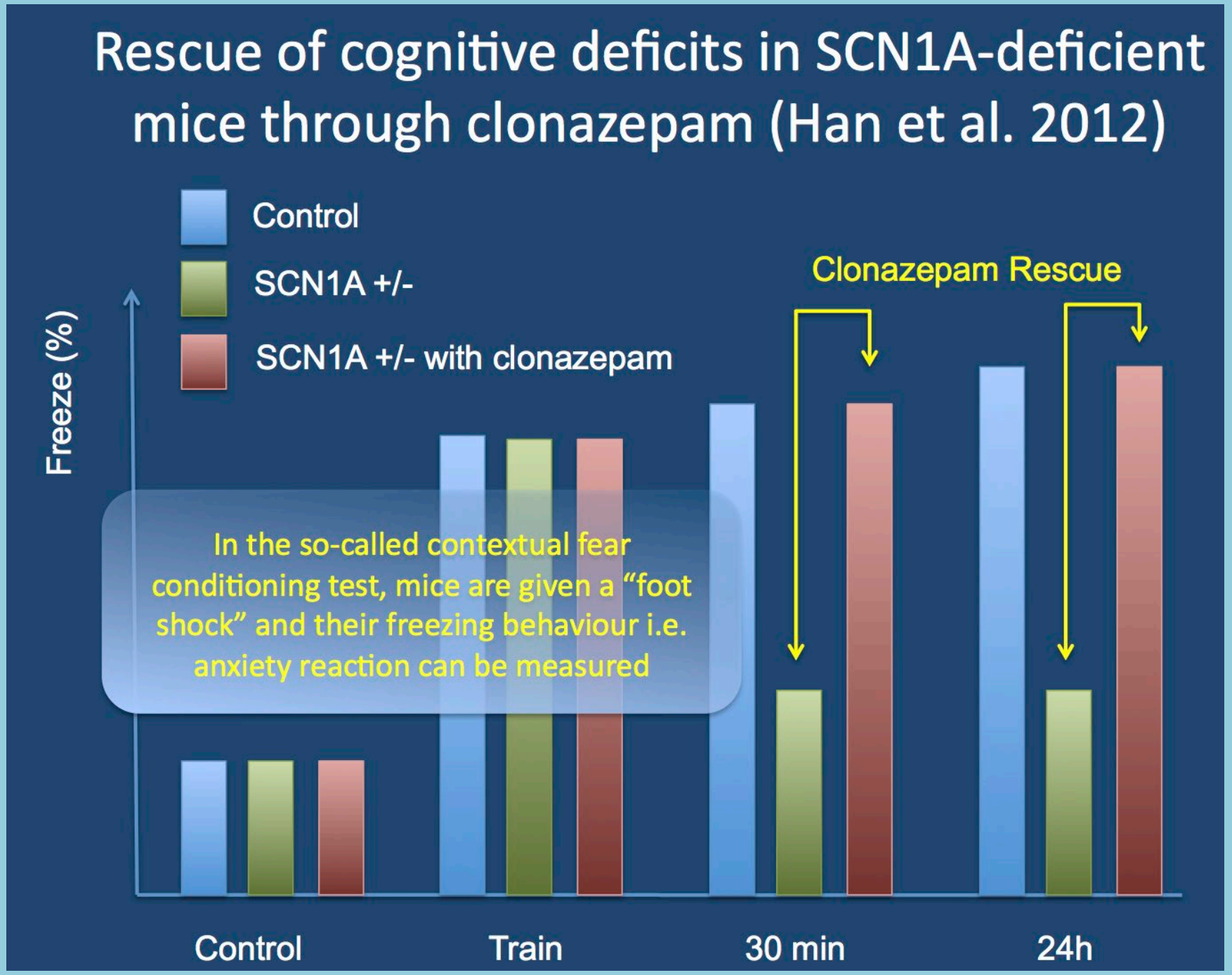
Am. J. Hum. Genet. 68:1327–1332, 2001

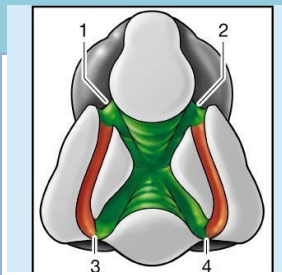
De Novo Mutations in the Sodium-Channel Gene *SCN1A* Cause Severe Myoclonic Epilepsy of Infancy

Lieve Claes,[1] Jurgen Del-Favero,[1] Berten Ceulemans,[2,3] Lieven Lagae,[3,4] Christine Van Broeckhoven,[1] and Peter De Jonghe[1,2]

[1]Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology (VIB), University of Antwerp, and [2]Department of Neurology, University Hospital Antwerp, Antwerp; [3]Epilepsy Center for Children and Youth, Pulderbos, Belgium; and [4]Department of Child Neurology, University Hospital Gasthuisberg, Leuven, Belgium

Rescue of cognitive deficits in SCN1A-deficient mice through clonazepam (Han et al. 2012)





Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in
Physiology

Dravet syndrome: a sodium channel interneuronopathy

William A Catterall

Co-morbidity	Symptoms in DS mice	Physiological correlates	Causal evidence for mechanism
Ataxia	Abnormal foot placement in walking	Failure of AP firing in GABAergic cerebellar Purkinje neurons	
Circadian rhythm	Long circadian cycle; weak light-induced phase shift; increased negative masking	Failure of AP firing in GABAergic neurons in the suprachiasmatic nucleus	Not observed in forebrain specific knockout mouse; reversed by clonazepam
Sleep impairment	Reduced non-REM sleep, delta wave power, sleep spindles	Failure of rebound AP firing in GABAergic neurons in the RNT	Observed in forebrain interneuron-specific knockout mouse
Cognitive deficit	Failure of spatial learning and memory	Failure of AP firing by GABAergic neurons in hippocampus and cerebral cortex	Observed in forebrain interneuron-specific knockout mouse and PV +SST-specific knockout; reversed by clonazepam
Autistic-like behavior	Impaired social interaction; repetitive behaviors	Failure of AP firing by PV-expressing GABAergic neurons in hippocampus and cerebral cortex	Observed in forebrain interneuron-specific and PV-specific knockout mouse; reversed by clonazepam

