Sudden Unexpected Death in Dravet Syndrome


Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in intractable epilepsies, but physiological mechanisms that lead to SUDEP are unknown. Dravet syndrome (DS) is an infantile-onset intractable epilepsy caused by heterozygous loss-of-function mutations in the SCN1A gene, which encodes brain type-I voltage-gated sodium channel Na\(_{\text{v}}\)1.1. We studied the mechanism of premature death in Scn1a heterozygous KO mice and conditional brain- and cardiac-specific KOs. Video monitoring demonstrated that SUDEP occurred immediately following generalized tonic-clonic seizures. A history of multiple seizures was a strong risk factor for SUDEP. Combined video-electroencephalography-electrocardiography revealed suppressed interictal resting heart-rate variability and episodes of ictal bradycardia associated with the tonic phases of generalized tonic-clonic seizures. Prolonged atropine-sensitive ictal bradycardia preceded SUDEP. Similar studies in conditional KO mice demonstrated that brain, but not cardiac, KO of Scn1a produced cardiac and SUDEP phenotypes similar to those found in DS mice. Atropine or N-methyl scopolamine treatment reduced the incidence of ictal bradycardia and SUDEP in DS mice. These findings suggest that SUDEP is caused by apparent parasympathetic hyperactivity immediately following tonic–clonic seizures in DS mice, which leads to lethal bradycardia and electrical dysfunction of the ventricle. These results have important implications for prevention of SUDEP in DS patients.

Commentary

Sudden unexpected death in epilepsy (SUDEP) is a rare, fatal complication of epilepsy defined as sudden death in an individual with epilepsy, in the absence of an obvious cause of death (1). The cause of SUDEP is unknown; however, it is hypothesized that there may be a disruption in respiration, heart rhythm, or cerebral shutdown (1). The population incidence of SUDEP in individuals with epilepsy is estimated to be 0.9 per 1,000 in adults and 0.4 per 1,000 in children (2). The risk of SUDEP in children with Dravet syndrome is estimated to be 15-fold greater than other childhood-onset epilepsies, making this a major concern for families and caregivers (3). Dravet syndrome is a severe epileptic encephalopathy that begins in infancy with prolonged hemiclonic or tonic–clonic seizures, often precipitated by fever. As the syndrome progresses, other seizure types emerge along with developmental and cognitive delays, behavioral impairments, and ataxia (4). In more than 80% of cases, Dravet syndrome is caused by mutation of the SCN1A gene that encodes the voltage-gated sodium channel Na\(_{\text{v}}\)1.1 (5). A mouse model of Dravet syndrome was generated by heterozygous deletion of the Scn1a gene. This mouse model recapitulates many features of Dravet syndrome, including spontaneous seizures, sensitivity to hyperthermia-induced seizures, cognitive deficits, and ataxia (6–8). Dravet mice also have a high rate of premature death that peaks in the juvenile period between 3–5 weeks of age (6).

In the current study, Kalume and colleagues more fully characterize the premature lethality phenotype in Dravet mice and begin to unravel the underlying mechanism. To more fully understand the relationship between seizures and premature lethality, they used continuous video monitoring during the period of highest lethality risk (postnatal days 23–27). They found a strong correlation between mortality risk and the number of generalized tonic-clonic seizures in the 24 hours preceding death, while the duration of each individual seizure was not correlated. All recorded sudden deaths occurred following a generalized tonic–clonic seizure of relatively short duration. Although they did observe mice that experienced lethal status epilepticus, these were excluded from the study in order to focus on sudden death in Dravet mice as a model of SUDEP in Dravet syndrome patients.

In addition to being expressed in the brain, Na\(_{\text{v}}\)1.1 is also expressed in the sinoatrial node of the heart, where it contributes to control of heart rate (9). Thus, a key question is whether elevated SUDEP risk in Dravet syndrome results from loss of Na\(_{\text{v}}\)1.1 function in the central nervous system or heart or both. To address this question, Kalume and colleagues made mice with tissue-specific deletion of Na\(_{\text{v}}\)1.1 in brain or heart and compared their phenotypes to Dravet mice with Na\(_{\text{v}}\)1.1 global deletion. Combined video-electroencephalography (EEG) and electrocardiography (ECG) of spontaneous seizures showed episodes of ictal bradycardia during the tonic phase of seizures in mice with global or brain-specific Na\(_{\text{v}}\)1.1 deletion.
but not cardiac-specific deletion. In addition, they observed an increased number of atrioventricular blocks and decreased interictal heart rate variability in mice with global or brain-specific Na\textsubscript{1.1} deletion. Consistent with this, children with Dravet syndrome exhibit decreased heart rate variability compared to age- and sex-matched children with other epilepsy syndromes or with healthy controls (10). This suggests that there may be abnormal regulation of sinoatrial node activity by the autonomic nervous system.

