The Lily Foundation Family Weekend
Epilepsy in mitochondrial disease

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Outline of talk

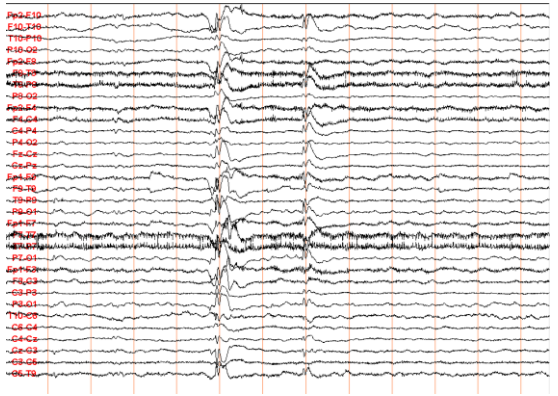
- Background of epilepsy in mitochondrial disorders
- Anti-epileptic drugs (AEDs)
- Cannabidiol
- The ketogenic diet
- Catamenial epilepsy

Background

What is epilepsy?

A seizure:

‘‘ a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain’’ *Fisher et al Epilepsia 2005;46:470–472*



Epilepsy:

-At least two unprovoked seizures occurring

>24 hours apart

-One unprovoked seizure *and at least a 60% probability of further seizures occurring over the next 10 years*

Fisher et al Epilepsia 55(4):475–482, 2014

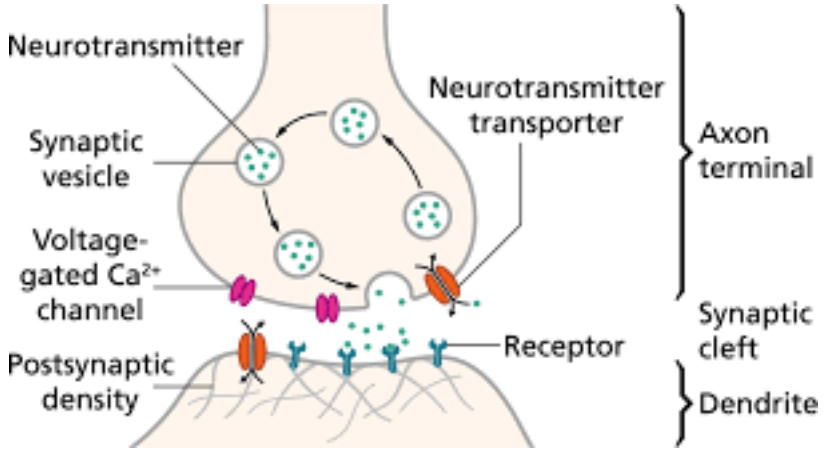
What causes seizure activity?

- A change in the balance between excitatory and inhibitory chemicals within the brain

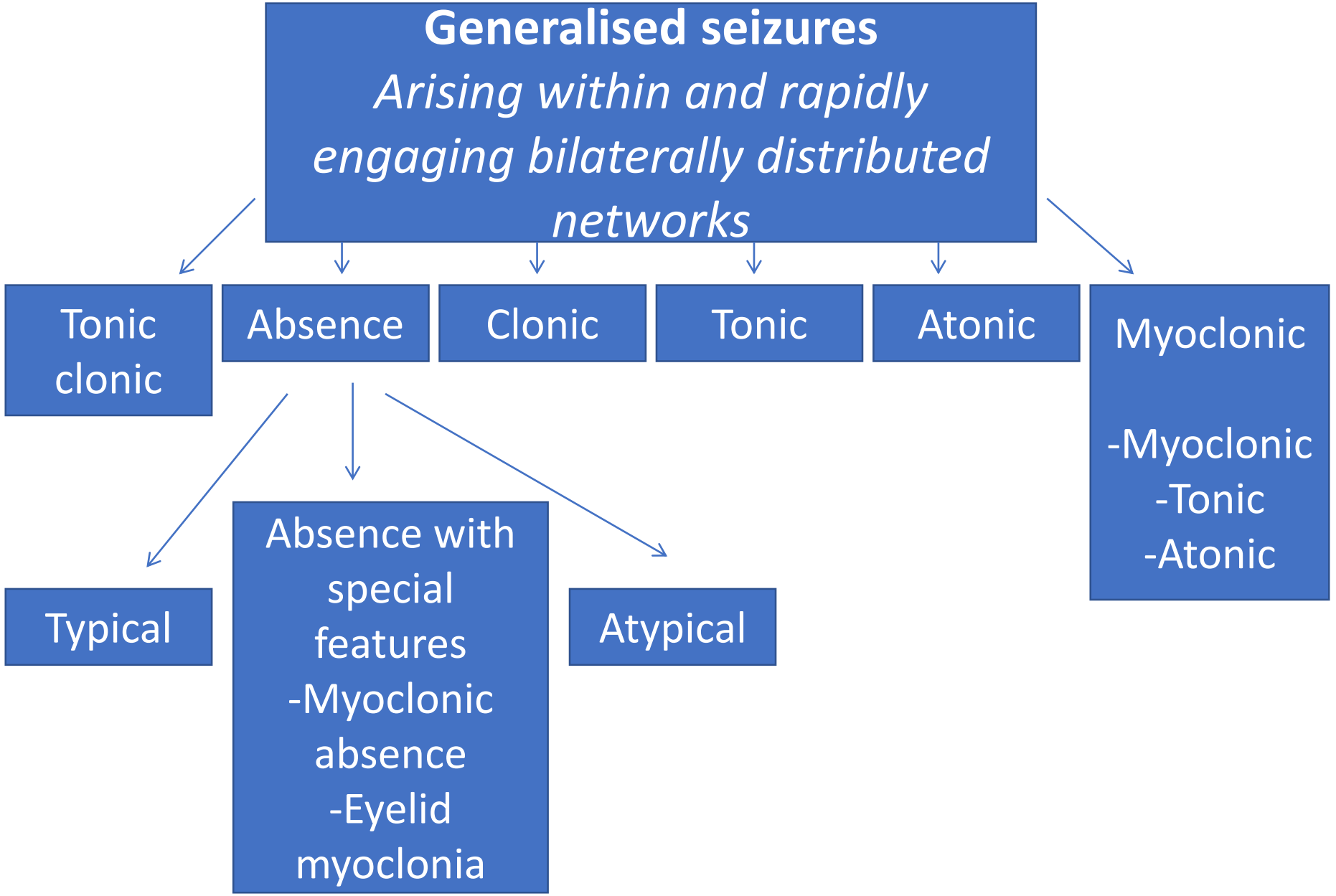
-Excitatory- *glutamate*

-Inhibitory- *Gaba*

- A change in the stability of the surface of the neurones within the brain



Classification of seizures ILAE 2010



Classification of seizures ILAE 2010

Focal seizures
Originating within networks limited to one hemisphere

↓

Characterised according to one or more features:
Aura
Motor Autonomic
Awareness/Responsiveness:
Altered (dyscogntive) *or* retained