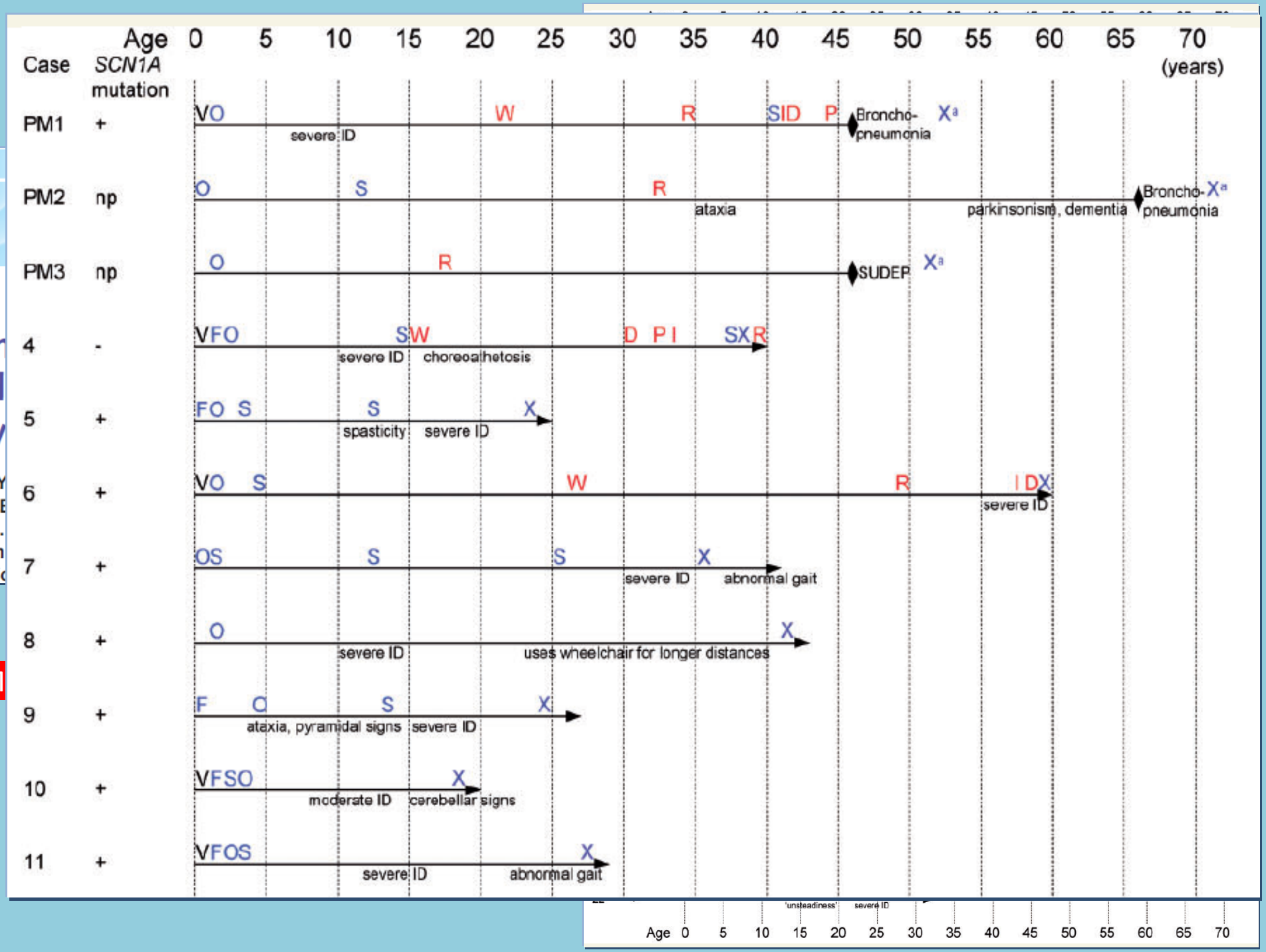
AP, action potential; SCN, suprachiasmatic nucleus of the hypothalamus; RNT, reticular nucleus of the thalamus; REM, rapid-eye-movement.

doi:10.1093/brain/awr129

BRAIN
A JOURNAL OF NEUROLOGY

Dravet syndrom
evidence from l
neuropathology

Claudia B. Catarino,[1,2] Joan Y
Robyn W. Labrum,[4] Rachael E
J. Helen Cross,[7,8,9] Richard E.
Susannah T. Bellows,[11] Thom
Lillian Martinian,[3] Ingrid E. Sc



Prognostic, clinical and demographic features in *SCN1A* mutation-positive Dravet syndrome

A. Brunklaus,[1,2] R. Ellis,[3] E. Reavey,[3] G.H. Forbes[3] and S.M. Zuberi[1]

Brain 2012: 135; 2329–2336

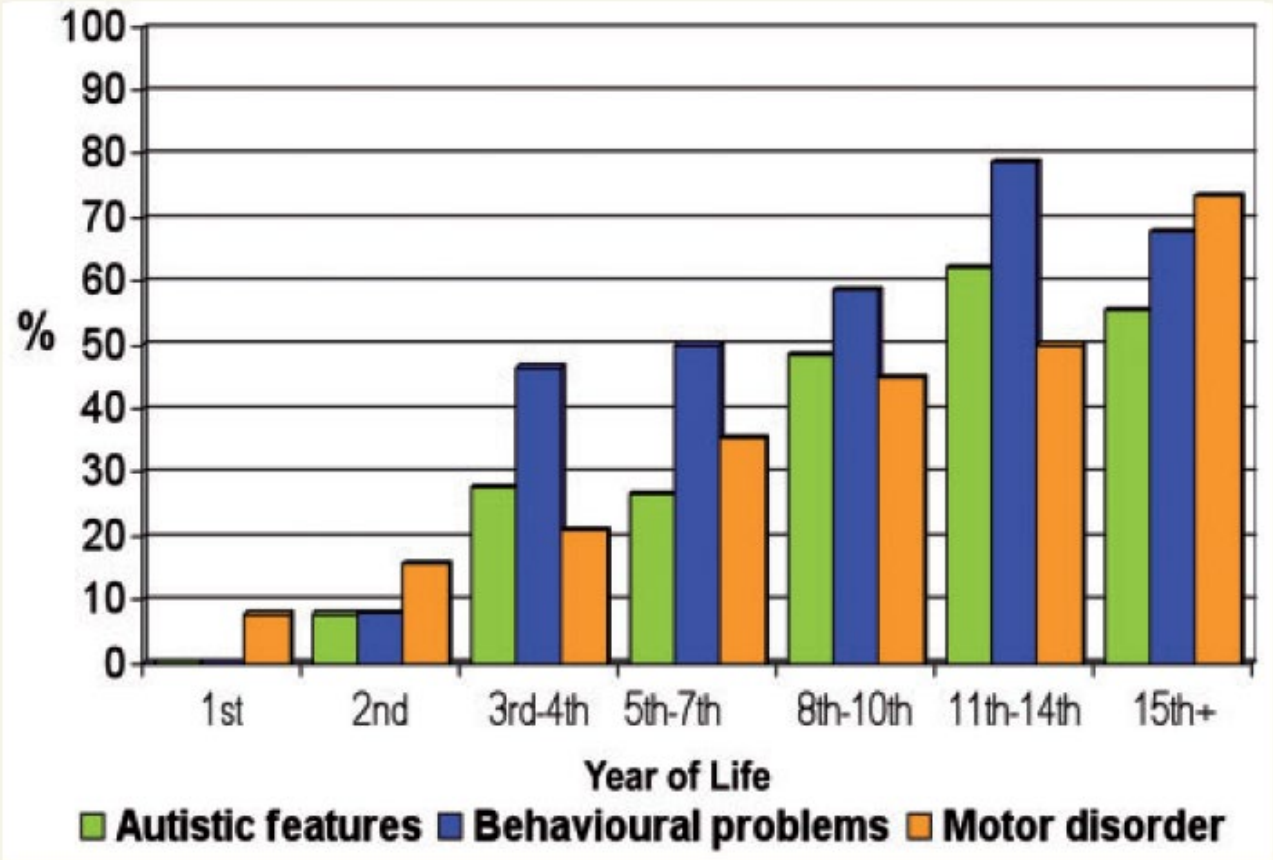


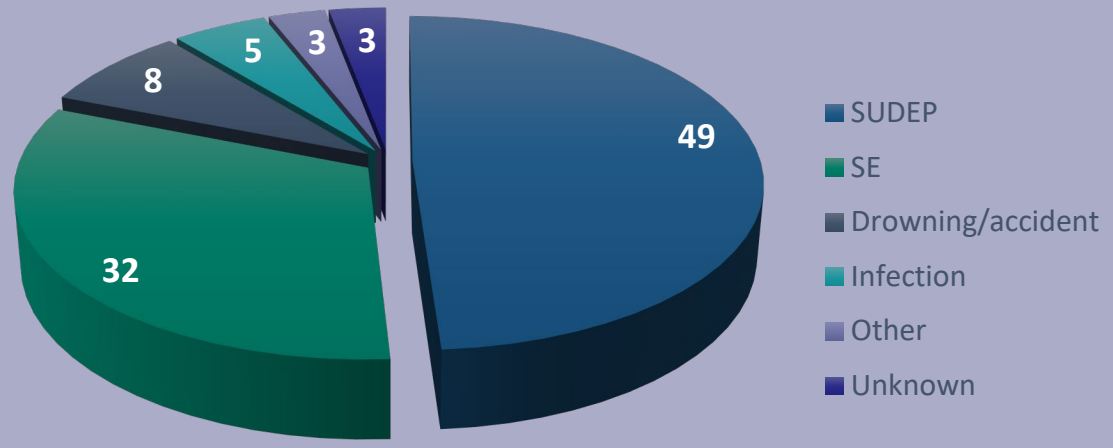
Figure 1 Cross-sectional analysis of acquired autistic features, behavioural problems and motor disorder over time.

