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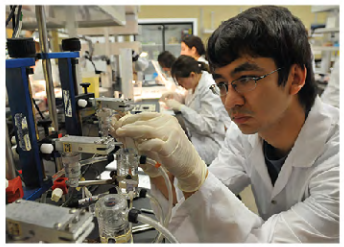

CONSEQUENCES OF STATUS EPILEPTICUS ON COGNITION IN PATIENTS WITH DRAVET SYNDROME

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UNIVERSITÉ DE SHERBROOKE

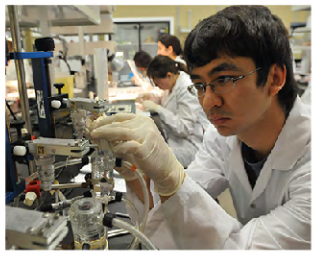
OBJECTIVES

- At the end of the presentation, participants will be able to:
  - Discuss cognitive changes associated with status epilepticus
  - Recognize specific aspects as related to Dravet syndrome
  - Discuss potential neuroprotective strategies
  - Apply risk-reduction strategies to Dravet syndrome

CONFLICT OF INTEREST

Dr Dufresne has no conflict of interest

There will be discussion of off-label therapies



STATUS EPILEPTICUS AND DEVELOPMENT

Many mecanisms for S.E. to impact cognition:

- Trauma
- Cardiovascular/respiratory insufficiency
- Treatment side-effects
- Neurobiological effects of the seizure

STATUS EPILEPTICUS AND DEVELOPMENT

Many mecanisms for S.E. to impact cognition:

- Trauma
- Cardiovascular/respiratory insufficiency
- Treatment side-effects
- **Neurobiological effects of the seizure**

EPILEPSY AND DEVELOPMENT

Cognitive impairment in epilepsy

- Common (QI <70 in up to 40-50% of patients[1,2])

EPILEPSY AND DEVELOPMENT

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EPILEPSY AND DEVELOPMENT

Cognitive impairment in epilepsy

- Common (QI <70 in up to 40-50% of patients[1,2])

- *Not only related to seizures*
- Correlates with aetiology[1]
- Correlates with drug resistance
  - Potential cognitive impact of medication[2,3]

1. Perrine K et al. Epilepsy Behavior. 1991:181-193
2. Meador KJ et al. Neurology. 1995;45:1494-1499
3. Farwell JR. N Engl J Med. 1990;322:364-369

EPILEPSY AND DEVELOPMENT

Cognitive impairment in epilepsy

- Common (QI <70 in up to 40-50% of patients[1,2])
- Correlates with aetiology[1]
  - *But also with age of apparition, disease duration*[3]
- Correlates with drug resistance[3]
  - *Correlates with amount of interictal epileptic activity*[4]

1. Park et al, Epilepsy Behav. 2013 (1): 166-171
2. Reilly et al, J Clin Exp Neuropsychol. 2015;37(4): 429-436
3. Berg et al, Neurology. 2012;79(13): 1384-1391
4. Van Bogaert et al, Neurophysiol Clin. 2012;42(1-2):53-58

EPILEPSY AND DEVELOPMENT

Underlying mecanisms:

- *Underlying aetiology – lesion/neuronal dysfunction*
- Excitotoxicity
- Ictal energy depletion
- Inflammation
- Synaptic modifications

EPILEPSY AND DEVELOPMENT

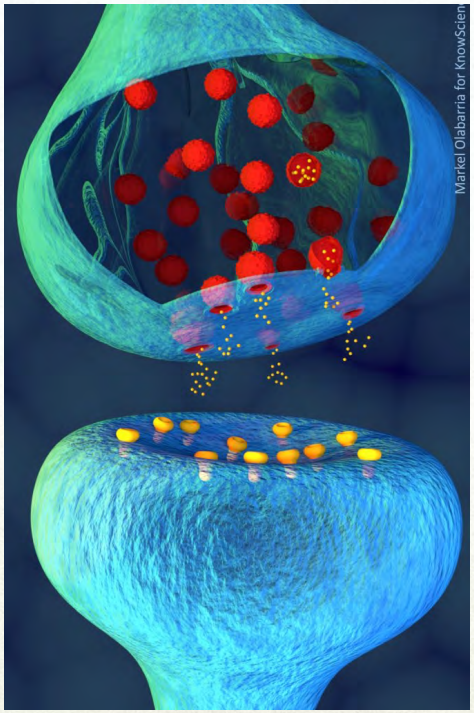
Underlying mecanisms:

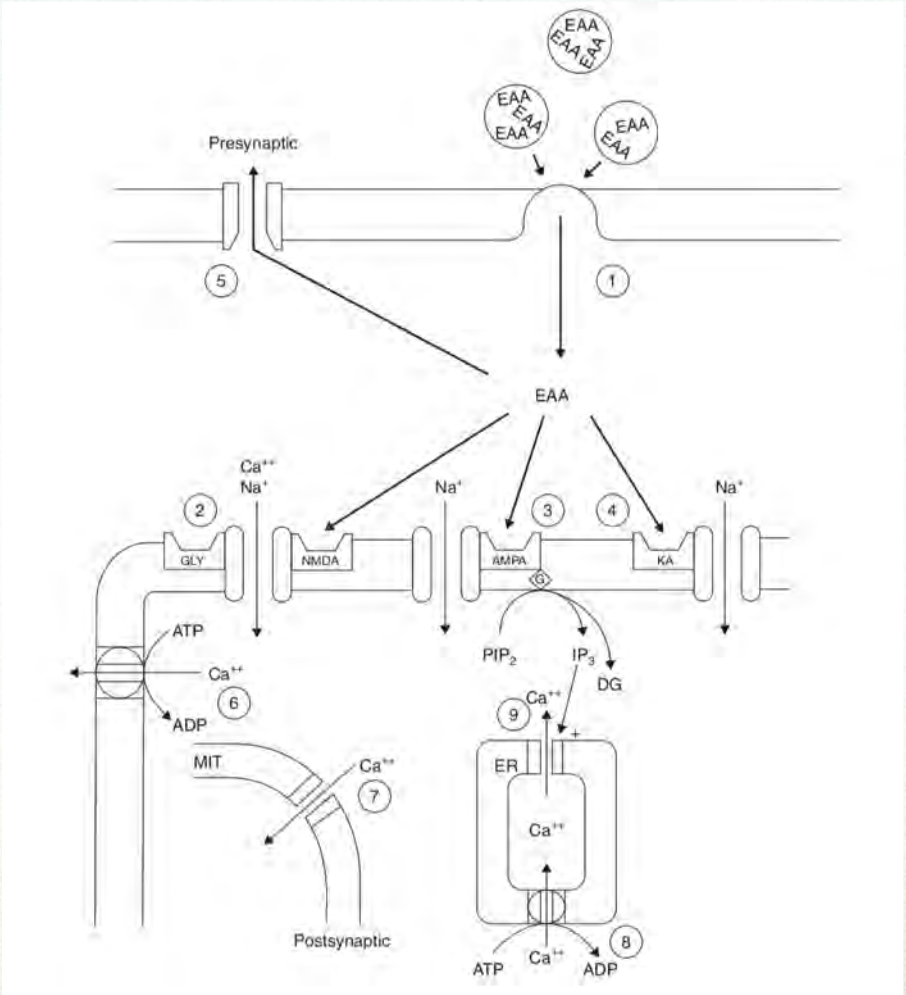
- Excitotoxicity
  - Excitatory neurotransmitters (glutamate)
    - > NMDA receptors > calcium influx > neuronal death
    - > AMPA receptors > second messengers > calcium influx > neuronal death

EPILEPSY AND DEVELOPMENT

Underlying mecanisms:

- Excitotoxicity?





Source: Pellock's Pediatric Epilepsy, Fourth Edition

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EPILEPSY AND DEVELOPMENT

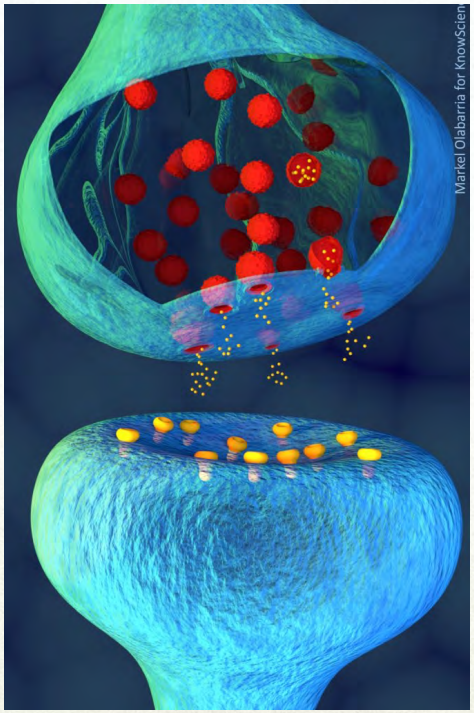
Underlying mecanisms:

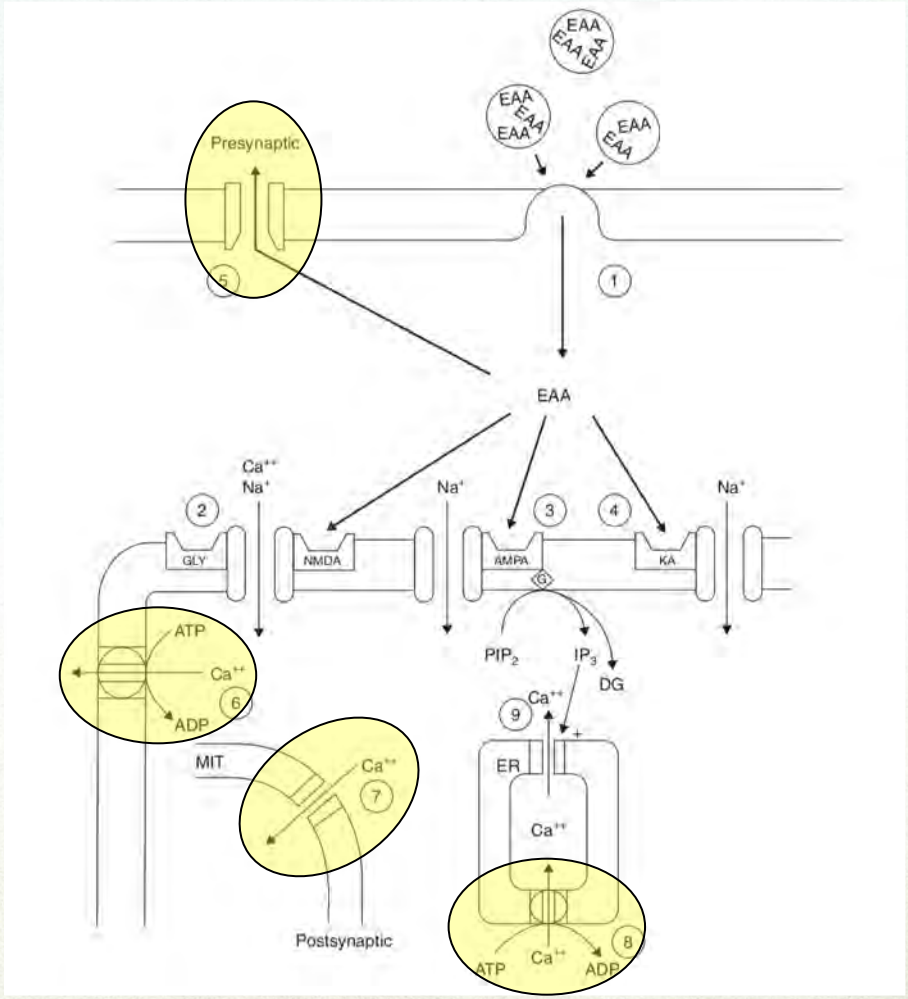
- Ictal energy depletion?
  - Short seizures well tolerated
  - Prolonged seizures (>30min)
    - Microscopic/cell-level energy depletion
    - Macroscopic-level energy depletion

EPILEPSY AND DEVELOPMENT

Underlying mecanisms:

- Ictal energy depletion?





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EPILEPSY AND DEVELOPMENT

Underlying mecanisms:

- Ictal energy depletion?
  - Short seizures well tolerated
  - Prolonged seizures (>30min)
    - Microscopic/cell-level energy depletion
      - Amplifies excitotoxicity
    - Macroscopic-level energy depletion

EPILEPSY AND DEVELOPMENT

Underlying mecanisms

- Inflammation
  - Excitatory NT >
    - Blood-brain barrier dysruption
    - Astrocyte dysfunction
  - $\downarrow O_2$/glucose / $\uparrow CO_2$ > blood vessels response

EPILEPSY AND DEVELOPMENT

Underlying mecanisms

- Synaptic modification
  - GABA overstimulation > GABAr downregulation
    - > NMDAr expression alteration
    - > *Long-term potentiation dysfunction*

EPILEPSY AND DEVELOPMENT

S.E.-associated cell death

- Specific localization
  - Hippocampal CA1/CA3/dentate gyrus
  - Amygdala
  - Pyriform cortex
  - Entorhinal cortex
  - Thalamus

EPILEPSY AND DEVELOPMENT

Evidence suggests cognitive impact from S.E.

