Incidence of Dravet Syndrome in a US Population

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- Marinus Pharmaceuticals- Contracted Research
- Epilepsy Study Consortium- Consultant
- Turing- Consulting fees
Incidence of Dravet Syndrome

Clinical DS in the US (1960-70’s) 1/40,000
UK 1/41,000
Sweden 1/29,000
Denmark 1/22,000

Kaiser Permanente Northern California (KPNC)

- 3.5 million patients (almost 50% of insured population)
- 8,000 physicians
- 21 hospitals
- Fully electronic medical record
Methods

- Retrospective population-based cohort study
- Birth cohort-infants born at KPNC in January 1, 2007-July 1, 2010

Data sources

- Inpatient/outpatient diagnoses
- Pharmacy records
- EEG and neuroimaging reports
- Encounter notes (ex. neurology, genetics, pediatrics, physical therapy)

Case ascertainment: electronic search

Patients with \( \geq 2 \) encounters with seizure diagnosis, before 12 months of age

- 345.xx Epilepsy
- 780.39 Convulsion, fit, seizure
- 780.31 Febrile convulsion
- 779.0 Neonatal seizure

Normal cognitive and motor development before onset of seizures

≥ 2 febrile or afebrile seizures by 12 months

Seizure semiology: myoclonic, hemiclonic or generalized tonic-clonic

2 or more seizures ≥10 minutes

Refractory epilepsy beyond age 2 (ie failure to resound to a first line AED)
Exclusions

- Brain malformations
- Traumatic or hypoxic-ischemic brain injury
- Neonatal onset <1 month
- Brain tumor
- Neurocutaneous syndromes
- Other genetic/metabolic disorder

Results: Electronic Search

N = 125,547 births

N = 730 with ≥ 2 seizures by 12 mos

492 No AED’s at age 2
149 Neonatal seizures

89 potential cases for medical record review

Methods

Clinical Dravet Syndrome-chart reviewed by 2 pediatric epileptologists (SM, JS) and 1 child neurologist (YW) to reach consensus.

SCN1A gene testing performed as part of routine clinical care
Results: Chart Review

N = 89 patient records

- 14 Neonatal brain injury
- 14 Brain malformation
- 12 no AED after age 2
- 11 other genetic or metabolic disorder
- 3 acute brain injury

8 cases of clinical DS

27 Seizure semiology not DS

Clinical characteristics

<table>
<thead>
<tr>
<th>SCN1A Abnormal</th>
<th>Age at Onset, mo</th>
<th>Seizure Types</th>
<th>Febrile Seizures by 12 Months, n</th>
<th>Prolonged Seizures by 12 Months, n</th>
<th>Brain MRI Findings (Age at Last MRI, mo)</th>
<th>Follow-up, y</th>
<th>Developmental Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3</td>
<td>GTC, hemiclonic, focal</td>
<td>3</td>
<td>2</td>
<td>Global atrophy (26)</td>
<td>3.2</td>
<td>Language delay, motor delay</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>GTC, myoclonic, focal</td>
<td>6</td>
<td>1</td>
<td>Myelination delay (36)</td>
<td>5.8</td>
<td>Language delay, autism</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>Myoclonic, focal</td>
<td>2</td>
<td>2</td>
<td>Normal (9)</td>
<td>5.9</td>
<td>Language delay, cognitive dysfunction</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>GTC, hemiclonic, focal</td>
<td>4</td>
<td>3</td>
<td>Normal (9)</td>
<td>6.0</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>Myoclonic, hemiclonic, focal</td>
<td>1</td>
<td>2</td>
<td>Normal (23)</td>
<td>3.9</td>
<td>Behavior problems, special education</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>GTC, focal</td>
<td>2</td>
<td>1</td>
<td>Thin corpus callosum (6)</td>
<td>5.4</td>
<td>Language delay, motor delay</td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>GTC, focal</td>
<td>2</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Normal (13)</td>
<td>3.5</td>
<td>Language delay, behavior problems</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>GTC, tonic</td>
<td>2</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>White matter lesion (32)</td>
<td>5.0</td>
<td>Language delay, motor delay</td>
</tr>
</tbody>
</table>

GTC, generalized tonic-clonic seizures.