May evolve to:

Bilateral convulsive seizure

Possible factors underlying epilepsy in mitochondrial disorders

- Energy failure
- Mitochondrial dysfunction with increased reactive oxygen species production
- Abnormal calcium handling
- Increased programmed loss of brain cells
- Seizures may be secondary to electrolyte disturbances arising from severe kidney disease affecting the renal tubules

Bhandarya S and Kripamoy A. Epilepsy Research 116 (2015) 40–52

Epilepsy and mitochondrial disorders

- The exact prevalence of mitochondrial epilepsy is not known
- Seizures have been reported to occur in ~35–60% of individuals with biochemically confirmed mitochondrial disease *(Urbanska et al., 1998 Yamamoto and Tang, 1996)*
- Epilepsy frequently difficult to treat
- Studies are lacking and more research is needed

Epilepsy and mitochondrial disorders

Onset in childhood:

-MELAS
-MERRF
-KSS
-Leigh syndrome
-myoclonic epilepsy myopathy sensory ataxia
-mitochondrial recessive ataxia syndrome (MIRAS)
-infantile onset spinocerebellar ataxia (IOSCA)
-Alpers-Huttenlocher syndrome

Finsterer J, Zarrouk Mahjoub S, Acta Neurol Scand. 2013;128:141-52

Which seizures occur in children with mitochondrial disorders?

Most common seizure types:

- Infantile spasms
- Focal seizures which generalise
- Myoclonic epilepsy
- Difficult to treat or recurrent status epilepticus
- Epilepsia partialis continua

Epilepsy and mitochondrial disorders

Onset in adulthood:

- MELAS with acute stroke like episodes
- LHON
- Ataxia and retinitis pigmentosa (NARP)
- Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis

Finsterer J, Zarrouk Mahjoub S Acta Neurol Scand. 2013;128:141-52.

Anti-epileptic medication

- Stabilise abnormal firing from the neurons
- Alter the excitatory/inhibitory balance in the brain
- Some AEDs have several ways of working
- Lack of trials in mitochondrial disorders

Anti-epileptic drug treatments

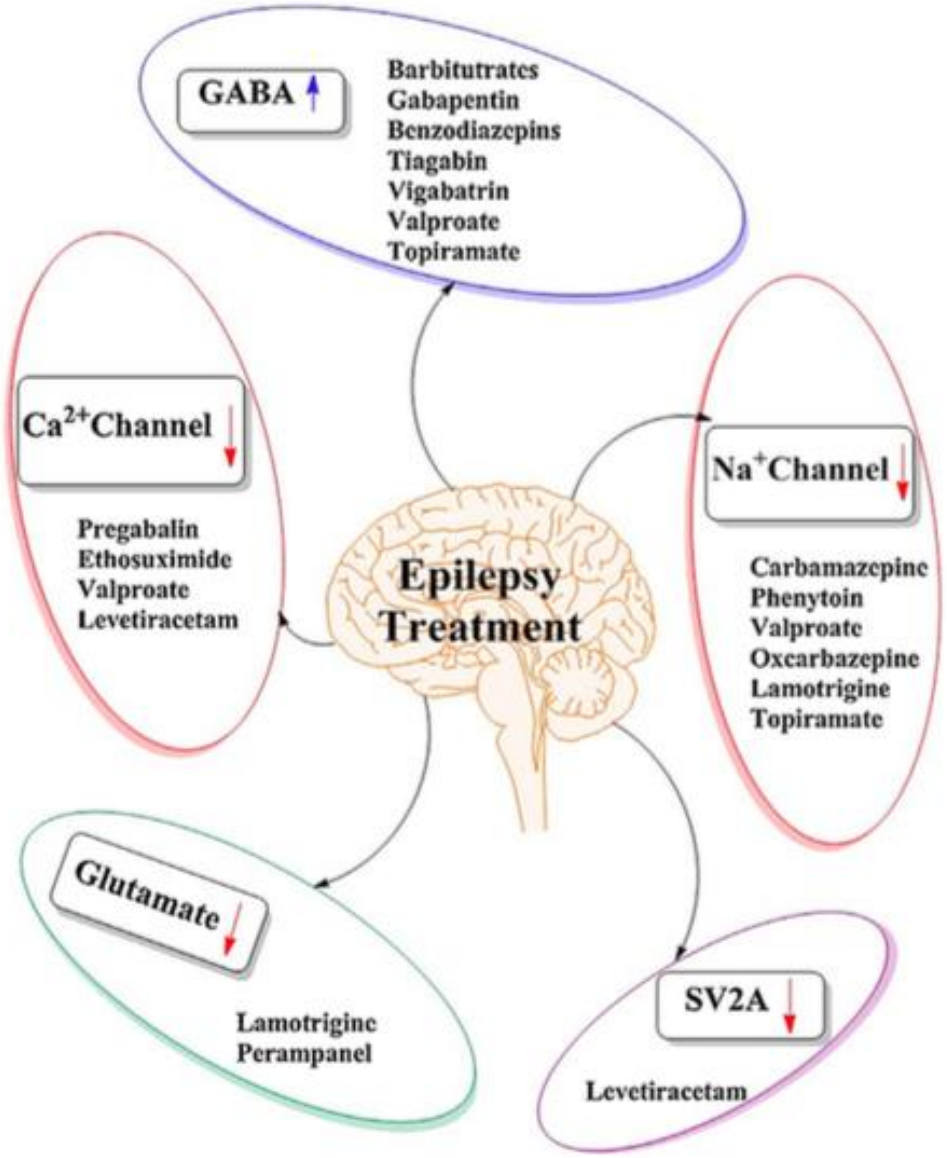


Fig. 3. Schematic representation of the commonly available AEDs and their possible mechanisms of action.

How are antiepileptic drugs (AEDs) chosen for epilepsy?

Consider:

- Seizure types
- Individual factors that may effect tolerability
- Possible interaction with other medications
- AEDs with a low mitochondrion- toxic potential: levetiracetam, lamotrigine, gabapentin, or zonisamide
- AEDs with higher mitochondrion-toxic potential: valproic acid, carbamazepine, phenytoin, or phenobarbital (*Finsterer J and Torres de Carvalho E H Can J Neurol Sci. 2017; 44: 654-663)*

Treatment of epilepsy

Realistic treatment goals

- To optimise quality of life (QOL)
- Reduce severity/number of seizures
- Reduce negative impact of seizures
- Avoid adverse effects of anti-epileptic drug treatment

Benefit Vs. Adverse effect

Cannabidiol

Cannabis and treatment for epilepsy

- D9-Tetrahydrocannabinol (D9-THC) is the major psychoactive ingredient and CBD

  -Linked with psychosis and addiction

- Cannabidiol (CBD) is the most abundant non- psychoactive cannabinoid in cannabis

  -Animal studies demonstrate anticonvulsant efficacy in multiple species and models.