- Camfield & Camfield (2012)
  - « Hard outcomes »:failed classes, high-school graduation, higher education attendance
  - No difference between patient with/without SE
- Adachi et al (2005)
  - 15 adult patients with SE, evaluated before/after SE: no difference

EPILEPSY AND DEVELOPMENT

Données suggèrent impact cognitif du status

- Roy et al (2011)
  - Single SE, febrile seizure controls, healthy controls
  - Psychometric testing differences between SE and others
  - Apparence of impact from age at SE
- FEBSTAT (2016)
  - Little difference at 1 month, possible language/motor
- Van Paesschen et al (2007)
  - Post-SE cognitive deficits; improvement in parallel with FDG-PET improvement
- Kanemura et al (2015)
  - Frontal atrophy and cognitive deterioration in Panayiotopoulos patients with SE

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:

- Caracteristic developmental slowing/stagnation after age 1
  - Almost universal[1,2,3], but base on small groups of patients
  - Anecdotal reports of cognitively normal patients[3,4]
  - Correlation between degree of cognitive impairment and epileptic activity[5,6]

1. Dravet C. Vie Méd. 1978;8:543-548
2. Dravet C. et al. Advances in epileptology. 1982;135-140
3. Buoni et al. 2006
4. Ragona et al. 2010
5. Cassé-Perrot C. et al. Neuropsychology of childhood epilepsy. 2001;131-140
6. Wolff M et al. Epilepsia. 2006;47(suppl 2):45-48

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:

- Caracteristic developmental slowing/stagnation after age 1
  - Typical (but not universal) profile[1,2,3,4]:
    - Behavioral, attention, impulse control disorders
    - Executive dysfunction, visuospatial organisation
    - Expressive language worse than receptive
  - School-age: relatively even distribution between mild, moderate and severe intellectual disability

1. Battaglia et al. Epilepsy res. 2013;106(1-2):211-221
2. Villeneuve et al. Epilepsy Behav. 2014;31:143-148
3. Acha J. et al. Child Neuropsychol. 2015;21(5):693-715
4. Chieffo D. et al. Epilepsy Behav. 2016;54:30-33

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet et al (2011)

- Cognitive deterioration in most patients

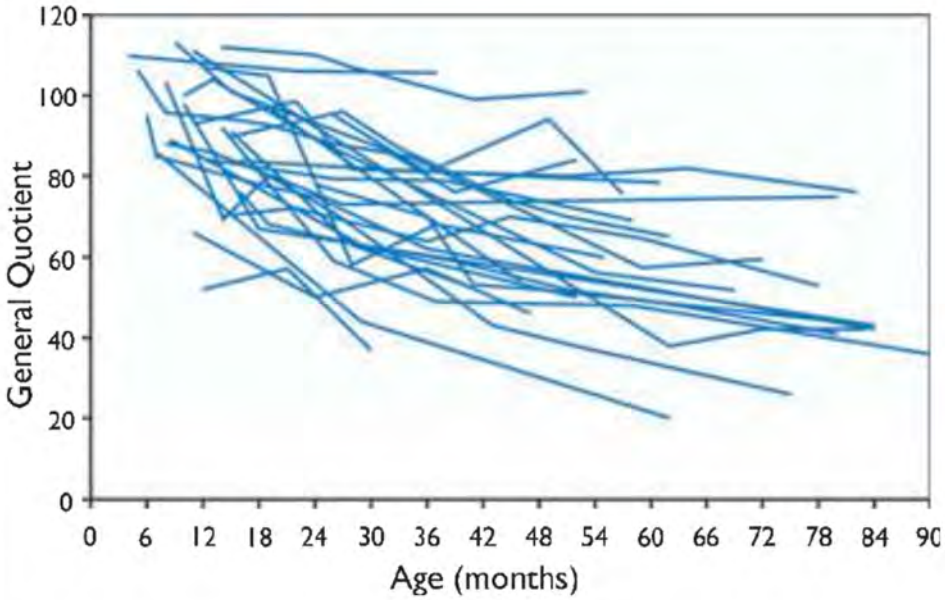


Figure 1.
Cognitive development of individual patients. Mean decrease of GQ is 33 points.
Epilepsia © ILAE

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet et al (2011)

- Variable profile
- Presence of myoclonia/absence: less favorable evolution (not statistically significant)

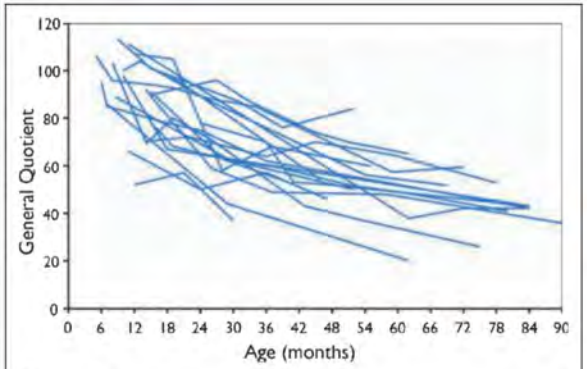


Figure 2.
Cognitive development of patients of group 1 (cases 1–19, Table 1), mean decrease of GQ is 39 points.
Epilepsia © ILAE

