Fatal Cerebral Edema With Status Epilepticus in Children With Dravet Syndrome: Report of 5 Cases

Kenneth A. Myers, MD, PhD,[a,b] Jacinta M. McMahon, BSc (hons),[a] Simone A. Mandelstam, MBChB,[c,d,e] Mark T. Mackay, MBBS,[e,f] Renate M. Kalnins, MD,[g] Richard J. Leventer, MBBS, PhD,[c,f,h] Ingrid E. Scheffer, MBBS, PhD[a,c,e,f]

abstract

Dravet syndrome (DS) is a well-recognized developmental and epileptic encephalopathy associated with *SCN1A* mutations and 15% mortality by 20 years. Although over half of cases succumb to sudden unexpected death in epilepsy, the cause of death in the remainder is poorly defined. We describe the clinical, radiologic, and pathologic characteristics of a cohort of children with DS and *SCN1A* mutations who developed fatal cerebral edema causing mass effect after fever-associated status epilepticus. Cases were identified from a review of children with DS enrolled in the Epilepsy Genetics Research Program at The University of Melbourne, Austin Health, who died after fever-associated status epilepticus. Five children were identified, all of whom presented with fever-associated convulsive status epilepticus, developed severe brain swelling, and died. All had de novo *SCN1A* mutations. Fever of 40°C or greater was measured in all cases. Signs of brainstem dysfunction, indicating cerebral herniation, were first noted 3 to 5 days after initial presentation in 4 patients, though were apparent as early as 24 hours in 1 case. When MRI was performed early in a patient's course, focal regions of cortical diffusion restriction were noted. Later MRI studies demonstrated diffuse cytotoxic edema, with severe cerebral herniation. Postmortem studies revealed diffuse brain edema and widespread neuronal damage. Laminar necrosis was seen in 1 case. Cerebral edema leading to fatal brain herniation is an important, previously unreported sequela of status epilepticus in children with DS. This potentially remediable complication may be a significant contributor to the early mortality of DS.

Dravet syndrome (DS) is a severe infantile-onset epilepsy syndrome, typically presenting with hemiclonic or generalized febrile status epilepticus in the first year after birth, followed by developmental plateau or regression and emergence of other seizure types.[1] Approximately 80% of patients have a mutation of *SCN1A* (Online Mendelian Inheritance in Man #182389), the gene encoding neuronal voltage-gated sodium channel subunit $Na_v1.1$. Children with DS commonly present with recurrent febrile status and, though most recover fully, variable degrees of developmental regression are often observed.[2,3]

The mortality in DS is high with 15% dying by 20 years,[4,5] which is much higher than epilepsy overall, but comparable to rates for other epileptic encephalopathies.[6] Death is attributed to sudden unexpected death in epilepsy in over 50%, with 36% due to status epilepticus with complications such as multiorgan failure.[5,7,8]

Acute encephalopathy after status epilepticus with moderate to severe

[a]*Epilepsy Research Centre, Department of Medicine and* [g]*Department of Pathology, Austin Health, The University of Melbourne, Heidelberg, Victoria, Australia;* [b]*Alberta Children's Hospital, Cumming School of Medicine, Department of Pediatrics, Section of Neurology, University of Calgary, Calgary, Alberta, Canada; Departments of* [c]*Paediatrics and* [d]*Radiology, The University of Melbourne, Parkville, Victoria, Australia;* [e]*The Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia;* [f]*Department of Neurology, Royal Children's Hospital, Parkville, Victoria, Australia; and* [h]*Murdoch Childrens Research Institute, Melbourne, Victoria, Australia*

Dr Myers collected the data, helped prepare figures, and drafted the initial manuscript; Ms McMahon phenotyped patients who met inclusion criteria and edited the manuscript; Dr Mandelstam reviewed the neuroimaging for all patients and edited the manuscript; Dr Mackay assisted with phenotyping and edited the manuscript; Dr Kalnins reviewed the pathologic specimens for most cases and edited the manuscript; Drs Leventer and Scheffer co-conceived the study, assisted with data collection, and edited the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Ingrid E. Scheffer, MD, PhD, Epilepsy Research Centre, Level 2, Melbourne Brain Centre, Austin Health, 245 Burgundy St, Heidelberg, VIC 3084, Australia. E-mail: scheffer@unimelb.edu.au