DS is characterised by high risk of epilepsy-related premature death

- **Cohort of 100 consecutive patients with DS[1]**
  - DS-specific mortality rate of 15.84/1000 patient years
  - DS-specific SUDEP rate higher than in adults with refractory epilepsy (9.32 vs 5.1/1000 patient years)
  - SUDEP in DS occurs mainly in childhood

- **Systematic review of 177 published cases of death in DS[2]**
  - SUDEP and SE were the most likely causes (figure)
  - Mean (SD) age at death 8.7 (9.8) years
  - 73% of deaths occurred before the age of 10 years
  - SUDEP in DS occurs at a younger age (73% before the age of 11 years) than in other epilepsy cohorts (3-9% at ≤10 years)

Review of 177 cases of death in DS patients[2]

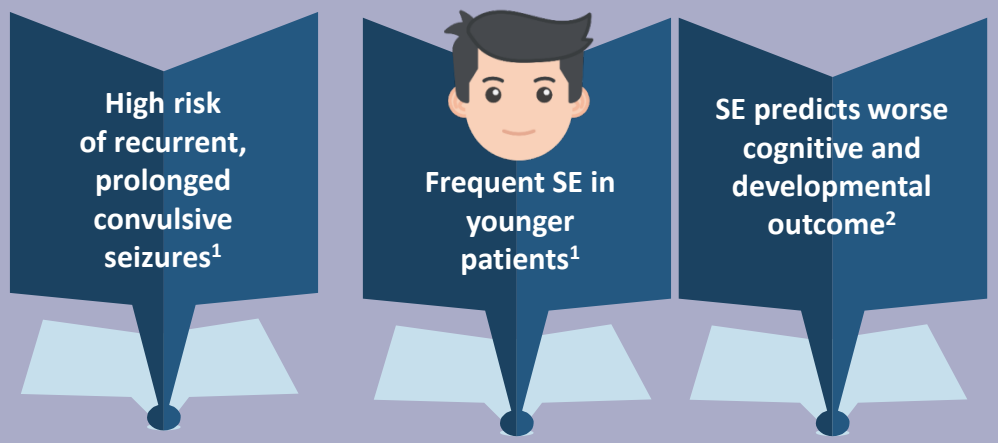


Adapted from: Shmuely S, et al. *Epilepsy Behav.* 2016;64:69–74

1. Cooper MS, et al. *Epilepsy Res.* 2016;128:43–47; 2. Shmuely S, et al. *Epilepsy Behav.* 2016;64:69–74;

DS, Dravet syndrome; IDEAL, International Dravet syndrome Epilepsy Action League; SD, standard deviation; SE, status epilepticus; SUDEP, sudden unexpected death in epilepsy

Status epilepticus



Age at SE-related death

DS[4]		Other epilepsies[5,6]	
≤10 years	86%	≤10 years	4%
≤20 years	98%	<20 years	4%

Up to one-third of all deaths in DS are due to SE; age at death due to SUDEP is lower than seen in other epilepsies[4]

Adapted from Shmuely S, et al. *Epilepsy Behav.* 2016;64:69–74; 5. Koubeissi M, Alshekhlee A. *Neurology*. 2007;69(9):886–893; 6. Wu YW, et al. *Neurology*. 2002;58(7):1070–1076.

33%

33% of patients admitted to the emergency room due to SE in the last year based on a parent-reported survey in a European population with DS[3]

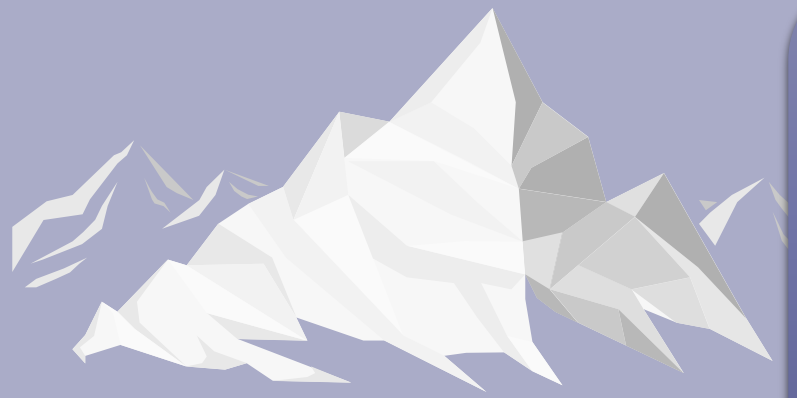
DS, Dravet syndrome; SE, status epilepticus; TC, tonic–clonic

1. Ziobro J, et al. *Curr Treat Options Neurol.* 2018;20:52; 2. Brunklaus A, et al. *Brain.* 2012;135:2329–2336; 3. Aras LM, et al. *Epilepsy Behav.* 2015;44:104–109; 4. Shmuely S, et al. *Epilepsy Behav.* 2016;64:69–74; 5. Koubeissi M, Alshekhlee A. *Neurology*. 2007;69(9):886–893; 6. Wu YW, et al. *Neurology*. 2002;58(7):1070–1076.

Treatment challenges in patients with DS

Limited literature and guidelines for diagnosis and treatment[1]

Multiple seizure types with a high degree of treatment resistance[1,2]



Adequate seizure control remains a significant concern for many patients despite currently available treatment options[3]

- **Complete seizure control is typically not achievable[1]**
- **High seizure burden results in poor quality of life for the child with DS and their family[1]**

Changing goals over time:[3]

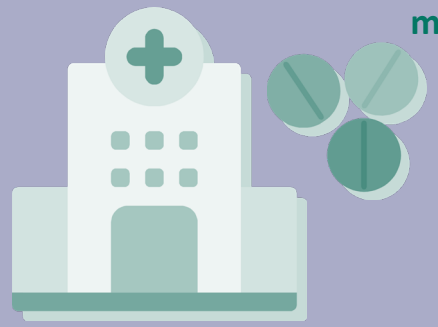
- **Younger children: prompt and early treatment with appropriate AEDs; SE management**
- **Older children and adolescents: reduction of nocturnal seizures to reduce risk of SUDEP**

Some AEDs may exacerbate seizures and should be avoided[3]

1. Wirrell EC, et al. *Pediatr Neurol.* 2017;68:18–34.e3;
2. Dravet C. *Epilepsia.* 2011;52:3–9; 3. Ziobro J, et al. *Curr Treat Options Neurol.* 2018;20:52

AED, anti-epileptic drug; DS, Dravet syndrome; SE, status epilepticus; SUDEP, sudden unexpected death in epilepsy

