CONSEQUENCES OF STATUS EPILEPTICUS ON COGNITION IN PATIENTS WITH DRAVET SYNDROME

Pr David Dufresne, MD
Professeur adjoint, département de pédiatrie
Service de neurologie pédiatrique
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 mechanisms for S.E. to impact cognition:
- Trauma
- Cardiovascular/respiratory insufficiency
- Treatment side-effects
- Neurobiological effects of the seizure
STATUS EPILEPTICUS AND DEVELOPMENT

Many mechanisms for S.E. to impact cognition:
- Trauma
- Cardiovascular/respiratory insufficiency
- Treatment side-effects
- Neurobiological effects of the seizure
Cognitive impairment in epilepsy
- Common (QI <70 in up to 40-50% of patients$^{1,2}$)
EPILEPSY AND DEVELOPMENT

Cognitive impairment in epilepsy
- Common (QI <70 in up to 40-50% of patients\textsuperscript{1,2})
EPILEPSY AND DEVELOPMENT

Cognitive impairment in epilepsy
- Common (QI <70 in up to 40-50% of patients\textsuperscript{1,2})

- Not only related to seizures
- Correlates with aetiology\textsuperscript{1}
- Correlates with drug resistance
  - Potential cognitive impact of medication\textsuperscript{2,3}

Cognitive impairment in epilepsy
- Common (QI <70 in up to 40-50% of patients\textsuperscript{1,2})
- Correlates with aetiology\textsuperscript{1}
  - \textit{But also with age of apparition, disease duration}\textsuperscript{3}
- Correlates with drug resistance\textsuperscript{3}
  - \textit{Correlates with amount of interictal epileptic activity}\textsuperscript{4}

1. Park et al, Epilepsy Behav. 2013 (1): 166-171
EPILEPSY AND DEVELOPMENT

Underlying mechanisms:
- Underlying aetiology – lesion/neuronal dysfunction
- Excitotoxicity
- Ictal energy depletion
- Inflammation
- Synaptic modifications
EPILEPSY AND DEVELOPMENT

Underlying mechanisms:
- Excitotoxicity
  - Excitatory neurotransmitters (glutamate)
    - > NMDA receptors > calcium influx > neuronal death
    - > AMPA receptors > second messengers > calcium influx > neuronal death
EPILEPSY AND DEVELOPMENT

Underlying mechanisms:
- Excitotoxicity?

Source: Pellock’s Pediatric Epilepsy, Fourth Edition
EPILEPSY AND DEVELOPMENT

Underlying mechanisms:
- Ictal energy depletion?
  - Short seizures well tolerated
  - Prolonged seizures (>30min)
    - Microscopic/cell-level energy depletion
    - Macroscopic-level energy depletion
EPILEPSY AND DEVELOPMENT

Underlying mechanisms:
- Ictal energy depletion?

Source: Pellock’s Pediatric Epilepsy, Fourth Edition
EPILEPSY AND DEVELOPMENT

Underlying mechanisms:
- 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 mechanisms
- Inflammation
  - Excitatory NT >
    - Blood-brain barrier disruption
    - Astrocyte dysfunction
- ↓O₂/glucose / ↑CO₂ > blood vessels response
EPILEPSY AND DEVELOPMENT

Underlying mechanisms
- 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
  - 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
  - Appearance 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
  - 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\textsuperscript{1,2,3}, but base on small groups of patients
  - Anecdotal reports of cognitively normal patients\textsuperscript{3,4}
  - Correlation between degree of cognitive impairment and epileptic activity\textsuperscript{5,6}

1. Dravet C. Vie Méd. 1978;8:543-548
3. Buoni et al. 2006
4. Ragona et al. 2010
DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:
- Characteristic developmental slowing/stagnation after age 1
  - Typical (but not universal) profile\textsuperscript{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

2. Villeneuve et al. Epilepsy Behav. 2014;31:143-148
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)
**DRAVET-SPECIFIC CONSIDERATIONS:**

Dravet et al (2011): no clear association with status
- Study insufficiently powered?

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

*Male; F, female; AEDs, antiepileptic drugs; GQ, general quotient; PB, Phenobarbital; VPA, Vigabatrin; BDZ, benzodiazepine; TMI, topiramate; GQ, general quotient.

*Compared between onset and last cognitive assessment.

*GQ obtained from a linear interpolation.

*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:
- Characteristic developmental slowing/stagnation after age 1
- Many hypotheses on aetiology
  - Nav1.1 dysfunction > interneurons > network dysfunction


Crédit: JE Hanson, A Bruce
**DRAVET-SPECIFIC CONSIDERATIONS:**

Dravet syndrome and cognition:
- Characteristic developmental slowing/stagnation after age 1
  - Many hypotheses on aetiology
    - Cerebral injury (cortex/white matter)\(^1\)
    - Cerebellar injury\(^1,2\)
      - Uncertain mechanism: neuronal dysfunction, ictal/interictal epileptic activity, status, Rx, restrictions...\(^3\)

DRAVET-SPECIFIC CONSIDERATIONS:

Dravet syndrome and cognition:
Impact of status epilepticus:
- Contradictory evidence:
    - OR 3.1 (3.1x status if cognitive impairment)
  - Other – smaller – series failed to find a correlation
Dravet syndrome and cognition:
Impact of status epilepticus:

- Inflammation
    - 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

SE prevention
- Effective treatment
  - Medication
  - Diet
- VNS

Interictal
DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences

SE prevention
- Effective treatment
- Trigger control

Interictal
DRAVET-SPECIFIC CONSIDERATIONS:

Status epilepticus: preventing consequences

Interictal

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

Ictal – neuroprotection

- Airway, blood pressure, temperature, intravenous access, electrocardiography, CBC, glucose, electrolytes, AED levels, ABG, tox screen; central line?
- Electromorphologic monitoring?
- Established status epilepticus
- Refractory status epilepticus
- Impending status epilepticus
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