Iceberg, Straight Ahead!
Introduction to Dravet Syndrome

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Disclosures

• Honoraria: Upsher-Smith, Compassionate Cultivation
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Objectives

• Briefly review the course of epilepsy in Dravet Syndrome
• Discuss diagnosis and treatment strategies in Dravet Syndrome
• Review the genetic etiology of Dravet Syndrome
• Introduce the multiple comorbidities associated with Dravet Syndrome
• Put us all on the same page as we start this wonderful conference
EPILEPSY

COGNITIVE/BEHAVIORAL

SLEEP

GAIT/ORTHOPEDIC

FEEDING/GASTROINTESTINAL

SOCIAL

AUTONOMIC

SUDEP
And so it began…

• First described in 1978\textsuperscript{1} as \textit{severe myoclonic epilepsy of infancy}, renamed for Dr. Charlotte Dravet in 1989

• Initial clinical criteria:
  • Family history of epilepsy or febrile convulsion
  • No previous personal history of disease
  • Seizures beginning in first year of life as generalized or unilateral febrile clonic seizures
  • Secondary appearance of myoclonic jerks and often partial seizures
  • EEG showing generalized SW and polySW, photosensitivity, and focal abnormalities
  • Developmental delays by second year of life
  • Simultaneous ataxia, pyramidal signs, and interictal myoclonus
  • Resistance to all forms of treatment
  • Intellectual deficiency and personality disorders in all affected children

And then it evolved...

• Modified in 2010
  • Family history of epilepsy or febrile convulsions is variable
  • Initial seizures are not always generalized or unilateral clonic but may be focal or myoclonic
  • Initial seizures are not always febrile
  • Atypical absences and absence status frequently appear
  • Photosensitivity may be associated with pattern sensitivity
  • Neurological signs are not always present
  • MRI is normal at the onset
  • Cognitive deficiency and personality disorders are present in all affected children but of variable degrees
The First Clues...

- Initial seizure between 5-8 months - may or may not be associated with **fever/modest hyperthermia**
- Clonic, generalized, **unilateral clonic type**
- **Duration** tends to be long, often evolving to status epilepticus
- EEG is most often normal at onset
- Initial diagnosis is often febrile seizure
- Seizures often recur in weeks to months
The Evolution…

- Other seizure types appear
  - Alternating hemiclonic
  - Generalized tonic clonic
  - Myoclonic
  - Absence/atypical absence
  - Focal dyscognitive
  - Tonic seizures are rare

- EEG demonstrates generalized spike wave/polyspike wave
The Evolution...

- Developmental delays become evident
- Regression may occur – particularly after status epilepticus
- Behavioral concerns with inattention and hyperactivity arise
- Neurological signs appear
  - Hypotonia
  - Ataxia
  - Pyramidal signs
The long term

- Seizures persist into adulthood
- Rarely prolonged as the patient ages
- Mostly occur in sleep
- Cognitive delay persists
- Gait apraxia
- Mortality by adulthood 15%
The Evaluation

• EEG
• MRI
  • Typically normal
  • Nonspecific white matter changes, cerebral/cerebellar atrophy¹-⁵
  • Hippocampal sclerosis

The Evaluation

• Genetic testing
• SCN1A mutations present in approximately 75% of patients with clinical DS
• Function: voltage gated Na channel (Na\textsubscript{\textit{V}}1.1) – highly expressed in the nervous system
• 90-95% of mutations are de novo
• 70% sequencing mutations, 2-3% CNV
The Evaluation

• Other genes associated with Dravet phenotype
  • PCDH19
  • GABRG2
  • SCN1B
  • SCN2A
Treatment of Dravet Syndrome

• Initial goals of seizure treatment
  • Control the seizures as best we can
  • Avoid seizure aggravators
  • Treatment/avoidance of status epilepticus
Treatment of Dravet Syndrome

- Traditional mainstays of therapy
  - Stiripentol\(^1\): 69% reduction in seizures compared to 7% increase in placebo
  - Valproic Acid: 50% seizure reduction in 22-48%\(^2,3\)
  - Clobazam: responder rates 28%

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1. Chiron et al 2000
Treatment of Dravet Syndrome