- Cannabis and D9-THC are anticonvulsant in most animal models but can be pro-convulsant in some healthy animals

Cannabidiol products in the UK

- Cannabidiol products are legal if they contain <0.2% THC
- Products containing more than 0.2% THC are illegal in the UK unless licensed and authorised for use, medicinally, by an approved government body such as the Medicines and Healthcare Products Regulatory Authority (MHRA)
- MHRA authorisation for use of a chemical / drug medicinally, requires:

-Demonstration of safety and benefit in well designed, randomised studies usually against placebo or current gold standard therapy

Cannabidiol products

- Oils advertised as containing CBD alone or with THC but less than 0.2% of THC are available in the UK (on-line and on the high street). May contain in varying strengths:

-CBD

-THC

-Combination of CBD and THC

-Other cannabinoids

- Legality of such oils may vary across international borders
- Formal testing has shown that what it says on the bottle is not always reliable-no quality assurance
- There is no information about dose or efficacy of these oils
- Doctors in the UK are currently unable to prescribe such products within their code of practice

Cannabidiol products

- Epidiolex (GW Pharma) cannabidiol less than 0.1% THC
- Clinical trials in the UK, Europe and USA:

-Effective in reducing seizures in two forms of rare epilepsy, Dravet Syndrome and Lennox-Gastaut Syndrome

- The data is currently with the regulatory authorities:

-The USA: FDA are likely to approve within a month for license

-The European Medicines Agency (EMA) likely to approve later this year

Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial

*Elizabeth A Thiele, Eric D Marsh, Jacqueline A French, Maria Mazurkiewicz-Bełdzinska, Selim R Benbadis, Charuta Joshi, Paul D Lyons, Adam Taylor, Claire Roberts, Kenneth Sommerville, on behalf of the GWPCARE4 Study Group**

Summary

Background Patients with Lennox-Gastaut syndrome, a rare, severe form of epileptic encephalopathy, are frequently treatment resistant to available medications. No controlled studies have investigated the use of cannabidiol for patients with seizures associated with Lennox-Gastaut syndrome. We therefore assessed the efficacy and safety of cannabidiol as an add-on anticonvulsant therapy in this population of patients.

Methods In this randomised, double-blind, placebo-controlled trial done at 24 clinical sites in the USA, the Netherlands, and Poland, we investigated the efficacy of cannabidiol as add-on therapy for drop seizures in patients with treatment-resistant Lennox-Gastaut syndrome. Eligible patients (aged 2–55 years) had Lennox-Gastaut syndrome, including a history of slow (<3 Hz) spike-and-wave patterns on electroencephalogram, evidence of more than one type of generalised seizure for at least 6 months, at least two drop seizures per week during the 4-week baseline period, and had not responded to treatment with at least two antiepileptic drugs. Patients were randomly assigned (1:1) using an interactive voice response system, stratified by age group, to receive 20 mg/kg oral cannabidiol daily or matched placebo for 14 weeks. All patients, caregivers, investigators, and individuals assessing data were masked to group assignment. The primary endpoint was percentage change from baseline in monthly frequency of drop seizures during the treatment period, analysed in all patients who received at least one dose of study drug and had post-baseline efficacy data. All randomly assigned patients were included in the safety analyses. This study is registered with ClinicalTrials.gov, number NCT02224690.

Findings Between April 28, 2015, and Oct 15, 2015, we randomly assigned 171 patients to receive cannabidiol (n=86) or placebo (n=85). 14 patients in the cannabidiol group and one in the placebo group discontinued study treatment; all randomly assigned patients received at least one dose of study treatment and had post-baseline efficacy data. The median percentage reduction in monthly drop seizure frequency from baseline was 43·9% (IQR −69·6 to −1·9) in the cannibidiol group and 21·8% (IQR −45·7 to 1·7) in the placebo group. The estimated median difference between the treatment groups was −17·21 (95% CI −30·32 to −4·09; p=0·0135) during the 14-week treatment period. Adverse events occurred in 74 (86%) of 86 patients in the cannabidiol group and 59 (69%) of 85 patients in the placebo group; most were mild or moderate. The most common adverse events were diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting. 12 (14%) patients in the cannabidiol group and one (1%) patient in the placebo group withdrew from the study because of adverse events. One patient (1%) died in the cannabidiol group, but this was considered unrelated to treatment.

Interpretation Add-on cannabidiol is efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut syndrome and is generally well tolerated. The long-term efficacy and safety of cannabidiol is currently being assessed in the open-label extension of this trial.