Potential benefits of effective seizure control



Prevention of SE with regular medication and emergency protocols may improve developmental outcome[3]

A greater degree of cognitive and behavioural impairment has been linked to higher seizure frequency[1]

Suppression of seizures may improve mental prognosis[2]

Nocturnal seizures

Reduction in nocturnal seizures may reduce the risk of SUDEP and improve QoL and developmental outcome[4,5]

It may be possible to reduce the risk of premature death in patients with DS by reducing convulsive seizure frequency and preventing evolution to SE[1]

Further research is required to establish the potential benefits of effective seizure control in patients with DS[2]

1. Wirrell EC. *Can J Neurol Sci.* 2016;43:S13–S18; 2. Akiyama M, et al. *Acta Med Okayama.* 2012;66:369–376; 3. Brunklaus A, et al. *Brain.* 2012;135:2329–2336; 4. Lamberts RJ, et al. *Epilepsia* 2012;53:253–257; 5. Licheni SH, et al. *Dev Med Child Neurol* 2018;60:192–198

DS, Dravet syndrome; QoL, quality of life; SE, status epilepticus; SUDEP, sudden unexpected death in epilepsy

Lennox-Gastaut syndrome: Prevalence and Incidence

- Prevalence is 1 to 10 % of all childhood epilepsy
- Incidence rate for LGS of all new onset epilepsies is 0.6 %

Diagnostic Criteria

Multiple Seizure Types- Tonic Seizures
Atypical absences
Tonic/Atonic drop attacks
Non-convulsive status epilepticus

Abnormal EEG
- Interictal slow spike –waves
- Paroxysmal Fast rhythms (non-REM sleep)

Cognitive Impairment
- Intellectual slowing/regression
- Behavioral problems

Bourgeios BFD et al. Epilepsia, 2014; 55 (Suppl. 4): 4-9

Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology

Alexis Arzimanoglou, Jacqueline French, Warren T Blume, J Helen Cross, Jan-Peter Ernst, Martha Feucht, Pierre Genton, Renzo Guerrini, Gerhard Kluger, John M Pellock, Emilio Perucca, James W Wheless

Lancet Neurol 2009; 8: 82–93

Panel 1: Summary of electroclinical features and progression of LGS

Onset

- Usually before the age of 8 years. Occurrence rates peak between 3 and 5 years of age, although late cases in early adulthood have been reported
- In young children with no obvious recognised cause (ie, cryptogenic), LGS usually begins with episodes of drop attacks, followed by other types of seizures
- The full clinical picture can also gradually develop after infantile spasms and West syndrome
- Interrictal EEG when the patient is awake is usually abnormal from the onset of the syndrome. Reactivity of background rhythms might be conserved; these rhythms are usually slow and poorly organised for the age of the child. EEG patterns when asleep can be normal at this stage
- Cause is heterogeneous. Brain damage (focal or multifocal abnormalities of cortical development, tuberous sclerosis, and, less commonly, acquired destructive lesions or metabolic diseases) plays a major role, whereas genetic factors are regarded to be less important
- Neurological symptoms can be absent, depending on the underlying cause
- Psychomotor development at the time of first seizures seems normal or the child might present with a homogeneous delay in development (of varying degrees) with or without signs of a personality disorder

Table 1. Demographic and clinical characteristics of LGS patients

#	Age at study (seizure onset age), years	Sex	Antiepileptic drugs at time of scan	Seizure types	Routine interictal EEG features	Structural MRI features	Presumed etiology (*=neuropathology)	Cognitive features (CI = cognitive impairment)
1	25 (0.5)	M	CBZ, LEV, TPM, VPA	Tonic, AA, GTCS	Background slowing, SSW, GPFA	Tuberous sclerosis, multiple lesions	Tuberous sclerosis complex	Moderately severe CI Nonverbal Autistic features
2	24 (0.5)	F	LEV, TPM	Tonic, AA	Background slowing, SSW, GPFA, bi-frontal discharges	Normal	Unknown	Severe CI Full-scale IQ < 50
3	41 (1)	F	CBZ, LTG, MDZ, VPA	Tonic, AA, myoclonic, GTCS	Background slowing, SSW, GPFA	Diffuse atrophy	Unknown	Severe CI Nonverbal
4	25 (2.5)	F	LTG, VPA	Tonic, AA, myoclonic, GTCS	Background slowing, SSW, GPFA, multifocal discharges	Normal	Chromosome 2q37 deletion syndrome	Moderately severe CI Full-scale IQ = 40 Autistic features
5	35 (2.5)	M	CLO, LTG, TPM, VPA	Tonic, AA, GTCS	Background slowing. SSW, GPFA	Normal	Unknown	Moderately severe CI Minimally verbal Autistic features
6	42 (3)	M	LEV, LTG, MDZ	Tonic, AA, GTCS	Background slowing, SSW, GPFA, bi-frontal discharges	L frontal and L temporal pole gliosis	Traumatic brain injury at age 2	Moderate CI Lives in supported accommodation
7	33 (4)	F	CBZ, LEV, LTG, VPA	Tonic, AA, FDS, GTCS	Background slowing, SSW, GPFA, bi-frontal discharges	Bilateral parietal double cortex	LIS-1 gene mutation (C.484G – A glycine 162 – serine)	Moderate CI Full-scale IQ = 60
8	44 (4)	M	CBZ, CLO, LTG, TPM, VPA	Tonic, AA, GTCS	Background slowing, SSW, GPFA, R frontal discharges	L frontal pole gliosis	Unknown	Moderate CI Lives in supported accommodation
9	11 (7)	M	CLO, ESX, TPM	Tonic, AA, spasms, GTCS	Background slowing, SSW, GPFA, multifocal discharges	Abnormal L temporal sulcation	Unknown	Moderately severe CI Full-scale IQ = 42 Autistic features
10	16 (9)	F	CLO, LEV, STH	Tonic, AA, GTCS	SSW, GPFA, R frontotemporal discharges	Normal	Unknown	Mild CI Borderline full-scale IQ
11	38 (9)	M	LEV, LTG, TPM, VPA	Tonic, FDS, GTCS	Background slowing SSW, GPFA, L frontal discharges	L frontal focal cortical dysplasia	Focal cortical dysplasia (*balloon cells)	Mild impairments in working memory, verbal fluency, psychomotor speed
12	38 (10)	F	LEV, LTG, OXC	Tonic, AA, GTCS	Background slowing. SSW, GPFA, R temporal/bi-frontal discharges	Normal	Unknown	Mild impairments in verbal recall, visuospatial processing
13	21 (12)	F	ESX, LTG, PHT	Tonic, AA, GTCS	SSW, GPFA	Normal	Unknown	Normal cognitive profile with recent academic difficulties

Epilepsia, 57(5):812–822, 2016

Available treatment options for patients with LGS are limited

Limited treatment options

01

Limited evidence base for pharmacological treatments[1]

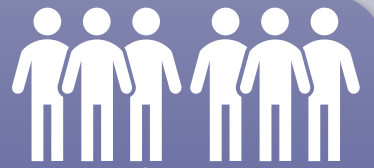
02

Management is complicated by multiple seizure types and comorbidities[1]

03

No single treatment has been shown to be highly efficacious[2]

04



Many patients receive polypharmacy without seizure control[2]

05

80–90%

Despite AED treatment, seizures persist in 80–90% of patients[3]

