North American Consensus – Optimizing the Diagnosis and Management of Dravet Syndrome

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 Goals

- Early, accurate diagnosis in a cost-effective manner
- Optimal management strategy:
  - Prophylactic treatment of seizures
  - Treatment of break-through seizures and status epilepticus
  - Screening for and management of co-morbidities
  - Family support
The Study Process
Methods

- Modified Delphi process which presents multiple iterations of questionnaires to a panel of experts in order to develop a consensus of opinion
Families of children with DS (N=5):
- identified through contact with Dravet Syndrome Foundation and Dravet.ca

Physicians (N=14):
- A core panel of 6 pediatric epileptologists with interest/expertise in DS was identified through PERC and CPEN
- Core panelists were asked to nominate clinicians in North America with noted expertise in DS. Panelists were then asked to rank their top choices.
- The core panel and top ranked 8 clinicians (including one adult epileptologist who had published several articles on DS) comprised the physician panel
Dr. Anne Berg, an epidemiologist who is internationally recognized for her expertise in pediatric epilepsy, was recruited to facilitate the study:

- Finalize each iteration of the questionnaire
- Send out questionnaires and assist in collating responses
The 6 physicians comprising the core panel reviewed the medical literature regarding specific topics:
- Diagnosis
- Genetic testing
- Prophylactic and abortive seizure treatment
- Co-morbidities including SUDEP
- Long-term outcome
- Cognition

These findings were summarized in a formal document, which was sent to all panelists for review prior to completion of questionnaires.
A draft questionnaire was created with input from family members/core panelists, and revised based on feedback sought from the above panelists.

This questionnaire was then sent to the expert panel electronically, as a RedCap questionnaire.
Respondents were asked to indicate their degree of agreement with statements (strongly agree, agree, somewhat agree, neutral, somewhat disagree, disagree and strongly disagree).

- For anything less than agree, they were asked to provide comments.

- 3 rounds of questionnaires were completed, and responses analyzed after each round.
Consensus was defined as:

- **Strong**: >75% strongly agree or agree
- **Moderate**: >75% somewhat agree, agree or strongly agree
- **Modest**: <75% agree to any degree, but nobody disagrees
- **No consensus**: <75% agree to any degree and some disagree at any level
Findings
**Clinical Diagnosis: Seizures**

- **Age at onset:** 1-24 mos
- **Seizure types:**
  - **First 2 yrs:**
    - GTCS or hemiconvulsive seizures are MANDATORY. These are often prolonged, but shorter convulsions are also typical.
    - Myoclonic seizures are seen in the MAJORITY by age 2 yrs.
  - **Other seizures:**
    - Focal dyscognitive, atypical absences and obtundation status TYPICALLY occur in children >2 yrs, but may be seen earlier.
    - Tonic seizures are UNUSUAL before 2 yrs, but may occur in older children.
    - Atonic seizures, typical absences and spasms are ATYPICAL.
Seizure Triggers:

- In MAJORITY: Hyperthermia. NO CONSENSUS on proportion of patients who become less sensitive to this with increasing age
- Flashing lights, visual patterns, bathing, eating, overexertion may trigger. NO CONSENSUS on percentage of patients that are triggered
- NO CONSENSUS on what proportion of females have catamenial provocation of seizures
## Misdiagnoses

<table>
<thead>
<tr>
<th>Children with DS are commonly-sometimes misdiagnosed as:</th>
<th>Children with the following epilepsy types are commonly-sometimes misdiagnosed as DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonic Atonic Epilepsy</td>
<td>Myoclonic Atonic Epilepsy</td>
</tr>
<tr>
<td>Lennox Gastaut Syndrome</td>
<td>Myoclonic Epilepsy in Infancy</td>
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<tr>
<td>Myoclonic Epilepsy in Infancy</td>
<td>PCDH19</td>
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<tr>
<td>GEFS+</td>
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<tr>
<td>Atypical febrile seizures</td>
<td></td>
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<tr>
<td>Lesional focal epilepsy</td>
<td></td>
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<tr>
<td>Mitochondrial disorders</td>
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</table>
Normal development prior to seizure onset

With time, virtually all have developmental delay, which is typically evident between 18 mos and 5 yrs of age

NO CONSENSUS if delays are global or selective

Regression may occasionally be seen following a prolonged seizure
Neurological Exam

- Abnormalities on the neurological exam are seen in over half of patients over time, and evident by 3-4 yrs of age in most patients.