Lancet 2018; 391: 1085–96

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See Comment page 1006

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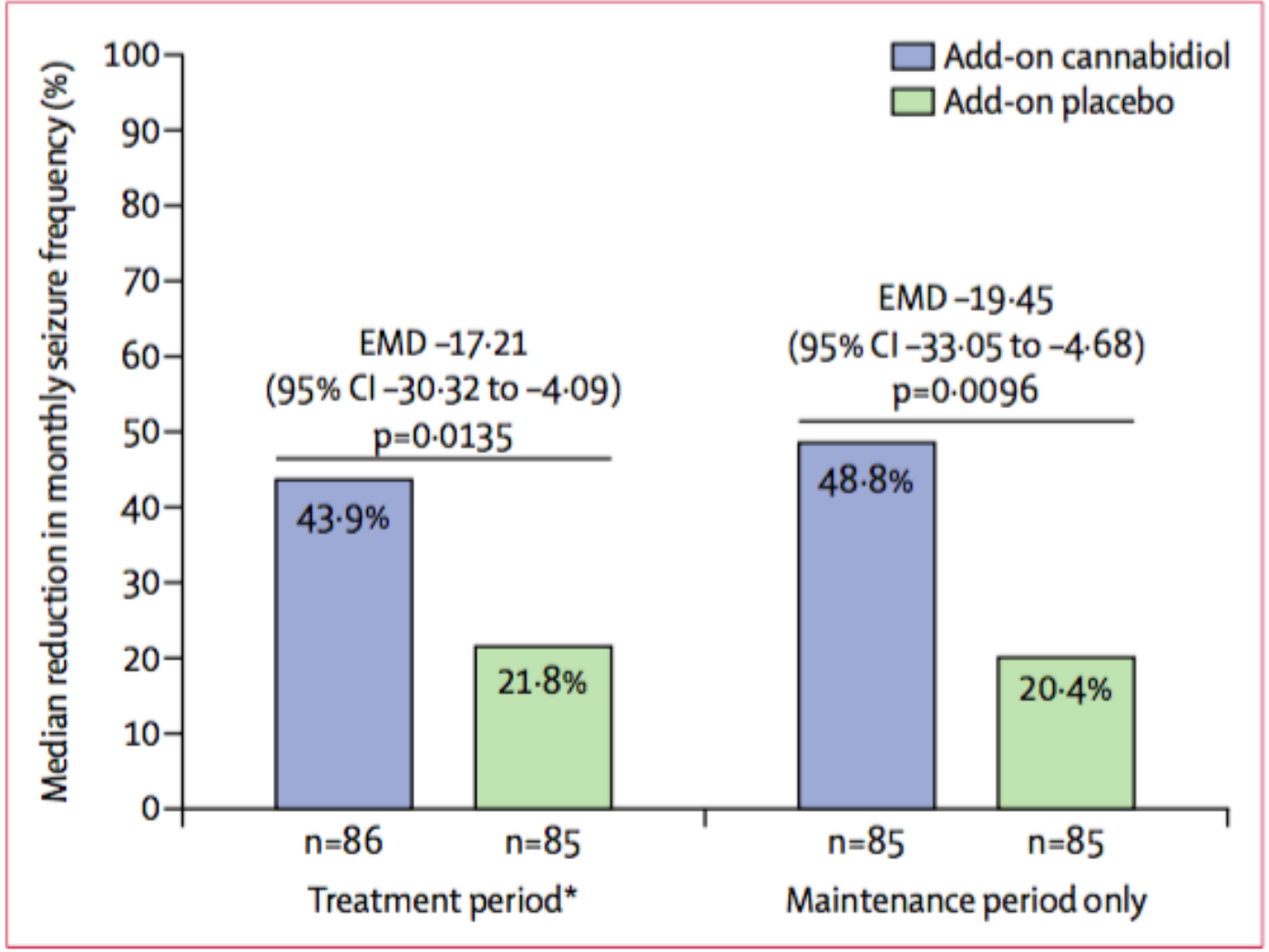

***Figure 2*: Reduction in drop seizure frequency during the treatment and maintenance period**

Median percentage reduction in monthly drop seizures during the 14-week treatment period (2 weeks of dose escalation plus 12-week maintenance period alone) in cannabidiol and placebo treatment groups. EMD=estimated median difference. *Primary endpoint.

Cannabidiol adverse effects

	Cannabidiol (n=86)		Placebo (n=85)	
	All cause	Treatment related	All cause	Treatment related
Diarrhoea				
Mild	12 (14%)	9 (10%)	6 (7%)	3 (4%)
Moderate	3 (3%)	2 (2%)	1 (1%)	0
Severe	1 (1%)	0	0	0
All	16 (19%)	11 (13%)	7 (8%)	3 (4%)
Somnolence*				
Mild	5 (6%)	5 (6%)	5 (6%)	4 (5%)
Moderate	8 (9%)	7 (8%)	3 (4%)	3 (4%)
All	13 (15%)	12 (14%)	8 (9%)	7 (8%)
Pyrexia				
Mild	7 (8%)	0	5 (6%)	1 (1%)
Moderate	4 (5%)	1 (1%)	2 (2%)	0
All	11 (13%)	1 (1%)	7 (8%)	1 (1%)
Decreased appetite				
Mild	7 (8%)	5 (6%)	1 (1%)	0
Moderate	3 (3%)	2 (2%)	1 (1%)	1 (1%)
Severe	1 (1%)	1 (1%)	0	0
All	11 (13%)	8 (9%)	2 (2%)	1 (1%)
Vomiting				
Mild	3 (3%)	3 (3%)	9 (11%)	3 (4%)
Moderate	5 (6%)	2 (2%)	5 (6%)	1 (1%)
Severe	1 (1%)	1 (1%)	0	0
All	9 (10%)	6 (7%)	14 (16%)	4 (5%)

Data are n (%). The most common adverse events, defined using Medical Dictionary for Regulatory Activities preferred terms, were events that occurred in more than 10% of patients. Event names were defined according to the Medical Dictionary for Regulatory Activities. *Nine (69%) of 13 patients in the cannabidiol group and seven (88%) of eight patients in the placebo group with somnolence were taking concomitant clobazam.

Table 2: **Most common adverse events**

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Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

ABSTRACT

BACKGROUND

The Dravet syndrome is a complex childhood epilepsy disorder that is associated with drug-resistant seizures and a high mortality rate. We studied cannabidiol for the treatment of drug-resistant seizures in the Dravet syndrome.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 120 children and young adults with the Dravet syndrome and drug-resistant seizures to receive either cannabidiol oral solution at a dose of 20 mg per kilogram of body weight per day or placebo, in addition to standard antiepileptic treatment. The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period.

From the New York University Langone Comprehensive Epilepsy Center, New York (O.D.); the University College London Great Ormond Street Institute of Child Health (J.H.C.) and GW Pharmaceuticals (S.W.) — both in London; Lurie Children's Epilepsy Center, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago (L.L.); the Children's Hospital of Philadelphia, Philadelphia (E.M.); Miami Children's Hospital, Miami (I.M.); Hôpital Necker–Enfants Malades, Paris (R.N.); Florey Institute, Austin Health and Royal Children's Hospital, University of Melbourne, Mel-

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI)	P Value†
			percentage points	
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	−38.9 (−100 to 337)	−13.3 (−91.5 to 230)	−22.8 (−41.1 to −5.4)	0.01

* CI denotes confidence interval.
† The P value was calculated with the use of a Wilcoxon rank-sum test with the Hodges–Lehmann approach.