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TABLE 1 Baseline Clinical Features

Patient No./Age	Epilepsy Diagnosis	*SCN1A* Mutation	Baseline Neurologic Status	Baseline Brain MRI (Age)	Febrile SE History	Premorbid Seizure Control	Maintenance Antiepileptic drugs
1[a]/5 y	Dravet	c.5347G>A p.Ala1783Thr (de novo)	Early milestones normal, plateaued in second year of life and had global developmental impairment.	Normal (18 mo)	Frequent febrile SE in infancy, occasionally refractory.	Periods of seizure freedom lasting up to 5 mo.	Topiramate, valproic acid
2[a]/8 y	Dravet	c.5741_5742delAA p.Gln1914fs*1943 (de novo)	Early milestones normal. Mild global developmental impairment.	Normal (25 mo)	At least 3 episodes of febrile SE from 7 mo to 3 y of age.	1–2 seizures per year, usually provoked by illness (not prolonged).	Topiramate, valproic acid
3[a]/11 y	Dravet	c.4633A>G p.Ile1545Val (de novo)	Mild intellectual disability. Prone to mood swings and some oppositional behavior.	- Mild delayed myelination (22 mo) - Diffuse restricted diffusion after SE (9 y)	Frequent febrile SE in early childhood starting from 8 mo. Had regression with febrile SE 18 mo previous, but no seizures since.	Seizure-free for 18 mo before death.	Topiramate, valproic acid, stiripentol
4[a]/5 y	Atypical multifocal Dravet	c.4970G>A p.Arg1657His (de novo)	Normal early milestones with mild social delay and memory impairment apparent by 5 y.	Normal (3 y)	Febrile SE began at 18 mo with an estimated 12 events total, despite initiation of valproate and lamotrigine. All but 1 event required medication to cease.	2 seizures (both febrile SE) in 9 mo before death.	Lamotrigine, valproic acid
5/0.8 y	Dravet	c.3136delG p.Asp1046Metfs*1055 (de novo)	Normal development.	Normal (4 mo)	No definite febrile SE, though temperatures rose to just below 38°C after prolonged seizures.	Average 1–2 hemiclonic seizures per month from 4 to 10 mo of age, sometimes evolving to generalized convulsions, lasting 20–150 min.	Topiramate, levetiracetam

SE, status epilepticus.
[a] The mutations in cases 1 to 4 were previously published in Harkin et al (2007)[12] as patients #48, 77, 40, and 87, respectively.

sequelae is described in DS, but fatal outcomes are rare.[9] Cytotoxic edema, both focal and generalized, has been described immediately after status epilepticus,[10,11] including in DS.[2,8,9,12,13] In these cases, follow-up MRI usually demonstrates an evolution to mild then moderate atrophy of the affected brain regions. Cerebral edema causing mass effect and death has not previously been described in DS.

METHODS

We identified patients with DS who died after status epilepticus with fever and had been recruited to The University of Melbourne, Austin Health Epilepsy Genetics Research Program. Over 17 years, 153 individuals with DS have been recruited, regardless of severity, from around Australia and we have ongoing contact with the families. A retrospective study was undertaken in which records, neuroimaging, and pathology of these individuals were reviewed. The Human Research Ethics Committee of Austin Health approved the study (Project No. H2007/02961); written informed consent was obtained from parents or legal guardians of all participants.

RESULTS

Five children died between 10 months and 11 years of age; 4 had classic DS and case 4 had atypical multifocal DS.[14] All but 1 had histories of recurrent febrile status epilepticus as is typically seen in DS. Genetic testing revealed a de novo *SCN1A* mutation in each case; however, these results were not available until after death in cases 4 and 5 (Table 1).[15] Baseline brain MRI revealed no significant abnormalities in any of the children. In all cases, seizure control had been relatively good before the acute presentation.