1. Cross HJ, et al. *Front Neurol.* 2017;8:Article 505; 2. Hancock EC, Cross HJ. *Cochrane Database of Systematic Reviews* 2013:Issue 2; 3. Bourgeois BFD, et al. *Epilepsia.* 2014;55:4–9

AED, anti-epileptic drug; LGS, Lennox-Gastaut syndrome

Seizures contribute to risk of death in children with LGS

Estimated 3–25% mortality rate[1,2]

3–25%
mortality

14 x
greater

The risk of death among children with LGS is reported as 14 times greater than that of the general population[4]

Compared with the general population, risk of death from neurological causes such as prolonged seizures and SE was 19 times greater in children with epilepsy and 179 times greater in children with LGS[4]

Death often results from accidents during seizures or complications of SE[3]

Since key risk factors for SUDEP include intractable epilepsy, high seizure frequency, use of polytherapy, onset of epilepsy at an early age and long duration of epilepsy, patients with LGS are particularly at risk of SUDEP[5]

1. van Rijckevorsel K. *Neuropsychiatr Dis Treat.* 2008;4(6):1001–1019; 2. Bourgeois BFD, et al. *Epilepsia.* 2014;55:4–9 3. Mastrangelo M. *Neuropediatrics.* 2017;48:143–151; 4. Autry AR, et al. *J Child Neurol.* 2010;25(4):441–447; 5. Kerr M, et al. *Epileptic Disord.* 2011;13(Suppl. 1):S15–26

LGS, Lennox-Gastaut syndrome; SE, status epilepticus; SUDEP, sudden unexpected death in epilepsy

Uncontrolled seizures have devastating consequences

≥50%

- Drop attacks: occur in at least 50% of patients and can result in falls and injuries; tend to happen suddenly; protective headgear is required[1–3]

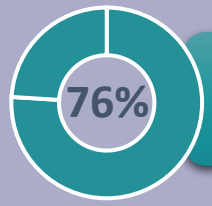
Non-convulsive SE is common (50–75% of patients)[1]

High seizure frequency
AND
Repeated episodes of SE
are poor prognostic indicators[4]

IEDs during sleep are a characteristic of LGS[5,6]

All LGS patients have tonic seizures during sleep[2]

Nocturnal IEDs and seizures in children are associated with poor sleep and subsequent attentional, cognitive, and psychosocial problems[7–9]



Severe lifelong cognitive impairment[1,2]

Cognitive ability worsens with high seizure frequency[1,2]

Cognitive impairment, behavioural problems and psychiatric disorders in LGS patients are linked to seizure activity early in life[5,10]

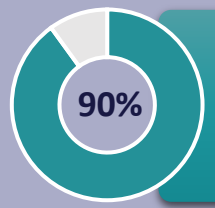
1. Mastrangelo M. *Neuropediatrics.* 2017;48:143–151; 2. Camfield PR. *Epilepsia.* 2011;52:3–9;
3. Gallop K, et al. *Seizure.* 2009;18:554–558; 4. Borggraefe I, Noachtar S. *Clin Med Insights Ther.* 2010;2:15–24;
5. Arzimanoglou A, et al. *Lancet Neurol.* 2009;8:82–93; 6. Sforza E, et al. *Epileptic Disord.* 2016;18:44–50;
7. Overvliet GM, et al. *Epilepsy Behav.* 2010;19:550–558; 8. Licheni SH, et al. *Dev Med Child Neurol.* 2018;60:192–198; 9. Gibbon FM, et al. *Arch Dis Child* 2018;0:doi: 10.1136/archdischild-2017-313421. [Epub ahead of print]; 10. Bourgeois B. *Epilepsia.* 2014;55(Suppl. 4):S4–9

IEDs, Interictal epileptiform discharges; LGS, Lennox-Gastaut syndrome; SE, status epilepticus

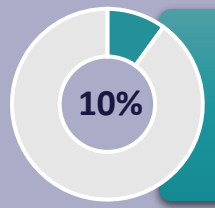
Potential benefits of improved seizure control

Reduction in seizure frequency or severity may

- Improve cognition and behaviour[1,3]
- Reduce the risk of injury[4]
- Increase participation in school[4]
- Improve a patient's ability to self care[4]
- Reduce impact on social and family relationships[4]



Children with intractable epilepsy agreed that small improvements in seizure control make a day-to-day difference[10]



Complete seizure freedom is unusual;[11,12] <10% of patients become seizure free[13]

Early treatment may improve the outcome[1,2]

Better seizure control might lead to reduced mortality[5]

Reductions in drop seizures have been associated with improved quality of life in clinical trials[6–8]

Further research is needed to examine the effects of treatment on behaviour and cognition[9]

1. Arzimanoglou A, Resnick T. *Epileptic Disord.* 2011;13(Supp.l 1):S3–S13; 2. Berg AT, et al. *Epilepsia.* 2018;DOI:10.1111/epi.14569; 3. Mastrangelo M. *Neuropediatrics.* 2017;48:143–151; 4. Gallop K, et al. *Seizure.* 2010;19:23–30; 5. Autry AR, et al. *J Child Neurology.* 2010;25(4):441–447; 6. Conry JA, et al. *Epilepsia.* 2009;50:1158–1166; 7. Ng YT, et al. *Epilepsy Behav.* 2012;25:687–694; 8. Montouris GD, et al. *Epilepsia.* 2014;55:10–20; 9. Arzimanoglou A, et al. *Lancet Neurology.* 2009;8:82–93. 10. Wheless JW. *Epilepsy Behav.* 2006;8:756–764. 11. Cross JH, et al. *Front Neurol.* 2017;8:Article 505; 12. Camfield PR. *Epilepsia.* 2011;52(Suppl. 5):S3–9; 13. Borggraefe I, Noachtar S. *Clin Med Insights Ther.* 2010;2:15–24

The burden of refractory epilepsies on the carer

Seizures represent only a portion of parent and caregiver concerns[1]

Physical

Caregiver health
- Anxiety, depression, pain[2]

Caregiver tasks
- Time commitment[2]
- Transportation[2]
- Personal care[2]
- Household tasks[2]

Concerns about **sleep issues**[1,3]
- **82%** of caregivers sleep with the patient[1]

Emergency care in the past 12 months
- **50%** had ≥1 **emergency admission**
- **46%** had ≥1 **ambulance call**[4]

Emotional

Many have **anxiety** or **depression**[1,2]
- **89%** need support in managing **ongoing stress**[5]
- **86%** experienced **grief** regarding their child's conditon[5]

Many feel helpless and are **sometimes afraid of their own child**[6]

Psychological

Communication issues, impacts on **siblings** and **cognitive impairment** are ranked as top concerns after seizure control[1]

Arranging **child care, communication** and managing **behavioural problems** present the greatest difficulties[2]

Financial

26% missed >1 day of work in the previous week[2]

43% report substantial impact on **work productivity**[2]

65% reported **switching, quitting or losing a job** due to caregiving responsibilities[2]

1. Villas N, et al. *Epilepsy Behav.* 2017;74:81–86; 2. Campbell JD, et al. *Epilepsy Behav.* 2018;80:152–161;
3. Jensen MP, et al. *Epileptic Behav.* 2017;74:135–143; 4. Lagae L, et al. *Dev Med Child Neurol.* 2018;60:63–72.
5. Skluzacek JV, et al. *Epilepsia.* 2011;52(Suppl. 2):S95–101; 6. Ceulemans B. *Dev Med Child Neurol.* 2011;53(Suppl. 2):19–23