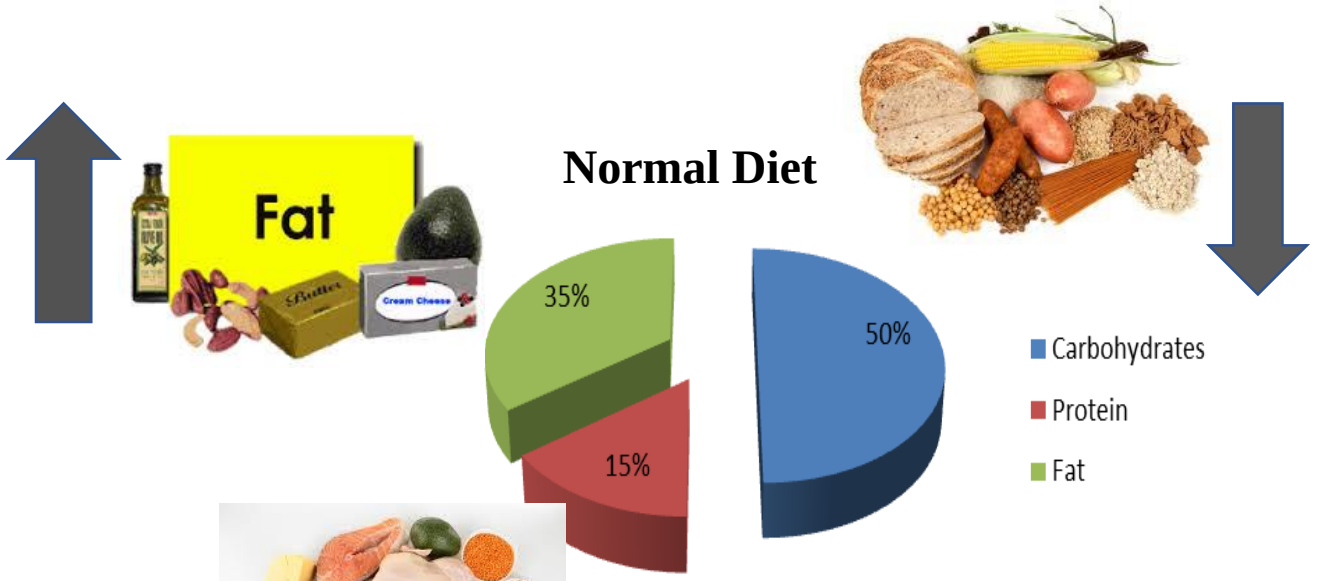
Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.*

System Organ Class and Preferred Term	Cannabidiol (N=61)	Placebo (N=59)
	no. of patients (%)	
Gastrointestinal		
Diarrhea	19 (31)	6 (10)
Vomiting	9 (15)	3 (5)
General		
Fatigue	12 (20)	2 (3)
Pyrexia	9 (15)	5 (8)
Infections: upper respiratory tract infection	7 (11)	5 (8)
Metabolism: decreased appetite	17 (28)	3 (5)
Nervous system		
Convulsion	7 (11)	3 (5)
Lethargy	8 (13)	3 (5)
Somnolence	22 (36)	6 (10)

* Events were classified according to the *Medical Dictionary for Regulatory Activities*, version 17.0.

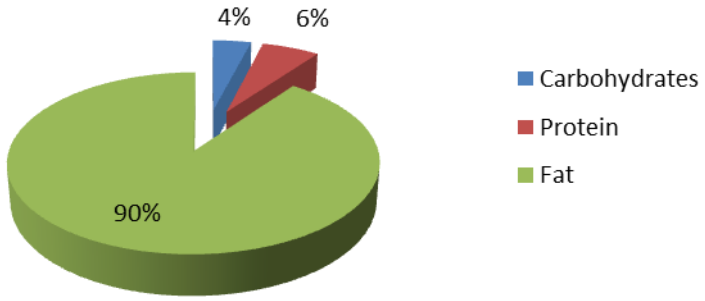
The ketogenic diet

What are ketogenic diets ?

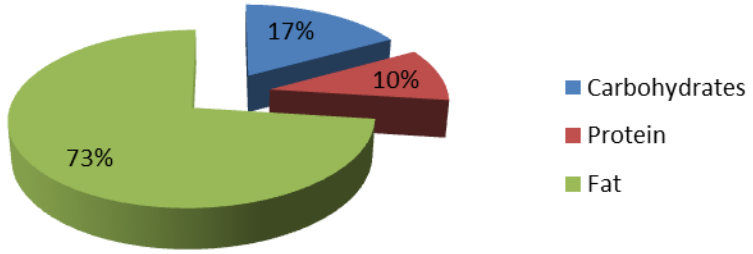


Energy from fat rather than carbs

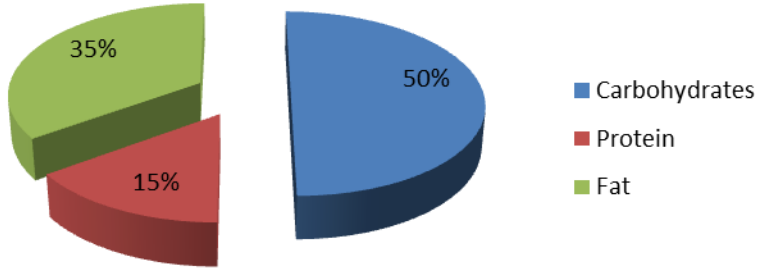
Classical Ketogenic Diet 4:1 ratio (LCT)



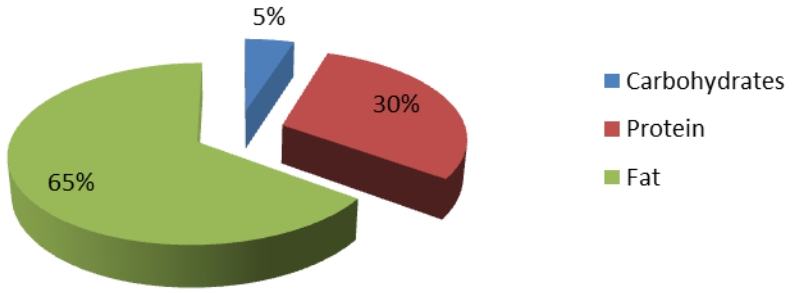
MCT Ketogenic Diet



Normal Diet



Modified Atkins Diet (1:1 ratio)



E. Neal, 2012
Dietary Treatment of Epilepsy, Wiley-Blackell

Classical Ketogenic Diet (CKD):

(Long Chain Triglycerides)

- Using standard food for composition of meals plans: 2:1, 3:1 or 4:1 - fat: (carbohydrate + protein) ratio
- Up to 90% of total calories from fat
- Meal/snack recipes, all in correct ratio

Ketogenic feeds

Ketocal 3:1

KetoCal 4:1 LQ

Nutritionally complete, provides calories and protein for growth as well as vitamins and minerals

Medium Chain Triglyceride (MCT) Ketogenic Diet

- 40-60% of daily calorie intake as MCT oil / MCT food product (overall 75% fat)
- less carbohydrate restricted (15-20% of total calories)
- (Possibly) Greater choice of foods

Newer studies: comparing KD vs control group (not on KD)

Study	N	Age (y)	Type of KD	Duration (months)	> 50% sz reduction	> 90 sz reduction	Seizure free
Neal et al 2008	145[1]	2-16	CKD MCT	3	**KD: 28/73 (38%)** C: 4/72 (6%)	**KD: 5/72 (7%)** C: 0	**KD: 0** C:0
Sharma et a 2013	102[2]	2-14	MKD	3	**KD: 26/50 (52%)** C: 6/52 (11.5%)	**KD:15/50 (30%)** C: 4/52 (7.7%)	**KD: 5 (10%)** C: 0
Lambrechts et al 2017	48[3]	1-18	MCT, CKD	4	**KD: 13/26 (50%)** C: 4/22 (18.5%)	**KD: 3/26 (11.5%)** C: 1/22(4.5%)	**KD: 3 (11.5%)** C: 2 (9%)

