EEG power spectral analysis in Dravet Syndrome

Pediatric Neurology Unit+ Service for Rare Disorders

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OVERVIEW
Dravet Syndrome

- An epileptic encephalopathy of early childhood with ominous course
- Unusually severe febrile seizures developing during the first year of life
- Towards the second year of life, various kinds of seizures appear (myoclonic, generalized tonic clonic, partial with generalization, partial complex and atypical absences)
- Towards the end of the second year of life developmental delay becomes evident
- Cognition continues to deteriorate and will ultimately lead to mental retardation, usually in the mild to moderate range
Discovery of the Underlying Genetic Defect

- SCN1A gene, encoding for the Nav.1.1. voltage gated sodium channel

- Hundreds of mutations have been described, some of them (nonsense or frameshift) leading to premature truncation of protein and severe clinical phenotype, while missense mutations may lead to milder clinical picture
Mechanism

• Nav.1.1. voltage gated sodium channel are mainly found in the inhibitory GABAergic interneurons in the hippocampus.

• Decrease in activity of the Nav.1.1. can lead to decline in inhibition of the hippocampus.

• The dysfunction of inhibitory neurons leading to imbalance between GABA inhibition (by GABAergic neurons) and excitation by glutamate causing the pathophysiology in Dravet.
Treatment

• Na channel blockers, which are the most used antiepileptic are a problem in Dravet.

• Increasing GABAergic transmission thus increasing inhibitory tone, control Dravet better.
EEG history

In 1929, Hans Berger

- Recorded brain activity from the closed skull
- Reported brain activity changes according to the functional state of the brain
  - Sleep
  - Hypnothesis
  - Pathological states (epilepsy)
10-20 System of Electrode Placement

- F = Frontal
- P = Parietal
- T = Temporal
- O = Occipital
- C = Central
- A = Auxiliary

Odd # = Left
Even # = Right
Frequency Ranges

**Beta:** 14 – 30 Hz

**Alpha:** 8 – 13 Hz

**Theta:** 5 – 7 Hz

**Delta:** 1 – 4 Hz
Recording from an epileptic epoch
QEEG

• EEG signals comprises a microvoltage time series in very high frequency of sampling (a lot of noise).

• The common sample rates are reduced to the limit of 256/sec

• Spectral analyses is used to separate the wave into different frequencies.
Spectral Analysis

- Fourier Transform analysis
Study Goals
• Assessment of background brain oscillation in DS children with truncating mutation in comparison with missense mutations.
• Assessment of background brain oscillation in DS children in comparison with controls.
• Influence of different epileptic drugs on background brain oscillation in DS children, focusing on Na channels blockers in comparison with increasing GABAergic inhibition.
Methods
12 children with SCN1A mutations (truncating/missense) on the DS/GEFS+ spectrum between the ages of 3-16

- Patients files were collected to sort out age/gender/mutation/drugs treated
- 52 EEGs collected from 10 of the 12 children with DS
- Sampling of 30 sec epochs of artifact-free during awake/eyes closed/sleep (slow wave sleep between spindles)
- Power spectral analysis of the samples is done. Recordings obtained form standard F3,Fz,F4,C3,Cz,C4 electrodes will be imported to Matlab 6.5 for Windows (Mathworks Inc.)be digitally and subsequently lowpass filtered with cut-off frequency ~ 40 Hz. Power spectrums will be generated utilizing Welch algorithm. Data between 1 and 40 Hz will be subjected to further analysis.
- Calculation of alfa/beta/delta/teta and mean frequencies
Results
• 12 patients
• 4 (33.33%) males, 8 (66.66%) females, 1:2 (M:F)
• Age: 7.91667 ±4.23102 (3-16)
• Mutations:
  – 5 Missense (41.6%)
  – 5 Truncating y (41.6%)
  – 1 Unknown significance (the splicing site) (8.4%)
  – 1 Polymorphism (8.4%)
• EEG recordings samples
  – Eyes open, awake: 20 (38.4%)
  – Eyes closed, awake: 7 (13.4%)
  – Sleep: 25 (48.2%)
<table>
<thead>
<tr>
<th>Patient #</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Mutation type</th>
<th>Domain</th>
<th>Drugs</th>
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<tr>
<td>1</td>
<td>F</td>
<td>3</td>
<td>missense</td>
<td>helical S6 repeat IV</td>
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<td>8</td>
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<td>helical S2- repeat III</td>
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<td>3</td>
<td>F</td>
<td>6</td>
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<tr>
<td>5</td>
<td>M</td>
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<td>splicing</td>
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<tr>
<td>6</td>
<td>F</td>
<td>11</td>
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<td>7</td>
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<td>4</td>
<td>missense</td>
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<td>interdomain repeat I-II</td>
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<tr>
<td>11</td>
<td>M</td>
<td>5</td>
<td>predicted polymorphysm</td>
<td>DEPALEPT, RIVOTRIL, PHENOBARBITONE</td>
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<tr>
<td>12</td>
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<td>4</td>
<td>missense</td>
<td>S5- repeat I</td>
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</table>
Mapping the SCN1A Mutations
SP- channel F3 patient asleep

![Graph showing brain activity](image)

<table>
<thead>
<tr>
<th>delta</th>
<th>teta</th>
<th>alfa</th>
<th>beta</th>
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<td>.1912</td>
<td>.1453</td>
<td>.2896</td>
<td>.3740</td>
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Mean frequency: 13.69171
SP- channel F3 patient eyes open

- Mean frequency: 13.66803
- Delta: .2001
- Theta: .1379
- Alpha: .2745
- Beta: .3874
What’s Next?

• Developing of a mathematical model of a two neuron system (GABA-ergic interneuron and glutaminergic excitatory neuron).

• The model will be built based on electrophysiological analysis of Nav 1.1 mutations as observed in heterologous expression system (Xenopus leaves oocyte and human embrionic kidney cell line).

• This model could be further used as a simple cost effective way of predicting effect of antiepileptic drugs on inhibitory neurons in real patients.
Any Questions... Just Ask!