DS, Dravet Syndrome

Summary

Factor	DS	LGS
Treatment availability	Limited options[2]	Limited options[1] Despite AED treatment, seizures persist in 80–90% of patients[3]
Mortality	Mortality rate of 15.84/1000 patient years[5]	The risk of death among children with LGS is reported as 14 times greater than that of the general population[4]
Consequences of uncontrolled seizures	High risk of recurrent, prolonged convulsive seizures[9] Frequent SE in younger patients[9]	Non-convulsive SE is common[6] Drop attacks occur in at least 50% of patients and can result in falls and injuries; tend to happen suddenly; protective headgear is required[6–8]

Potential benefits of seizure control	• Greater degree of cognitive and behavioural improvement[13]
	• Management of nocturnal seizures may:
	  • Improve QoL, developmental outcomes, and seizure control[14]
	  • Reduce the risk of SUDEP[15]
		• Improve cognition and behaviour[6,10,11]
		• Reduce the risk of injury[12]
		• Increase participation in school[12]
		• Improve a patient's ability to self care[12]
		• Reduce impact on social and family relationships[12]

1. Cross HJ, et al. *Front Neurol.* 2017;8:Article 505; 2. Wirrell EC, et al. *Pediatr Neurol.* 2017;68:18–34.e3; 3. Bourgeois BFD, et al. *Epilepsia.* 2014;55:4–9; 4. Autry AR, et al. *J Child Neurol.* 2010;25(4):441–447; 5. Cooper MS, et al. *Epilepsy Res.* 2016;128:43–47; 6. Mastrangelo M. *Neuropediatrics.* 2017;48:143–151; 7. Camfield PR. *Epilepsia.* 2011;52:3–9; 8. Gallop K, et al. *Seizure.* 2009;18:554–558; 9. Ziobro J, et al. *Curr Treat Options Neurol.* 2018;20:52; 10. Arzimanoglou A, Resnick T. *Epileptic Disord.* 2011;13(Supp.l 1):S3–S13; 11. Berg AT, et al. *Epilepsia.* 2018;DOI:10.1111/epi.14569; 12. Gallop K, et al. *Seizure.* 2010;19:23–30; 13. Wirrell EC. *Can J Neurol Sci.* 2016;43:S13–S18; 14. Licheni SH, et al. *Dev Med Child Neurol* 2018;60:192–198; 15. Lamberts RJ, et al. *Epilepsia* 2012;53:253–257

‘Global care’ of epilepsy patients

- Make solid clinical diagnoses
  - syndrome, seizure types, EEG features, triggering factors

- Educate, inform, and support the patient and the parents

Thanks for your attention

Istituto Giannina Gaslini

piano strategico

Istituto pediatrico di ricovero e cura a carattere scientifico

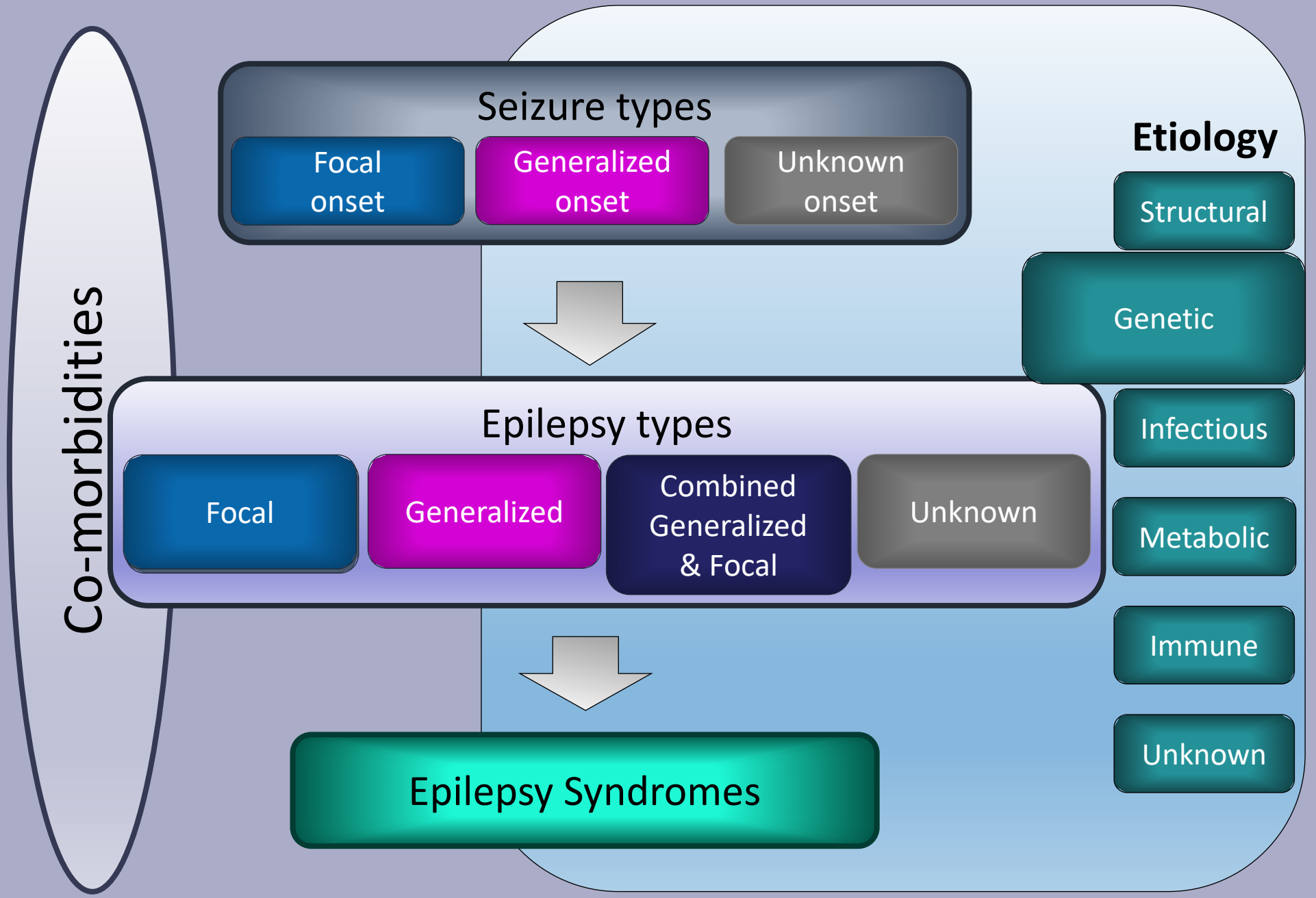
Comorbidità nel bambino con epilessia

PROF. PASQUALE STRIANO

IRCCS Istituto 'G. Gaslini' e DINOGMI-Universita' di Genova

Vicepresidente Società Italiana di Neurologia Pediatrica (SINP)

DINOGMI 2018-2022 | DIPARTIMENTO DI ECCELLENZA MIUR



ILAE Position Paper, 2017

Topical Review Article

Comorbidities in Pediatric Epilepsy: Beyond "Just" Treating the Seizures

L. D. Hamiwka, MD, and E. C. Wirrell, MD

Journal of Child Neurology
Volume 24 Number 6
June 2009 734-742

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http://online.sagepub.com

- Epilepsy is the most common childhood neurologic disorder, affecting 0.5–1.0% of children younger than 16 years.
- Epilepsy in children is associated with variable comorbidities although the frequency of such manifestations is often difficult to determine.
- Some of these comorbidities may occur as early as in newly diagnosed epilepsy prior to treatment and in children with controlled epilepsy.