TABLE 2 Clinical Features of the Acute Presentation (Further MRI Information and Images in Fig 1)

Patient No./ Age	Prodrome	SE Duration Estimated	Temperature	SE Acute Management	Neuroimaging After SE Onset	Multiorgan Dysfunction	Brainstem Signs	ICH Measures	Outcome
1/5 y	Fever and viral URTI symptoms (influenza A positive on nasopharyngeal aspirate).	75 min	40°C	Midazolam, phenytoin, thiopentone	- CT (day 2): Mild cerebral edema - MRI (day 4): Bilateral restricted diffusion in central sulci - CT (day 7): Diffuse edema and tonsillar herniation - MRI (day 9): Diffuse edema and tonsillar herniation; diffuse restricted diffusion throughout remainder of parenchyma	None.	Day 3: Pupils unequal Day 4: Pupils unreactive	Mannitol, cooling	Brain death confirmed before withdrawal of supportive care; death 9 d after initial SE.
2/8 y	Fever, abdominal pain, diarrhea.	90 min	43.7°C	Midazolam, phenytoin	- CT (day 4): Diffuse cerebral edema - MRI (day 4): Diffuse cerebral edema and multifocal areas of restricted diffusion including the right frontal and bilateral occipital regions; MRA normal	↑d creatine kinase, lipase, lactate, ALT, urea. DIC. Hypotension.	Day 4: Right pupil fixed and dilated	Mannitol, EVD, head-up tilting, cooling, hyperventilation	Supportive care withdrawn; death 9 d after initial SE.
3/11 y	Fever, sore throat.	2 h	41°C	Midazolam, phenobarbital	- CT and MRI (day 6): Diffuse cerebral edema with effacement of sulci and basal cisterns, as well as tonsillar herniation; diffuse restricted diffusion of the cortex, white matter and thalami, bilaterally	↑d creatine kinase, lipase, lactate, ALT, creatinine, urea, myoglobinuria.	Day 6: Fixed, dilated pupil. Day 7: Gag and corneal reflexes absent	Mannitol, cooling, hyperventilation, head-up tilting	Somatosensory evoked potentials absent. Supportive care withdrawn; death 9 d after initial SE.
4/5 y	Fever and viral URTI symptoms.	4 h. Status recurred 14 h after admission.	40°C	Midazolam, diazepam, phenytoin, thiopentone, phenobarbital	- CT (day 2): Normal - MRI (day 8): Diffuse patchy restricted diffusion and edema causing compression of basal cisterns and midbrain structures; MRA normal	Metabolic acidosis (pH 6.86 on arrival).↑d creatine kinase, lipase, lactate, ALT, creatinine, urea. DIC. Hypotension.	Day 2: Intermittent pupil dilation and asymmetry noted Day 7: Pupils bilaterally fixed and dilated	None	Supportive care withdrawn; death 8 d after initial SE.
5/0.8 y	Fever and viral URTI symptoms. Sister had been unwell recently.	1.5 h	40°C	Clonazepam, midazolam, phenytoin	- CT (29 h): Diffuse cerebral edema	Metabolic acidosis (lowest pH 6.86); ↑d creatinine (101), ALT, lactate; DIC Hypotension. Hypoglycemia (blood glucose 1.9 mmol/L).	28 h: Pupils bilaterally fixed and dilated	Hypertonic saline	Supportive care withdrawn; death 36 h after initial SE.

ALT, alanine aminotransferase; DIC, disseminated intravascular coagulopathy; EVD, external ventricular drain; ICH, intracranial hypertension; MRA, magnetic resonance angiography; SE, status epilepticus; URTI, upper respiratory tract infection.