[1] 14 (~ 10%) with LGS, [2] 47 (46%) with LGS, [3] 1 patient with LGS

Ketogenic Diet - Side Effects

- **Gastrointestinal symptoms:**
  - nausea, vomiting (worsening of Gastro-oesophageal Reflux), constipation
- Low blood Sugar (occasionally in initiation phase)
- Excess ketosis – acidosis (initiation phase)
- **Renal stones (3-6%)**
  - Risk factors: young age, hypercalciuria, (tx with carbonic anhydrase inhibitors: Topiramate, Zonisamide)
  - Prevention – potassium citrate (alkalinisation of urine) reduction from 6.7 to 0.9 % (McNally et al, Pediatrics, 2009)
- Increased Bruising (Berry-Kravis et al, Ann Neurol 2000)
- **Weight loss, Inadequate growth**
- Pancreatitis
- **Hyperlipidaemia**
- Decreased bone density – fractures (Long-term treatment)

When to consider KD treatment

- Seizures despite adequate AED treatment (usually - failure of ≥ 2 AEDs)
- Poor tolerance to AEDs

- (Rare) Metabolic disorders affecting
  - transport of glucose from blood into brain
    - Glut 1 transporter deficiency syndrome

  - Metabolism of glucose
    - Pyruvate dehydrogenase deficiency

When would be the KD be contraindicated ?

- Metabolic conditions
  - Beta-Fatty oxidation defects
  - Familial hyperlipidaemia
  - Organic acidurias
  - Pyruvate carboxylase deficiency (lactic acidosis)
- Relative contraindications
  - Feeding difficulties (food refusal)
  - Dysphagia (alternative feeding route: NG tube or PEG)
  - Severe gastro-oesophageal reflux (frequent vomiting)

How does the ketogenic diet work?– hypotheses

Bough &Rho Epilepsia 48 (1):43-58, 2007
Rho & Stafstrom Epilepsy Research 2011

- Anti-epileptic effect not only mediated by ketone bodies – but by adaptive metabolic processes induced by ketosis
- Effects mediated by polyunsaturated fatty acids
- Ketosis induces shifts in brain amino acid handling favouring GABA production
- Suppression of seizures mediated by adenosine acting on adenosine A1 receptors

Neuroprotective effects of KD

Maalouf et al 2009 , Brain Research Reviews

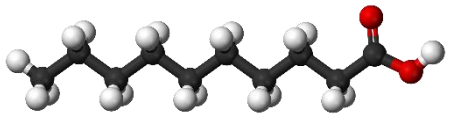
Modulation of oxidative stress and mitochondrial function by the ketogenic diet

Julie Milder, Manisha Patel*

Potential role of KD
following brain trauma and
in neurodegenerative
conditions

- Improvement of mitochondrial function
- Decrease of reactive oxygen species – reduction of oxidative stress
- Increased ATP production
- Inhibition of apoptosis
- Anti-inflammatory effects

C 10 (decanoic acid)



Potential explanation why MCT diet works

- Increases number and function of mitochondria in cells

  Hughes SD et al, J Neurochem, 2014

  - C10 (also C9) decrease of epileptiform discharges - in vitro model

    Chang et al, Neuropharmacolgy 2013

- Can suppress epileptiform activity by blocking AMPA receptors (receptor for excitatory neurotransmitter Glutamate)

  Chang et al, Brain 2016

- On-going first study to evaluate feasibility of new MCT food product (higher percentage of C10)
  Chief Investigator: Prof M Walker

The ketogenic diet for mitochondrial disorders

- 14 patients: 9 Complex I defects, 1 Complex II defect, 3 Complex IV defects, and 1 had combined Complex I and IV defects
- 7 patients became seizure-free after commencing the KD
- 3 of completed the diet for 6 months without relapse
- 1 patient with a greater than 90% seizure reduction, and 2 patients with seizure reductions between 50% and 90%, remained on the diet
- 4 patients (2 with the Leigh diseased) did not show any favorable responses to the diet or ceased the diet due to complications
- Low blood sugar in 1, lactic acidosis in 1

*Lee YM, Kim HD, Lee JS, and Slama A Epilepsia, **48**(1):82–88, 2007 Kang HC*

J Inherit Metab Dis (2017) 40:237–245
DOI 10.1007/s10545-016-0011-5

ORIGINAL ARTICLE

Ketogenic diet in pyruvate dehydrogenase complex deficiency: short- and long-term outcomes

Kalliopi Sofou[1] · **Maria Dahlin**[2] · **Tove Hallböök**[1] · **Marie Lindefeldt**[2] · **Gerd Viggedal**[1] · **Niklas Darin**[1]

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Abstract
Objectives Our aime was to study the short- and long-term effects of ketogenic diet on the disease course and disease-related outcomes in patients with pyruvate dehydrogenase complex deficiency, the metabolic factors implicated in treatment outcomes, and potential safety and compliance issues.
Methods Pediatric patients diagnosed with pyruvate dehydrogenase complex deficiency in Sweden and treated with ketogenic diet were evaluated. Study assessments at specific time points included developmental and neurocognitive testing, patient log books, and investigator and parental questionnaires. A systematic literature review was also performed.
(3-hydroxybutyric acid) was 3.3 mmol/l. Poor dietary compliance was associated with relapsing ataxia and stagnation of motor and neurocognitive development. Results of neurocognitive testing are reported for 12 of 19 patients.
Conclusion Ketogenic diet was an effective and safe treatment for the majority of patients. Treatment effect was mainly determined by disease phenotype and attainment and maintenance of ketosis.