<sup>a</sup> Both patients developed refractory and prolonged seizures after 1 year of age.
SCN1A mutations (n=7/8)

**TABLE 2** SCN1A Abnormalities Identified in 7 Patients With Clinical Dravet Syndrome

<table>
<thead>
<tr>
<th>Age of Onset, mo</th>
<th>Mutation Likely Pathogenic</th>
<th>De Novo</th>
<th>SCN1A Abnormality</th>
<th>Protein Domain</th>
<th>Mutation Predication Programs</th>
<th>Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nucleotide</td>
<td>Amino Acid</td>
<td></td>
<td>Polyphen-2</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>c.5516T&gt;C</td>
<td>p.Leu1839Pro</td>
<td>C terminal</td>
<td>Probably damaging</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>c.3034delins28</td>
<td>p.Leu1012delins9</td>
<td>Loop 2</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>No</td>
<td>c.1806G&gt;A</td>
<td>p.Glu602Glu</td>
<td>Loop 1</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>c.1156A&gt;T</td>
<td>p.Glu385Asp</td>
<td>DIS5-S6</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>c.5164A&gt;G</td>
<td>p.Thr1722Ala</td>
<td>D4S5-S6</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>Yes$^a$</td>
<td>c.974_976del</td>
<td>p.Tyr325del</td>
<td>DIS5-S6</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>Yes$^a$</td>
<td>c.4655G&gt;A</td>
<td>p.Cys1552Tyr</td>
<td>D4S1</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not applicable because not an amino acid substitution.

$^a$ Maternal testing revealed no SCN1A mutation. The father was not available for testing.
EEG / MRI

ALL initial EEG’s were normal

Brain MRI

All NORMAL Between 4-13 months of age (n=8)

Repeat MRI at 26-37 months of age (N=3)

Global atrophy

Delayed myelination

White matter T2 abnormality in temporal lobe

Population incidence

- Clinical Dravet Syndrome
  - 8 Cases
  - 1 per 15,700 (1/40,000 US, 1/29,000 UK)

- Dravet WITH pathogenic SCN1A mutation
  - 6 Cases
  - 1 per 20,900 (1/41,000 UK, 1/22,000 Denmark)

Parental age

- Mean maternal age was not significant
- Paternal age was between 24-45 years
  - 3 fathers were > 40 years
- Paternal ages not available for entire study population

Predictors of Dravet?

Among 89 infants with > 2 seizures by 12 months who were prescribed AEDs at 24 months:

- Prolonged seizures (>10 mins) by 12 months
  - Mean 2.4 in DS vs 0.2 not DS (p<0.0001)

- Febrile seizures by 12 months
  - Mean 2.9 in DS vs 0.8 not DS (p<0.005)
**Relationship of 1st seizure to vaccines**

N = 80 infants with ≥ 2 seizure diagnoses by 12 mos, on AED’s at 2 years, no exclusion criteria

<table>
<thead>
<tr>
<th></th>
<th>&lt;7 days after vaccine</th>
<th>&gt;7 days after vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet</td>
<td>3(43%)</td>
<td>4(57%)</td>
</tr>
<tr>
<td>No Dravet</td>
<td>5(7%)</td>
<td>68(93%)</td>
</tr>
</tbody>
</table>

p<0.02 (Chi squared Fisher’s exact) OR=10.2 (95% CI 1.1-78.)

Hattori scoring system

Table 3. A proposed risk score for a screening test

<table>
<thead>
<tr>
<th>Predictive risk factors</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical score</td>
<td></td>
</tr>
<tr>
<td>Onset $\leq$ 7 months</td>
<td>2</td>
</tr>
<tr>
<td>Total number of seizures $\geq$ 5</td>
<td>3</td>
</tr>
<tr>
<td>Hemiconvulsion</td>
<td>3</td>
</tr>
<tr>
<td>Focal seizure</td>
<td>1</td>
</tr>
<tr>
<td>Myoclonic seizure</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged seizure</td>
<td>3</td>
</tr>
<tr>
<td>Hot water--induced seizure</td>
<td>2</td>
</tr>
<tr>
<td>Genetic score</td>
<td></td>
</tr>
<tr>
<td>SCN1A missense mutation</td>
<td>1</td>
</tr>
<tr>
<td>SCN1A truncated mutation</td>
<td>2</td>
</tr>
</tbody>
</table>

Clinical score $>6$  $\rightarrow$  SCN1A testing

Hattori J, Epilepsia 2008
Did we miss any?

- Solicited all 12 KPNC child neurologist
- Identified 14 additional children with Dravet
  - 12 born outside of study years
  - 2 born at another hospital (not in birth cohort)
Limitations

- May have missed cases (we provide a minimum estimate of incidence)
  - If 1st seizure was after 12 months
  - if left KPNC (92% followed >12 months)
- Retrospective study, did not get direct history or examine patients
Conclusions

- Dravet Syndrome is over twice as common in the US as previously described.
- Genetic testing should be considered in children with 2 or more prolonged febrile seizures by 1 year of age.

Impact?

- Increased awareness could lead to earlier diagnosis and more targeted treatment regimens
- Eligibility for new therapies currently in clinical trials
  - Epidiolex
  - Fenfluramine
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