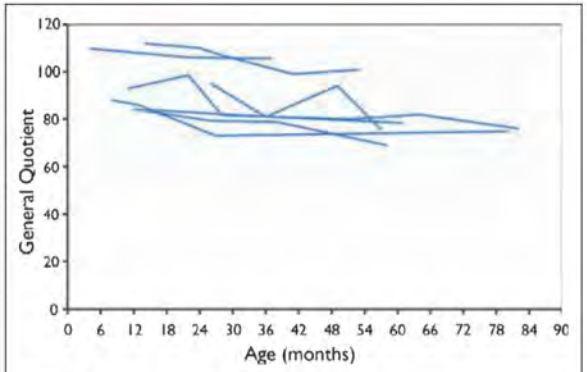


Figure 3.
Cognitive development of patients of group 2 (cases 20–26, Table 1), mean decrease of GQ is 12 points.
Epilepsia © ILAE

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet et al (2011): no clear association with status

- Study insufficiently powered?

Table 1. Clinical data of the series

Case, gender, present age (years)	AEDs during the first 18 months of life	Differential GQ (GQ 12 months – GQ 60 months)	GQ at 12 months[a]	GQ at 60 months[a]	Age at onset (months)	Number of epileptic status <18 months	Mean number of prolonged seizures per year[b]	Number of months with absences and/or myoclonus during the first 3 years of life	Genetic analysis
Group 1									
1, M, 19	PB	77	108	31	6	0	0.1	0[c]	Truncating
2, F, 6.5	VPA	73	93	20	4	0	0.3	14	Truncating
3, F, 8	VPA, VPA + BDZ	56	74	18	4	1	0.3	14	Truncating
4, M, 17	PB, VPA	56	101	45	8	0	0.6	0	Negative
5, F, 11	PB, VPA + BDZ	50	105	55	7	2	6.4	0	Negative
6, F, 9	VPA, VPA + BDZ	45	101	56	8	0	0	12	Truncating
7, M, 8.5	VPA, PB + BDZ	43	78	35	3	2	1.5	14	Missense
8, F, 12	PB, PB + VPA, VPA + BDZ	40	56	16	3	2	8	6	Negative
9, M, 11	VPA	36	105	69	6	2	0.6	0	Truncating
10, M, 14	PB	34	97	63	5	6	2.1	30	Truncating
11, F, 7.5	VPA	32	98	66	4	2	6.4	12	Truncating
12, F, 15	VPA, VPA + PB	32	76	44	4	2	4.8	0	Truncating
13, F, 10	PB	31	80	49	8	0	0.6	2	Truncating
14, M, 15	VPA + PB	30	83	53	4	3	1.4	2	Truncating
15, M, 13	VPA + TPM	28	84	56	6	0	6	0[c]	Truncating
16, M, 18	VPA, VPA + BDZ	26	78	52	8	2	8.6	4	Truncating
17, F, 8.5	VPA + PB	23	83	60	5	7	7	0	Negative
18, F, 19	PB, VPA + BDZ	22	73	51	5	1	2.1	24	Truncating
19, M, 9.5	PB + VPA, VPA	21	62	41	3	1	0.3	24	Truncating
Group 2									
20, M, 8.5	VPA + PB	19	98	79	10	4	2.2	0[c]	Missense
21, F, 7	PB	17	113	96	8	1	0.2	0	Truncating
22, F, 7.5	VPA, VPA + BDZ	16	85	69	4	2	0.8	0	Truncating
23, M, 13	VPA	13	93	80	9	3	2.4	0[c]	Negative
24, M, 15	VPA	8	84	76	3	1	10	10	Negative
25, M, 7	VPA	6	84	78	8	3	1.4	0	Missense
26, M, 5.5	PB	6	108	102	4	1	1	0	Truncating

M, male; F, female; AEDs, antiepileptic drugs; GQ, general quotient; PB, Phenobarbital; VPA, valproate; BDZ, benzodiazepine; TPM, topiramate; GQ, general quotient.
[a]GQ as obtained from a linear interpolation.
[b]Computed between onset and last cognitive assessment.
[c]Myoclonia appeared in the fourth year of life.