Introduction

Ketogenic diet in pyruvate dehydrogenase complex deficiency: short- and long-term outcomes

- Nineteen patients
- Majority having prenatal disease onset
- Treated with ketogenic diet for a median of 2.9 years
- All patients living at a median age of 6 years
- Positive effects: epilepsy, ataxia, sleep disturbance, speech/language development, social functioning, and frequency admissions
- Safe (1 patient pancreatitis)
- The median plasma concentration of ketone bodies (3-hydroxybutyric acid) was 3.3 mmol/l
- Poor dietary compliance associated with poorer outcomes

Sofou K, Dahlin M, Hallböök T, Lindefeldt, Viggedal G & Darin N . J Inherit Metab Dis (2017) 40:237–245

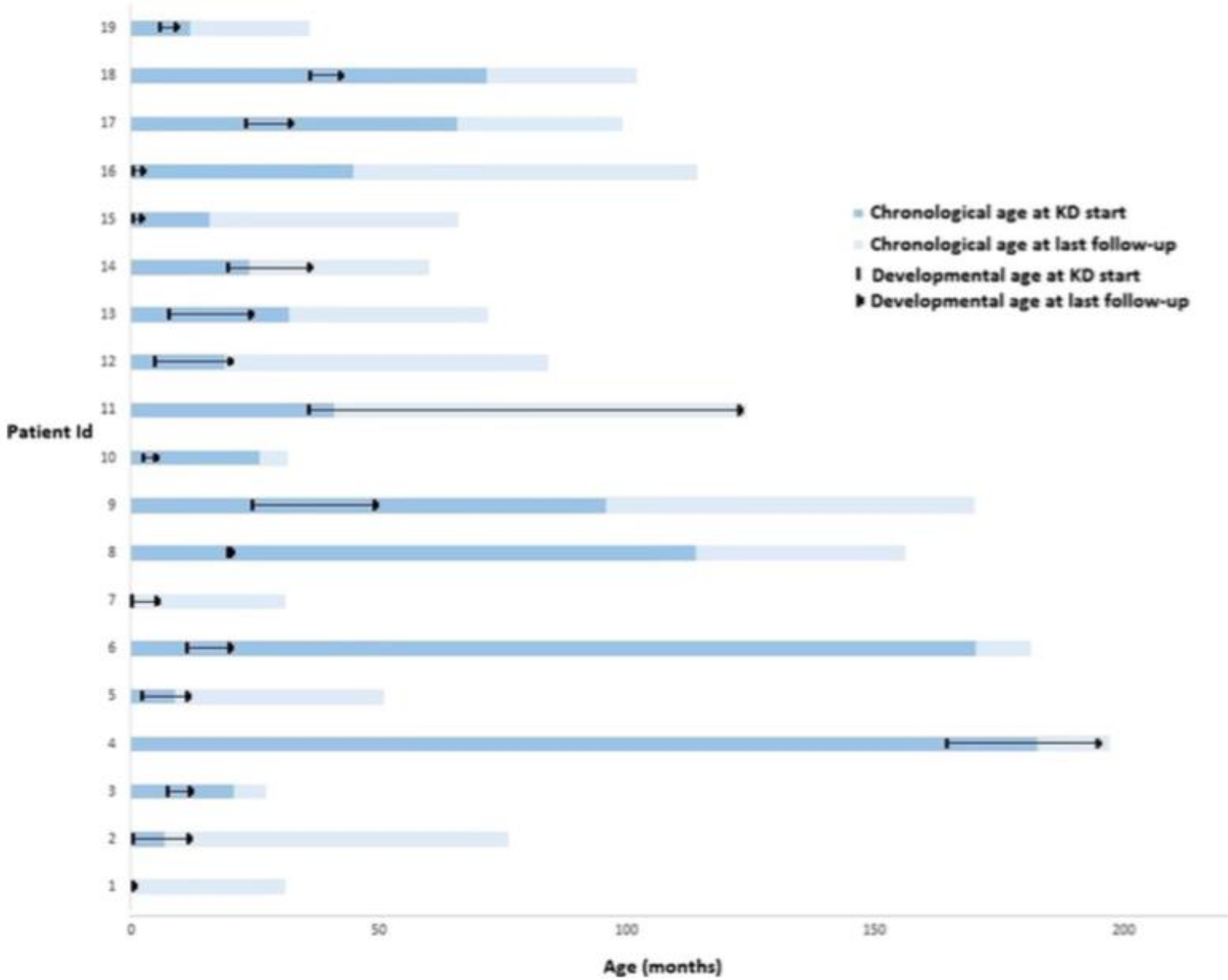


Fig. 1 Gross motor development at baseline and during treatment ($n = 19$)