• Second lines of treatment
  • Levetiracetam
  • Topiramate
  • Zonisamide
  • Bromides
  • Ketogenic diet
  • Vagal nerve stimulation
  • Perampanel
Treatment of Dravet Syndrome

- CBD: 12.4sz/m -> 5.9sz/m (39% reduced) versus placebo 14.9sz/m- >14.1 (13%) [p=0.01]
- 43% (CBD) had > 50% reduction in seizures vs. 27% (placebo) [p=0.08]
- 3 sz free (CBD) vs 0 (placebo)
- CGIC 62% (CBD) vs 34% (placebo) (p=0.02)
Treatment of Dravet Syndrome

• Fenfluramine
  • Mean 64% (0.8mg/kg/d) reduction compared to placebo (p<0.001)
  • Mean 34% (0.2mg/kg/d) reduction compared to placebo (p=0.019)

<table>
<thead>
<tr>
<th></th>
<th>ZX008 0.8 mg/kg/day (N=40)</th>
<th>ZX008 0.2 mg/kg/day (N=39)</th>
<th>Placebo (N=40)</th>
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<tbody>
<tr>
<td>Patients with ≥50% reduction in monthly convulsive seizures</td>
<td>70.0% (p&lt;0.001)</td>
<td>41.0% (p=0.001)</td>
<td>7.5%</td>
</tr>
<tr>
<td>Patients with ≥75% reduction in monthly convulsive seizures</td>
<td>45.0% (p=0.001)</td>
<td>20.5% (p=0.033)</td>
<td>2.5%</td>
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<td>Longest seizure-free interval (median)</td>
<td>20.5 days (p&lt;0.001)</td>
<td>14 days (p=0.011)</td>
<td>9 days</td>
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</tbody>
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Treatment of Dravet Syndrome

• Avoid aggravators
  • Sodium channel drugs: lamotrigine, carbamazepine, phenytoin, rufinamide, oxcarbazepine
  • Overheating/hyperthermia

• Have a seizure rescue plan
  • Rescue therapy at home
  • Clear plan for EMS and ED with explanation of the syndrome
The comorbidities

• Cognitive Development – epileptic encephalopathy vs channelopathy (or both?)
  • Initial normal development*
  • Steep falling curve over the first 4 years
    • Relationship to seizures, medications, and the underlying gene mutation still unclear
  • Gradual decrease/stagnation/some positive improvement
  • Cognitive impairment mild 34%, moderate 41%, severe 26%¹

• Behavior
  • Hyperactivity/inattention
  • Autistic traits

The comorbidities

• Sleep
  • 75-82% of parents report some sleep concern\textsuperscript{1,2}
  • Difficulty with sleep initiation and transition are most commonly reported
  • Extrinsic vs intrinsic sleep dysfunction

The comorbidities

• Orthopedic
  • Progressive gait deterioration and skeletal malalignment beginning around 6y\textsuperscript{1}
  • Crouched gait (decreased hip/knee extension), loss of foot arch, external tibial torsion
  • Decrease in mobility and endurance over time
  • Osteopenia

Gait in Dravet
The comorbidities

• Gastrointestinal\textsuperscript{1,2}
  • 99% of families report problems with appetite
    • Prolonged meal times, needing assistance with feeding, food fads
  • Up to 40% report difficulty swallowing
  • Constipation

1. Villas N et al Epilepsy Behav 2017
2. Knupp K et al Ped Neurol 2017
The comorbidities

• Other
  • Autonomic – temperature dysregulation, decreased sweating, bradycardia/tachycardia
  • Endocrine – precocious puberty
  • Immune – frequent infections
  • Mortality\(^1\) – early mortality in estimated 20% (SUDEP and SE most common cause)

The comorbidities

• Family impact\textsuperscript{1,2}
  • Two thirds of caregivers report symptoms of anxiety/depression
  • 75\% report concern for the impact on siblings
  • Adverse impact on employment
  • Average annual financial burden $106,000\textsuperscript{3}

1. Campbell JD, et al. Epil Behav 2018
2. Villas N et al. Epil Behav 2017
Conclusion

Severity

Age (y)

0 2 4 6

Epilepsy
Development
Sleep
Gait
Epilepsy
This is Dravet Syndrome
QUESTIONS?
Cook Children's 100 Years
You're the 1 in our 100!