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:

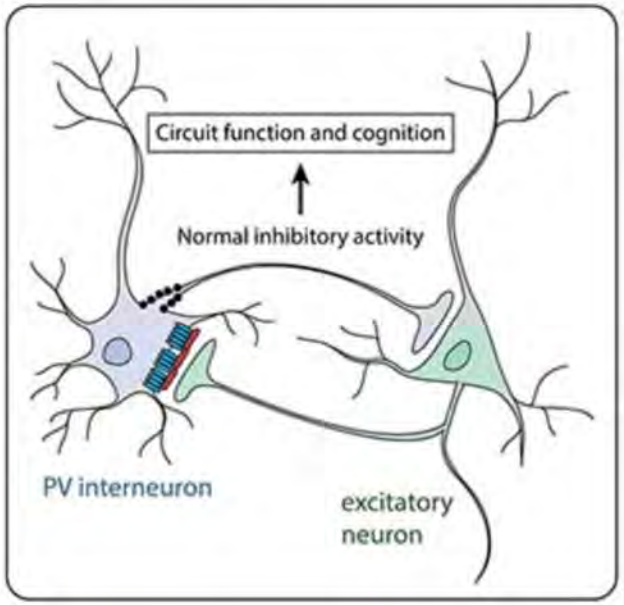
- Deterioration vs lack of improvement?[1]
  - Lack of improvement suggests SE is *not* the main factor
    - Unless if cause is LTP

1. Ragona et al. 2010

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:

- Caracteristic developmental slowing/stagnation after age 1
  - Many hypotheses on aetiology
    - Nav1.1 dysfunction> interneurons > network dysfunction[1]



Crédit: JE Hanson, A Bruce

1. Bender AC el al. PLoS One. 2016;11(3):e0151538

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:

- Caracteristic developmental slowing/stagnation after age 1
  - Many hypotheses on aetiology
    - Cerebral inury (cortex/white matter)[1]
    - Cerebellar injury[1,2]
      - Uncertain mecanism: neuronal dysfunction, ictal/interictal epileptic activity, status, Rx, restrictions…[3]

1. Pérez et al. Epilepsy Res. 2014;108(8):1326-1334
2. Battaglia et al. Epilepsy Res. 2013; 106(1-2):211-221
3. Guerrini et al. Dev Med Child Neurol. 2011;53(supp 2):11-15

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:

Impact of status epilepticus:

- Contradictory evidence:
  - Brunklaus et al (2012): 241 patients
    - OR 3.1 (3.1x status if cognitive impairment)
  - Other – smaller – series failed to find a correlation
    - Dravet et al (2011), Villeneuve et al (2014)

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:

Impact of status epilepticus:

- Inflammation
  - Myers et al (2017)
    - 5 death in context of status epilepticus
    - Early imaging: evidence of focal cytotoxic edema
    - Later: evidence of significant, diffuse edema
- Anoxia/ischemia
  - Chipaux et al (2010): 3 patients, prolonged SE (2, 7, 12h)
    - MRI changes compatible with sequellae from ischemia
    - No arrhythmia/hypotension/anoxia noted
      - Vascular changes due to medication?
      - (see above) > hypoperfusion secondary to inflammation?

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition

Impact of status epilepticus:

- *In summary*
  - *Little available data in Dravet syndrome*
  - *Part of the cognitive dysfunction is not epileptic in origin*

  But
  - *Convincing evidence of impact of SE in general*
  - *Association between a more severe epilepsy and cognitive dysfunction in Dravet children*

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:

Impact of status epilepticus:

WHAT DO WE DO?

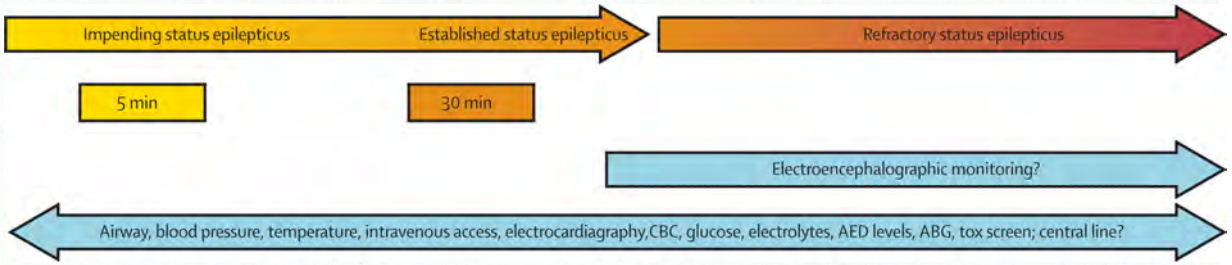
DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences

DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences

Interictal



Ictal

DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences

Interictal

SE prevention

- Effective treatment
  - Medication
  - Diet
  - VNS

DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences

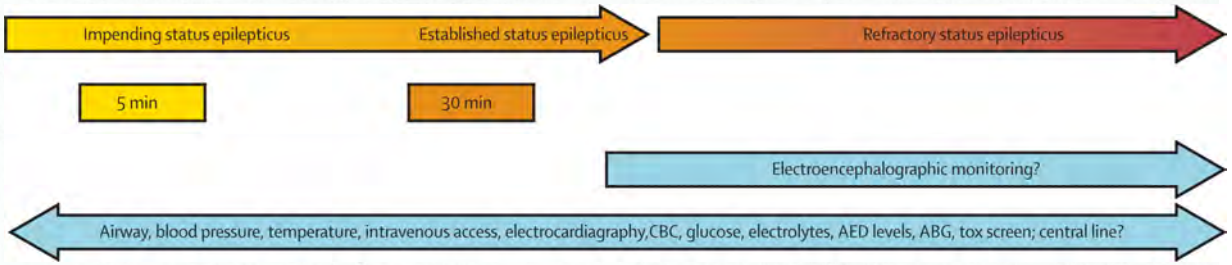
SE prevention

- Effective treatment
- Trigger control

Interictal

DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences



Interictal

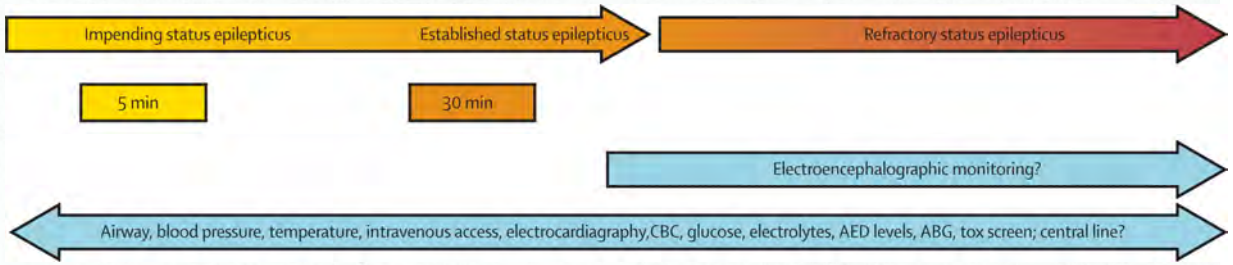
Ictal

Rapid treatment

Neuroprotection

DRAVET-SPECIFIC CONSIDERATIONS:

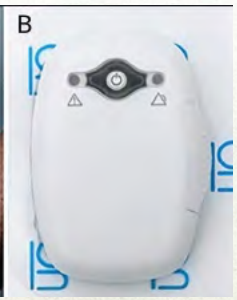
Status epilepticus: preventing consequences



Interictal

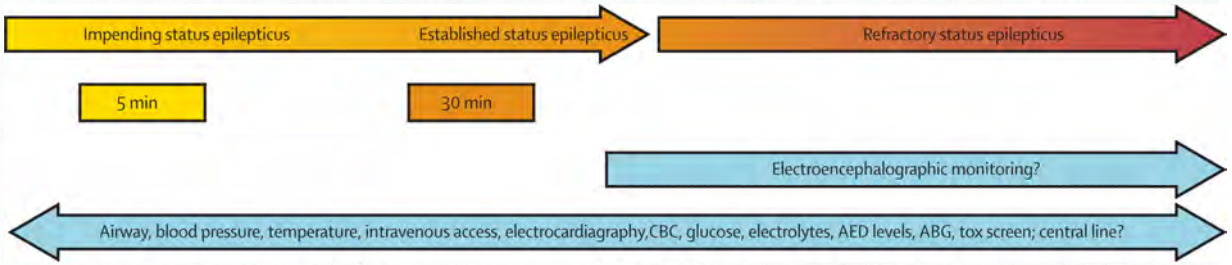
Ictal – rapid treatment

- Alarms



DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences



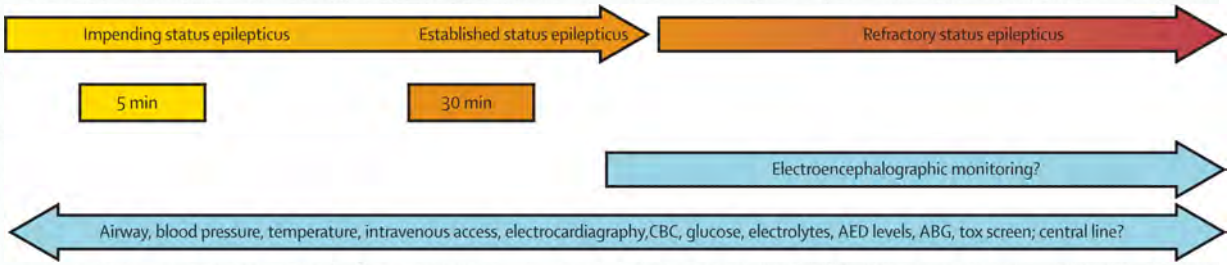
Interictal

Ictal – rapid treatment

- Emergency home treatment
  - Diastat, nasal midazolam
  - Vagal nerve stimulator
    - Magnet, automatic stimulation (model 106)
  - (Paramedic-administered treatment)
- Rapid transport to the hospital

DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences



Interictal

Ictal – neuroprotection

- *Mostly theoretical at the moment*
- Conservative measures
  - Vital signs control, homeostasis maintenance

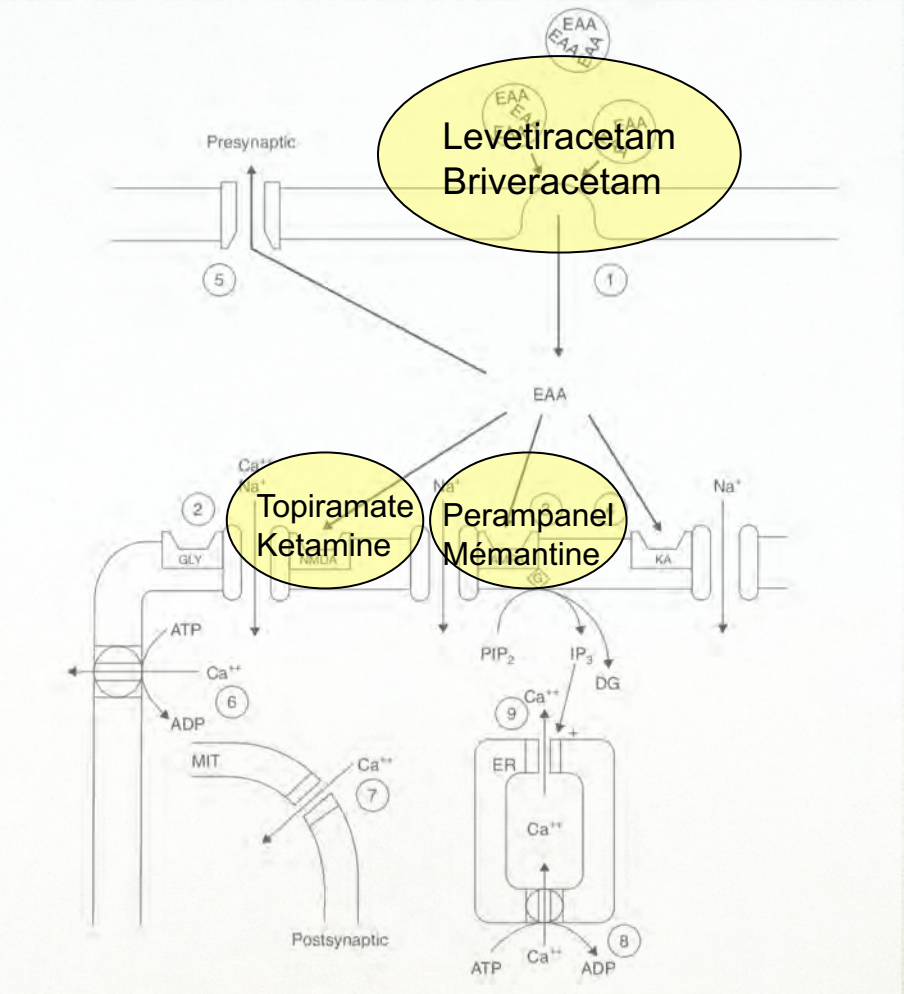
DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences

Ictal – neuroprotection

- Other measures
  - Anti-inflammatories? (cf: Myers et al)
  - Resveratrol? Anti-inflammatory/anti-oxydant effect (Mishra et al, 2015; rats)
  - G-CSF? Anti-apoptotic effect (Zhang et al, 2010; rats)
  - EPO? neuro-protective if administered before SE (Jun et al, 2009; rats)
  - Memantine? Anti-NMDA (Zenki et al, 2018)
  - New/specific anti-epileptics? (Stepien et al, 2005)
    - Perampanel > anti-AMPA
    - Topiramate > NMDA modulation, Ca blockade
    - Levetiracetam, briveracetam
    - (vigabatrin, felbamate, zonisamide, gabapentin/prégabalin/oxcarbazépine)
    - Ketamine

DRAVET-SPECIFIC CONSIDERATIONS:



Source: Pellock's Pediatric Epilepsy, Fourth Edition

IN SUMMARY

- Cognitive impairment almost universal in Dravet
- SE probably exerts an effect on cognition
  - Relative contribution of SE vs underlying disease not established

- Most effective protective strategies are also the easiest to implement:
  - Prevent SE
  - Treat rapidly
  - Treat effectively

QUESTIONS?

Thank you for your attention