- Hypotonia and gait problems (crouch gait) are the most common motor abnormalities.

- Fine motor deficits include incoordination and impaired dexterity.
A first degree family history of epilepsy or febrile seizures is found in \( \leq 25\% \) of cases.
MRI findings

- MRI is *usually* normal but generalized atrophy or hippocampal sclerosis is *not uncommon*

- White matter changes or cerebellar atrophy *may be seen but is not typical*

- Malformations of cortical development, tumors or thinning of the corpus callosum are *not consistent*
EEG Findings

- **Background:**
  - Under age 2 yrs: normal or slow
  - ≥2 yrs: typically slow

- **Interictal discharges:**
  - May be multifocal, focal and/or generalized
  - May be seen at all ages, but present in >50% after age 2 yrs
  - PPR may occur in children and adolescents but is rare in adults
Genetic testing should be pursued for all patients with DS and has led to an earlier diagnosis of DS

If the clinical history is very suggestive of DS, either an SCN1A or epilepsy panel should be done, but NO CONSENSUS which is better. A microarray is not needed

If the history is somewhat suggestive but atypical features are present, an epilepsy panel is preferred over SCN1A, and there is NO CONSENSUS regarding microarray

Karyotype is not needed in a patient with suspected DS
Genetic Counselling

- Must be provided to families by a provider with expertise in genetic counselling. Should cover:
  - Mode of inheritance
  - Risk in subsequent siblings
  - Description of how genetic change results in clinical symptoms
<table>
<thead>
<tr>
<th>Genetic Testing Not Needed</th>
<th>Genetic Testing Should Be Done</th>
<th>No Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 mos, single prolonged febrile convulsion</td>
<td>&lt;12 mos, 2 or more prolonged focal febrile seizures (opposite sides)</td>
<td>&lt;12 mos, 2 or more prolonged generalized febrile seizures</td>
</tr>
<tr>
<td></td>
<td>&lt;12 mos, 2 or more prolonged febrile seizures, at least one focal</td>
<td>&lt;12 mos, 2 or more prolonged focal febrile seizures (same side)</td>
</tr>
<tr>
<td></td>
<td>12-35 mos, &gt;1 prolonged or brief FS before 18 mos and myoclonic and/or atypical absence szs refractory to &gt;1 AED</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-dysmorphic teen or adult with pharmacoresistant early life focal and/or genld szs, with non focal exam and normal MRI</td>
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</table>
Early diagnosis of DS (by age 2) is associated with modestly to moderately improved cognitive outcome and improved seizure control.
What Should Families Be Told and When?

The following should be conveyed to families within 2-4 weeks of clinical diagnosis:

- Complete seizure control is typically not achievable
- Status epilepticus is common, esp in young children
- Exacerbating AEDs and seizure triggers should be avoided
- Realistic expectations of developmental outcome
- Risk of SUDEP
## Management: Environmental

<table>
<thead>
<tr>
<th>STRONG</th>
<th>MODERATE</th>
<th>MODEST</th>
<th>NOT HELPFUL</th>
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<tbody>
<tr>
<td>Allow child to nap if tired</td>
<td>Avoid photic triggers</td>
<td></td>
<td>Prophylactic antibiotics with febrile illness</td>
</tr>
<tr>
<td>Avoid overexertion</td>
<td>Cooling vests</td>
<td></td>
<td>Avoiding immunizations</td>
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<tr>
<td>Avoid high ambient temperature</td>
<td>Sunglasses</td>
<td></td>
<td>Avoiding swimming</td>
</tr>
<tr>
<td>Prophylactic antipyretics with vaccine or illness</td>
<td>Avoid placing patient in bath</td>
<td></td>
<td>Patching one eye</td>
</tr>
<tr>
<td>Prophylactic benzodiazepines with illness</td>
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Management: AEDs

- **NO CONSENSUS** on typical level of seizure control achievable

- **First-line therapies:**
  - Clobazam and Valproic acid

- **Next-best options if these fail:**
  - Stiripentol or Topiramate
  - Stiripentol is effective when combined with VPA and CLOB. No data support its use as monotherapy
Management: AEDs