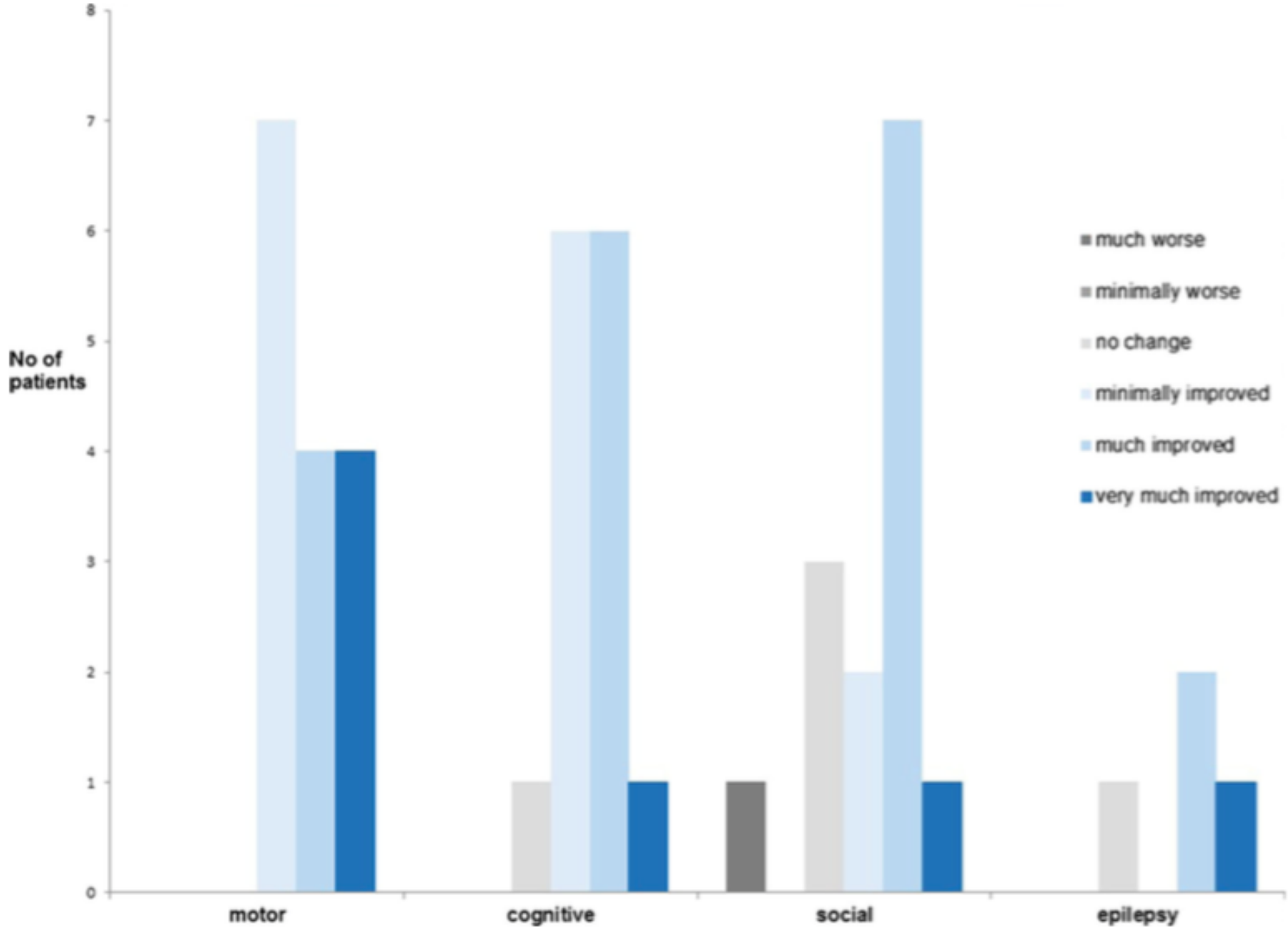


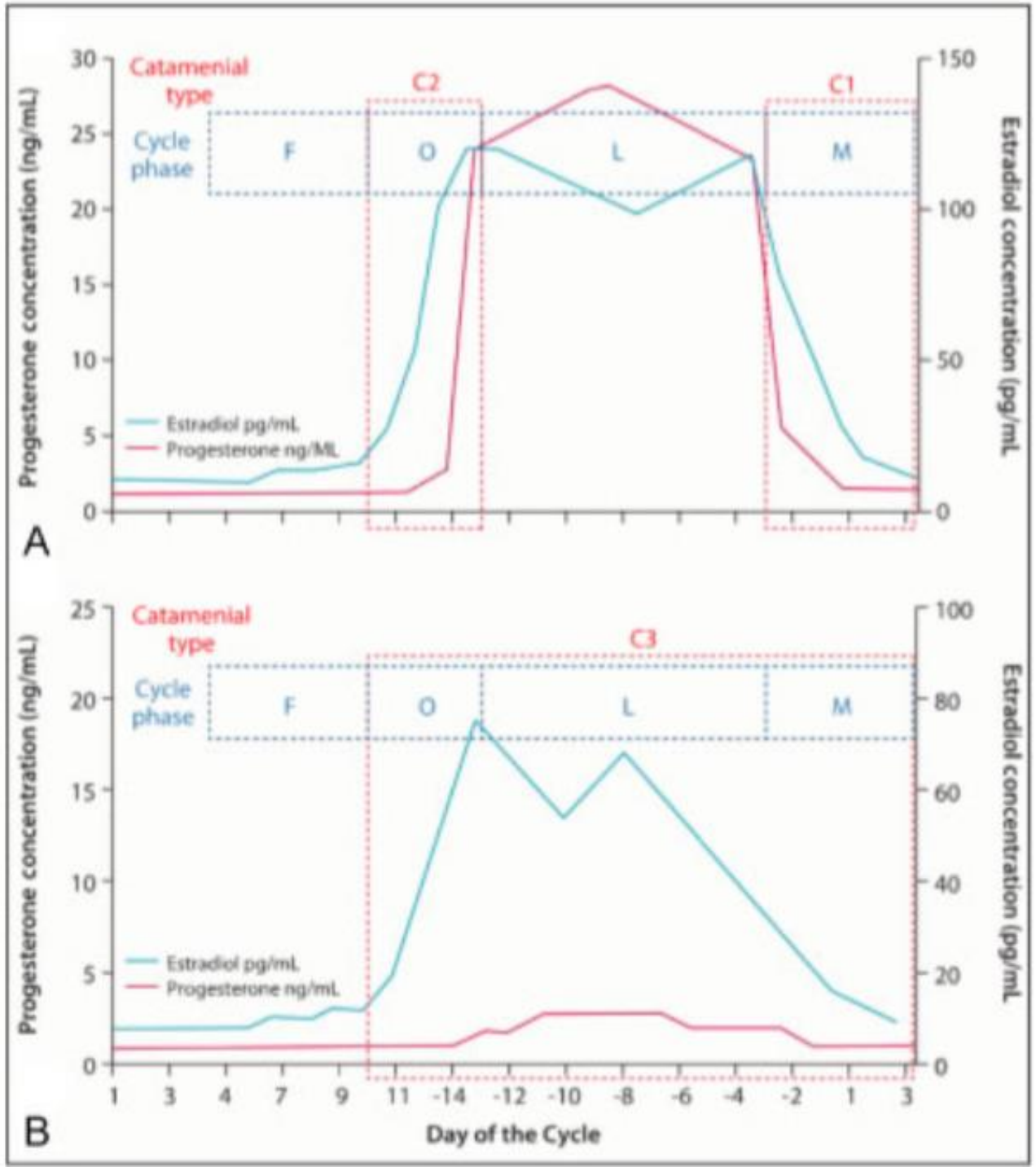
Fig. 3 Parental impression of patient's global improvement from baseline to last follow-up ($n = 15$)

Catamenial epilepsy

Catamenial epilepsy

- ‘‘Catamenial epilepsy’’ -cyclic seizure exacerbation in relation to the menstrual cycle
- Variations in seizure frequency according to the day, phase and ovulatory status of the menstrual cycle
- Three commonly recognized patterns:

1. Perimenstrual (C1: Day 3 to +3),
2. Peri-ovulatory (C2: Day 10 to 3)
3. The entire luteal phase in anovulatory cycles (C3: Day 10 to 3).



(A)Normal cycle with normal ovulation. C1 pattern is associated with exacerbation of seizures in the perimenstrual phase (day -3 to day þ3 of next cycle), and C2 pattern is associated with exacerbation of seizures in the periovulatory phase (day þ10 to day -13)

(B) Inadequate luteal phase cycle with anovulation. The C3 pattern is associated with exacerbations during the entire inadequate luteal phase (day þ10 to day þ3 of the next cycle)

Voinescu and Pennell Semin Neurol 2017;37:611–623

Management of catamenial epilepsy

- Evidence for progesterone treatment of the perimenstrually exacerbated subtype
- A study of natural progesterone treatment showed benefit for women with clear perimenstrual seizure exacerbations (C1 pattern)
- Not effective for women with other catamenial patterns or for women with epilepsy of reproductive age who did not have catamenial seizure exacerbations

Navis, A. & Harden, C. Curr Treat Options Neurol (2016) 18: 30. https://doi.org/10.1007/s11940-0413-6

Management of catamenial epilepsy

- Cyclic progesterone treatment

- Stopping menstrual cycle

-Medroxyprogesterone (Depo- Provera)

-Oral contraceptive pill

- Clobazam

- Acetazolamide

Summary

- Treatment of epilepsy associated with mitochondrial disorders can be difficult
- There is a role for the ketogenic diet
- Treatments with different modes of action are being developed
- Worsening of seizures with the menstrual cycle may be helped with hormonal treatment
- Research is required specifically for mitochondrial disorders

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