Hamiwka & Wirrell, 2009

Comorbidity and Childhood Epilepsy: A Nationwide Registry Study

Kari Modalsli Aaberg, MD,[a,b] Inger Johanne Bakken, PhD,[a] Morten I. Lossius, MD, PhD,[b] Camilla Lund Søraas, MD, PhD,[a] Siri Eldevik Håberg, MD, PhD,[a] Camilla Stoltenberg, MD, PhD,[a,c] Pål Surén, MD, PhD,[a,b] Richard Chin, MD, PhD[d]

TABLE 1 Comorbid Disorders (Including Potentially Causative Comorbid Disorders) in Children With Epilepsy (CWE) compared with the General Child Population (GCP)

Category	CWE (N = 6635)		GCP (N = 1 125 161)		CWE vs GCP
Disorders	*N*	%	*N*	%	OR (99% CI)
Medical disorders	3627	54.7	286 361	25.5	3.5 (3.3–3.7)*
Gastrointestinal disorders	1264	19.1	60 840	5.4	4.3 (3.9–4.6)*
Congenital nonneurologic malformations	1206	18.2	81 289	7.2	3.4 (3.1–3.7)*
Musculoskeletal disorders	1018	15.3	49 934	4.4	3.3 (3.0–3.6)*
Chronic lower respiratory disorders	683	10.3	45 431	4.0	2.8 (2.5–3.1)*
Malnutrition/eating difficulties	670	10.1	9398	0.8	16.1 (14.4–17.9)*
Skin disorders	480	7.2	42 329	3.8	2.0 (1.8–2.3)*
Chromosomal abnormalities	355	5.4	3245	0.3	19.6 (16.9–22.7)*
Hearing impairment/deafness	342	5.2	12 716	1.1	4.6 (4.0–5.3)*
Endocrine disorders	307	4.6	12 627	1.1	3.6 (3.1–4.2)*
Urinary tract disorders	272	4.1	13 483	1.2	3.3 (2.8–3.9)*
Genital disorders	212	3.2	21 899	2.0	1.5 (1.2–1.8)*
Cardiovascular disorders	200	3.0	7379	0.7	4.3 (3.6–5.2)*
Sleep disorders	192	2.9	2491	0.2	13.0 (10.6–15.8)*
Hematologic conditions	188	2.8	7676	0.7	4.4 (3.6–5.4)*
Benign neoplasms	171	2.6	15 506	1.4	1.8 (1.5–2.2)*
Metabolic disorders	129	1.9	2750	0.2	7.3 (5.8–9.2)*
Visual impairment/blindness	125	1.9	652	0.1	30.6 (23.7–39.5)*
Obesity	123	1.9	5173	0.5	3.2 (2.5–4.0)*
Nutritional deficiency	62	0.9	1477	0.1	7.4 (5.3–10.4)*
Malignant neoplasms	56	0.8	1613	0.1	5.2 (3.7–7.4)*
Immune disorders	42	0.6	834	0.1	8.6 (5.7–13.0)*

Comorbidities of epilepsy in children

Neurological comorbidities	Psychological comorbidities	Physical comorbidities
Cognitive impairment	Autism spectrum disorders	Bone loss
Language impairment	Attention deficit/hyperactivity disorder	Immunological disturbances
Migraine & headache	Mood disorders (anxiety and depression)	Retardation of body height growth
Sleep problems	Psychosocial & familial problems	Hypothyroidism
	Rare: psychosis, oppositional defiant or conduct disorders, & tic disorders	Polycystic ovary syndrome
		Body weight changes
		Dyslipidemia

Journal of the Formosan Medical Association (2015) 114, 1031—1038

Neurological comorbidities (1)

- **Cognitive impairment**

Several population-based prevalence studies of children with epilepsy reported that intellectual disability (full-scale intelligence quotient < 70) was the most common comorbidity (30–40%).

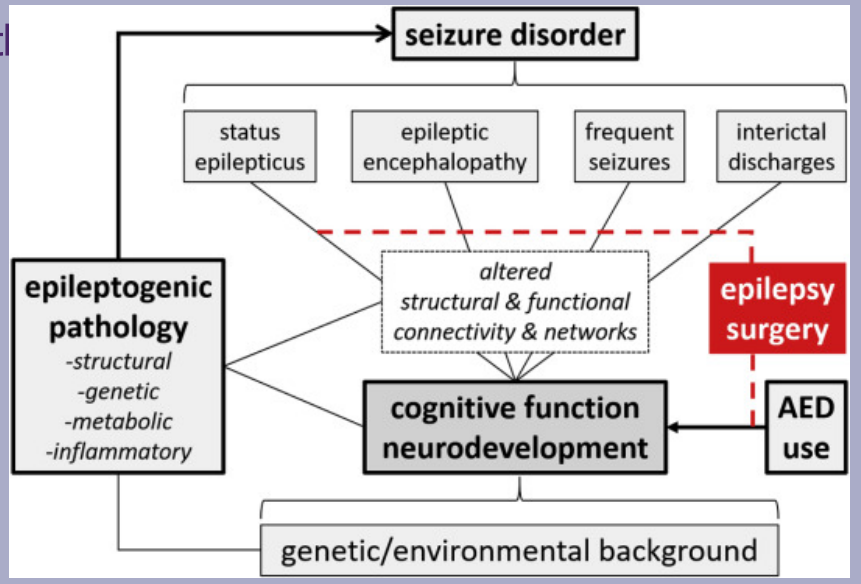
The various epilepsy syndromes of childhood differ greatly in terms of cognitive outcome.

The long-term risk of learning problems exists even in those with initially normal IQs or well-controlled seizures.

- **Language impairment**

The occurrence of speech disorders may be as high as 27.5% in children with epilepsy. Compared wit their siblings, children with epilepsy have significantly lower language scores in word knowledge, category fluency, and response to commands of increasing length and complexity, especially in those with an earlier age of onset.

Some epileptic syndromes have been well documented in association with language impairment, e.g. Landau–Kleffner syndrome (LKS) and the epilepsy with continuous spike waves during slow-wave sleep (CSWS)



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Neurological comorbidities (2)

- **Migraine**

Migraine and epilepsy are highly comorbid and individuals with each disorder are more than twice as likely to have the other.

Children with epilepsy had a 4.5-fold increased risk of developing migraine headache than tension-type headache.

Headache usually start in the same year or after the diagnosis of epilepsy and occur mostly in children older than 10 years with genetic/non lesional epilepsy.

- **Sleep problems**

Children with epilepsy have significantly more sleep problems, including parasomnias, sleep fragmentation, daytime drowsiness, parent/child interaction during the night. Children with refractory seizures have more sleep problems than seizure-free children.

Children with epilepsy have abnormal stage 1 sleep percentage and latency to rapid eye movement (REM) sleep compared with controls.

REM latency, length of apnea, and periodic leg movement correlate with depression, inattentiveness and hyperactivity, and/or oppositional behavior. Persistent daytime drowsiness in children with epilepsy is not always due to the side effects of therapy.

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Psychiatric comorbidities

- Psychiatric disorders can emerge in children early in the course of their illness or even prior to the onset of seizures. The most common include attention deficit/hyperactivity disorder (ADHD), and depressive and anxiety disorders.

- Children with autism spectrum disorder (ASD) have an increased prevalence (up to 25%) of seizures. However, the prevalence of ASD in children with epilepsy is similar but varies depending on age, types of epilepsy, and method of evaluation.
- ADHD is more prevalent in children with epilepsy compared to healthy controls (31% vs. 6%), especially in frontal lobe epilepsy, childhood absence epilepsy, and rolandic epilepsy, and may antedate seizure onset.
- Mood disorders had been reported in 12–26% of children with epilepsy. Emotional disorders can occur in 16.7% of children with epilepsy (compared with 4.2% in the general population).
- Certain psychiatric disorders, including primary mood disorders, increase the risk for suicide in adults with epilepsy.