To more systematically examine the basis for sudden death, Kalume and colleagues induced seizures using hyperthermia, a reliable stimulus for seizures in Dravet mice that approximate febrile seizures. Mice with global and brain-specific deletion of Na\textsubscript{1.1} exhibited bradycardia at the beginning of hyperthermia-induced seizures, followed by tachycardia, then bradycardia at the end of seizures. This indicates that there is excessive parasympathetic tone at onset and end of seizures during the tonic phase and increased sympathetic tone during the tonic-clonic phase. The duration of ictal bradycardia was significantly longer in mice that died, suggesting that this may be a critical factor. To probe the relationship of autonomic nervous system function and fatal seizures, they treated the mice with propranolol, which blocks sympathetic signaling; atropine, which blocks parasympathetic signaling; or scopolamine, which blocks peripheral parasympathetic signaling. Treatment with atropine or scopolamine prevented bradycardia and improved survival, while treatment with propranolol was ineffective. This indicates that ictal bradycardia is caused by hyperactivation of parasympathetic input to the heart. This observation suggests that there may be an imbalance in the central homeostatic regulation of autonomic nervous system similar to the imbalance between excitatory and inhibitory neurotransmission that results in seizures. Further, because this was observed both in mice with global or forebrain-specific Na\textsubscript{1.1} deletion, it suggests that this is due to a failure of central regulation of the autonomic nervous system. Consistent with this, there are reports of other dysautonomic symptoms in patients with Dravet syndrome, including difficulty with temperature regulation, sweating and gastric emptying (3).

At this point, it is unclear whether the autonomic nervous system dysfunction and ictal bradycardia are a direct consequence of Na\textsubscript{1.1} deletion or a secondary effect of remodeling of autonomic centers or the cardiac sinoatrial node. Although many features were similar in mice with global and forebrain-specific Na\textsubscript{1.1} deletion, there were also some subtle differences: For example, mice with forebrain-specific Na\textsubscript{1.1} deletion had fatal seizures with bradycardia of shorter duration than mice with global deletion, suggesting that they are somehow less resilient. Further study of the differences between mice with global Na\textsubscript{1.1} deletion and region-specific or temporal-specific deletions may provide clues about the contribution of remodeling to the SUDEP phenotype. Future studies should also include systematic measurement of respiratory function. Another interesting experiment to consider is to induce seizures in mice with cardiac-specific Na\textsubscript{1.1} deletion to examine peri-ictal effects on heart function. Given that these mice are unlikely to have spontaneous seizures that would lead to SUDEP with their lack of brain abnormalities, seizure induction may be necessary to bring out effects of loss of Na\textsubscript{1.1} on the stressed heart.

Although the precise mechanism has yet to be defined, the key finding of this study is the observation that SUDEP risk in mice with Na\textsubscript{1.1} deletion is correlated with profound ictal bradycardia and that limiting the duration of bradycardia via parasympathetic modulation improved survival. This suggests that implantable pacemakers may be an effective treatment for preventing SUDEP in some Dravet syndrome patients, although defining those at particularly high risk remains a significant challenge.

by Jennifer Kearney, PhD

References

American Epilepsy Society
Epilepsy Currents Journal
Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today’s Date: 3/28/12

2. First Name  Jennifer      Last Name  Kearney  Degree  Ph.D.

3. Are you the Main Assigned Author?    ☒ Yes   ☐ No

If no, enter your name as co-author:

4. Manuscript/Article Title: Sudden unexpected death in Dravet syndrome

5. Journal Issue you are submitting for: 13.6

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grant</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Support for travel to meetings for the study or other purposes</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Payment for writing or reviewing the manuscript</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or administrative support.</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Other</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.
Section #3  Relevant financial activities outside the submitted work.
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type of relationship (in alphabetical order)</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td></td>
<td>X</td>
<td>Gilead Sciences</td>
<td>Investigator-initiated grant (role: Co-I)</td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Payment for manuscript preparation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Patents (planned, pending or issued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td></td>
<td>X</td>
<td>X</td>
<td>Gilead Sciences</td>
<td>Research reagent</td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock(stock options</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel(accommodations/meeting expenses unrelated to activities listed.**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Other (err on the side of full disclosure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4  Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- [ ] No other relationships/conditions/circumstances that present a potential conflict of interest.
- [ ] Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.
Epilepsy Currents Editorial Board