- Clonazepam, Levetiracetam, Zonisamide and Ketogenic Diet are moderately effective
- Ethosuximide and Phenobarbital may be effective
- Carbamazepine, Oxcarbazepine, Lamotrigine, Phenytoin and Vigabatrin often exacerbate seizures
Management: Other agents

- IVIG, Steroids, SSRIs – few respondents had experience with these agents – no consensus on efficacy

- Verapamil – 61% had experience with verapamil, but 73% of those who used it felt it was not effective

- Cannabinoids – 67% had experience with CBD, and 89% felt it was moderately efficacious
Management: Dietary Therapy

- **Traditional ketogenic diet:**
  - The best option for children <6 yrs and a good option for children aged 7-12 yrs
  - Can be used in teens/adults but other dietary options may be preferable

- **Modified Atkins Diet:**
  - Reasonable choice for children 2-12 yrs and the best option for teens and adults

- Dietary treatment has a moderately positive impact on cognition and behavior
Management: Surgical Therapy

Before considering any surgery, including VNS, patients MUST be evaluated at an epilepsy center with expertise in DS to ensure other therapies have been maximized.
Management: VNS

- May be considered but only after failure of 1st (CLB and VPA) and 2nd line (STP, TOP, KD) treatments
- Has a moderate to minimal impact on seizure reduction and generally less efficacious than KD
- NO CONSENSUS on how effective the magnet is to prevent prolonged seizures
- Has no significant benefit on cognition or development in most patients
Management: Corpus Callosotomy or Temporal Lobectomy

- The benefits of these procedures in DS are unclear, and the potential risk/benefit ratio must be carefully considered, disclosed to and discussed with the family prior to surgery.

- **Callosotomy** may be considered in intractable drop seizures but only after failure of CLB, VPA, STP, TOP, LEV and ketogenic diet.

- **Temporal lobectomy** may be considered with intractable focal seizures localizing to one temporal lobe and MTS on MRI, but only after failure of the above therapies.
All patients need a rescue medication and seizure rescue protocol which can be carried out at their local hospital

**Recommended rescue medications**

<table>
<thead>
<tr>
<th>&lt;2 years</th>
<th>2-6 yrs</th>
<th>7-12 yrs</th>
<th>Teen/Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam pr</td>
<td>Midazolam nasal/buccal</td>
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<tr>
<td>Midazolam nasal/buccal</td>
<td>Diazepam pr</td>
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</tbody>
</table>
When to Give Rescue Meds

- *Immediately* with convulsive seizure, in patient with recent history of convulsive seizures which are typically prolonged

- Otherwise, within 3-5 minutes of onset of the convulsive seizure

- A second full dose of rescue medication should be given after 5-10 minutes in patients who continue to convulse after their first dose
When to Give Rescue Meds

- Give for brief convulsive seizures that are clustering
- NO CONSENSUS on whether to give for brief nonconvulsive seizures that are clustering
Treatment of Status Epilepticus in ER

- IV benzodiazepine is the initial treatment of choice. This dose should be repeated x1 if seizure persists.

- Recommended next option:
  - Strong consensus that VPA load is a preferred next choice (88%)
  - Strong physician consensus that neither a propofol (82%) nor a pentobarbital infusion is recommended as the next choice (77%)
  - Poor consensus for other abortive medications
Some differences between family members and MDs

- Physicians were:
  - more likely to recommend a loading dose of phenobarbital (62% vs 0%, p=0.04)
  - less likely to recommend a third dose of IV benzodiazepine (23% vs 50%, p=0.04) or a midazolam infusion (15% vs 100%, p=0.009).

- Phenytoin/Fosphenytoin in SE:
  - Strong MD consensus that this agent is not contraindicated
  - Strong family member/caregiver consensus that it should not be used
Management: Co-morbidities

- **Development:**
  - The neurologist/epileptologist should routinely query development at clinic visits.
  - All children should undergo formal developmental assessment prior to starting school. Earlier assessment may be indicated if clinical concerns are present.
  - Early enrichment is helpful even before delays are evident.
Management: Co-morbidities

- **Behavior:**
  - The neurologist/epileptologist should routinely include questions on behavioral concerns at clinic visits
  - Subspecialty referral for behavior assessment is only indicated if clinical concerns are present
  - Risperidone and stimulants may be effective for behavior and attention concerns but data on efficacy in DS is lacking
Motor/Gait Problems:

- All children should be assessed by PT, OT and SLP prior to school entry. Earlier referral is indicated if clinical concerns are present.
- Ataxia and crouch gait are often present by early adolescence but may appear earlier. Routine screening for gait disorders should be performed at follow-up visits beginning in early childhood.
- If gait problems are noted, referral to PT is indicated.
Management: Co-morbidities

- **Sleep:**
  - Sleep disorders are commonly reported in DS, and should be routinely queried at clinic visits starting at, or shortly after diagnosis.
  - There is no consensus regarding the type of sleep disorder that affects patients with DS.
  - Referral to a sleep specialist and/or polysomnography is only indicated in the presence of clinical concerns.
  - Melatonin is at least somewhat helpful for sleep problems.
Management: Co-morbidities

- **GI:**
  - Constipation and dysmotility may be seen but the exact incidence is not known

- **Endocrine:**
  - NO CONSENSUS on type or prevalence of endocrine problem

- **Dysautonomia:**
  - Dizziness, syncope, hypertension, abnormal flushing, cool extremities may be seen but incidence of such symptoms is unknown
  - NO CONSENSUS on pharmacologic management of such symptoms
Management: Co-morbidities

- **Cardiology:**
  - NO CONSENSUS regarding need for routine cardiac screening, including ECG
  - Referral to a cardiologist is only needed if there are clinical concerns
SUDEP

- SUDEP should be discussed with ALL families at or shortly after diagnosis

- NO CONSENSUS on recommendations regarding bed sharing, room sharing or seizure lattice pillows

- While seizure detection devices may help to reduce the risk of SUDEP, rigorous scientific evidence for such a claim is lacking
Seizure Detection Devices

- **Recommended detection devices:**
  - Baby monitor in room
  - NO CONSENSUS for any other type of device or home oximetry

- **Benefits:**
  - Alert caregiver of a seizure so rescue medication can be given
  - Improves sleep and QOL for caregivers

- **Drawbacks:**
  - False positive alarms result in sleep disruption
  - Not 100% effective in detecting an actual seizure
  - Cost of device, which is often not covered by insurance
Home oxygen

- NO CONSENSUS:
  - Patient with prolonged convulsive seizures who lives a significant distance from hospital or EMS
  - Patient with prolonged convulsive seizures and documented ictal hypoxemia

- MDs unlikely to recommend for patient with prolonged convulsive seizures within 5-10 minutes of EMS care
Home Care

- Home care (not necessarily RN) indicated for:
  - Patients with inadequate parent/caregiver support
  - Patients with gait problems at risk of falls
  - Patients with severe behavior or sleep problems

- Home nursing care needed for:
  - Patients with frequent convulsive seizures
Dravet Syndrome Clinic

- **Essential providers:**
  - Epileptologist, Social Worker, Epilepsy Nurse, Ketogenic dietician, Pharmacist
  - OT, PT, SLP should be available thru the clinic or hospital

- **Access to the following should be available:**
  - Psychologist, Psychiatrist, Developmental Peds
  - Physiatrist, Orthopedic Surgeon
  - Cardiologist, Gastroenterologist, Endocrinologist
  - Geneticist and genetics counsellor
  - Sleep medicine specialist
Minimum Frequency of Clinic Visits:

- <2 yrs – q1-6 mos
- 2-6 yrs – q3-6 mos
- 7-12 yrs – q3-12 mos
- ≥13 yrs – q6-12 mos
Family Support

- Dravet specific organizations and websites are excellent resources for families
- More generic epilepsy resources may be of less benefit
Summary: Reasonable consensus

- Identification of criteria that should lead to testing for DS (with some concerns)
- Proposal for prophylactic management of seizures
- Need for home rescue medication
- Screening recommendations for comorbidities
Summary: Areas to address in further research

- Management of Status Epilepticus after failure of BZDs
- Exact nature and prevalence of certain comorbidities
- Use of seizure detection devices and home oxygen
Thanks to:

- **Core Panel:**
  - Families: M Meskis, M Welborn
  - MDs: K Knupp, J Sullivan, L Laux, I Miller, E Donner
  - Facilitator: A Berg

- **Larger Expert Panel:**
  - Families: N Villas, K Fisher, P Bryant
  - MDs: P Camfield, M Connolly, A Lortie, P Pearl, R Saneto, D Dlugos, D Andrade

- **Funding Source:**
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