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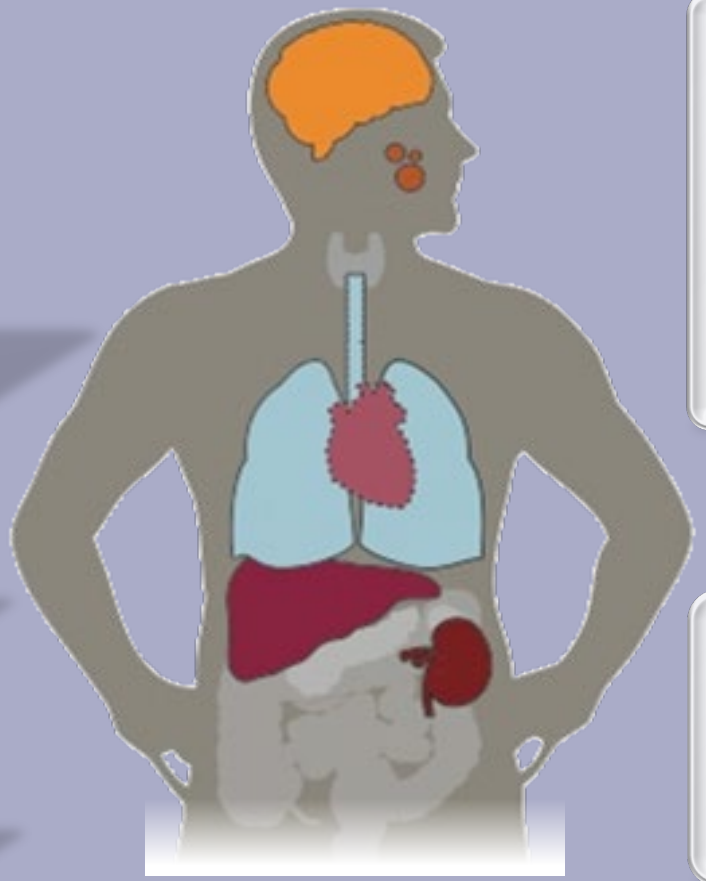
Physical comorbities: the paradigm of TSC

Skin
- Facial angiofibroma (57.3% of patients)
- ≥3 hypomelanotic macules (66.8% of patients)
- Shagreen patches (27.4% of patients)

Lung
- LAM (6.9% of patients)

Heart
- Cardiac rhabdomyoma (34.3% of patients)



Brain/CNS
- Epilepsy (83.5% of patients)
- Cortical tuber (82.2% of patients)
- SEN (78.2% of patients)
- SEGA (24.4% of patients)
- Cerebral white matter radial migration lines (20.5% of patients)

Kidney
- Renal angiomyolipoma (47.2% of patients)
- Multiple renal cysts (22.8% of patients)

Information based on TuberOus Sclerosis registry to increase disease Awareness (TOSCA), N=2223. The rates of features reported in TOSCA reflect the age range and referral patterns of clinics contributing patients to the registry. CNS, central nervous system; LAM, lymphangioleiomyomatosis; SEGA, subependymal giant cell astrocytoma; SEN, subependymal nodules.
Kingswood JC et al. *Orphanet J Rare Dis.* 2017;12(1):2.

Physical comorbidities caused by specific drugs in children with epilepsy

- Most well-known adverse effects of treatment, including allergic reaction, cytopenia, electrolyte imbalance, and renal or hepatic impairment, are reversible after ceasing drug use.

- Some physical comorbidities related to drugs, including disturbances of hormonal balance, may potentially have a long-term impact on the medical health and quality of life of the children with epilepsy.

Comorbidities	Type of AEDs
Bone loss	TPM,[a] VPA, LMT, PB
Immunological disturbances	CBZ, VPA
Hypothyroidism	CBZ, VPA
Polycystic ovary syndrome	VPA
Weight gain	VPA,[a] GBP, PGB, VGB
Weight loss	TPM, FBM, ZNS
Dyslipidemia	CBZ, PB
Carnitine deficiency	VPA,[a] OXC. CBZ, PHT, PB

CBZ = carbamazepine; FBM = felbamate; GBP = gabapentin; LMT = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; PGB = pregabalin; PHT = phenytoin; TPM = topiramate; VGB = vigabatrin; VPA = valproic acid; ZNS = zonisamide.

[a] More significant than the other drugs.

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Choice of AEDs related to comorbidities in epilepsy

Comorbidities	Choose	Avoid
Obesity ± DM	TPM, ZNS	GBP, PGB, VPA, PRP
Migraine	TPM, GBP, PGB, ZNS, VPA	
Skin rashes	LEV, GBP, PGB, TPM, VPA, PER, LCM	CBZ, LTG, OXC, PHT, PB
Neuropathic pain	PGB, GBP, CBZ, OXC, PHT, LTG	
Depression ± behavioral dis	LTG, CBZ, OXC, VPA, PGB	LEV, PB, TPM, ZNS, PER
Cognitive dysfunction	LTG, LEV, OXC, LCM	PB, TPM, ZNS
Concomitant drugs	GBP, LEV, PGB, LCM, ZNS	Enzyme- inducers or inhibitors
Cancer	LEV, VPA, PER	Enzyme- inducers
Cardiac arrhythmia		Sodium channel blockers
Glaucoma		TPM
Gait disturbances		CBZ. PHT, PER
Heat stroke		TPM, ZNS
Hematological disorder		CBZ, VPA
Hyponatremia		OXC, ESL, CBZ
Hepatic disease	Drugs excreted by renal excretion	VPA
Renal disease	Drugs excreted by hepatic metabolism	GBP, PGB, LEV
Hyponatremia		OXC, ESL, CBZ
Osteoporosis	LTG, LEV	Enzyme inducers, TPM, VPA, ZNS
Restless leg syndrome	GBP, PGB, CZP, PER	
Parkinson dis	ZNS	
Tremor	TPM, PB, PRM	

CBZ; carbamazepine, CZP; clonazepam, GBP: gabapentine, LCM; lacosamide LEV: levetiracetam, LTG; lamotrigine, OXC; oxcarbazepine, PB; phenobarbital, PRM; primidone, PER: perampanel, PGB; pregabalin, TPM; topiramate, VGB; vigabatrin, VPA; valproic acid, ZNS; zonisamide.

Lee BI et al, *Epilepsy Research* 2019

Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment

- Identify and characterize the full range and age specificity of comorbidities in people with epilepsy
- Identify predictors and underlying mechanisms that contribute to comorbidities
- Determine the optimal treatments for the neuropsychiatric and cognitive comorbidities in people with epilepsy

Perspective strategies and recommendations

- Neurological and non neurological comorbidities are common in children with epilepsy, and sometimes even more disabling than the seizures themselves.
- Management strategies focus not only on controlling seizures, but also on early diagnosis and therapy of comorbid conditions which should be assessed as integral part of management in childhood epilepsy.
- Clinicians should screen and assess the comorbidities both in children with newly diagnosed epilepsy and those with regular follow-up after treatment.
- Many factors may contribute to the development of physical morbidities, such as the detrimental effects of chronic seizures and therapies. When a physical comorbidity is suspected to result from a specific medication, alternatives should be considered.
- Because of a significant impact of childhood epilepsy on children and their families, further work should also focus on the educational strategies of psychosocial support to reduce the patient's burden and familial stress.