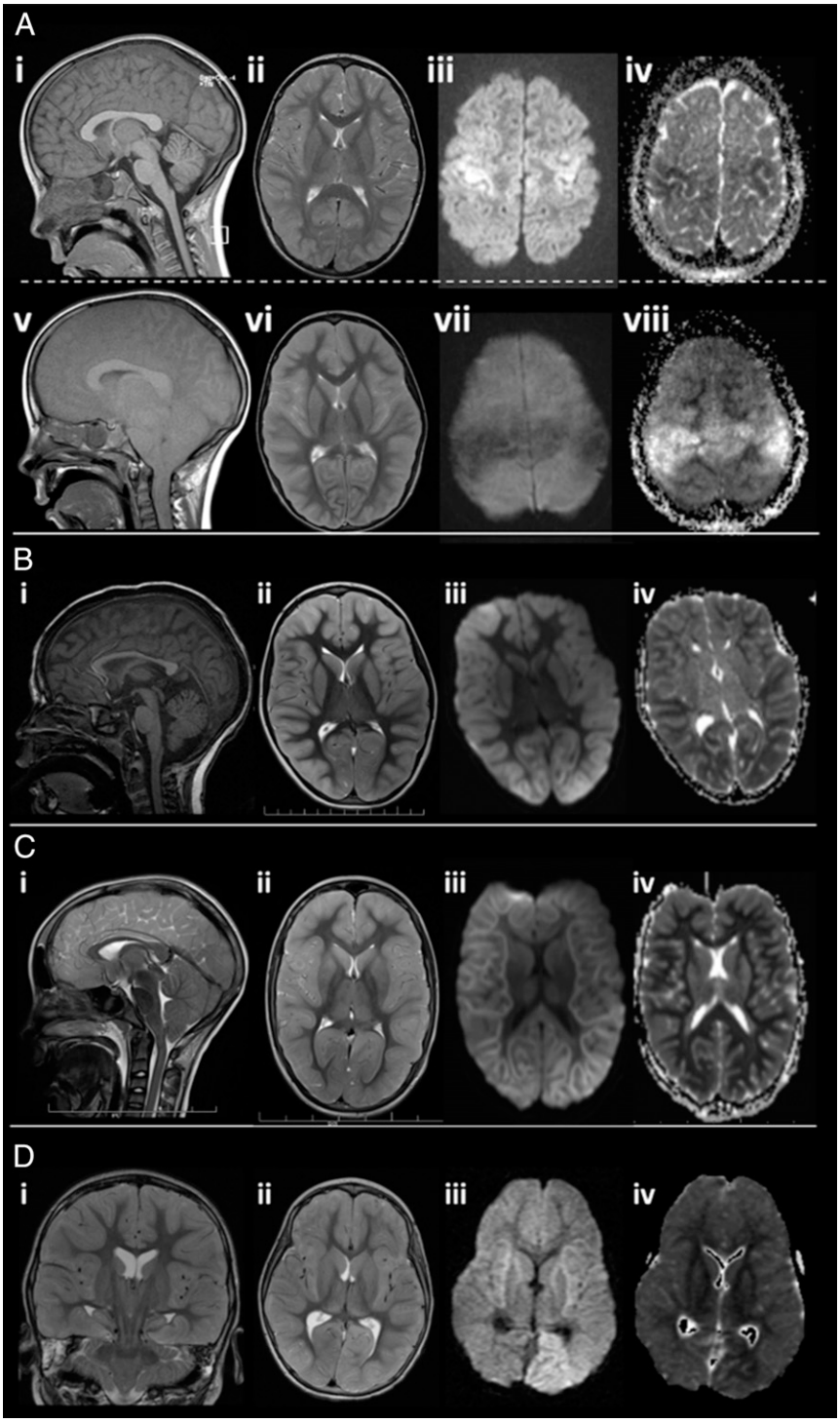

FIGURE 1
Brain MRI studies of cases 1 to 4. A, Case 1 (days 4 and 9). On day 4, diffusion-weighted imaging (DWI) (iii) and apparent diffusion coefficient (ADC) (iv) sequences reveal bilateral symmetrical perirolandic cortical restricted diffusion. Similar, subtler changes were present in the left medial parietal cortex (not shown). Sagittal T1 (i) and axial T2 (ii) are normal. On day 9, there is a striking evolution on sagittal T1 (v) to diffuse cerebral edema with uncal, transtentorial, and inferior tonsillar herniation resulting in brainstem compression and cervical cord edema. Axial T2 (vi) reveals diffuse cortical edema. DWI (vii) and ADC (viii) sequences reveal that the earlier regions of focal restricted diffusion have evolved to facilitated diffusion in keeping with chronic injury. The previously normal white matter now reveals extensive diffusion restriction. B, Case 2 (day 4). Axial T2 (ii) reveals diffuse edema of the cortex and deep gray structures. DWI and ADC sequences (iii and iv) reveal diffusion

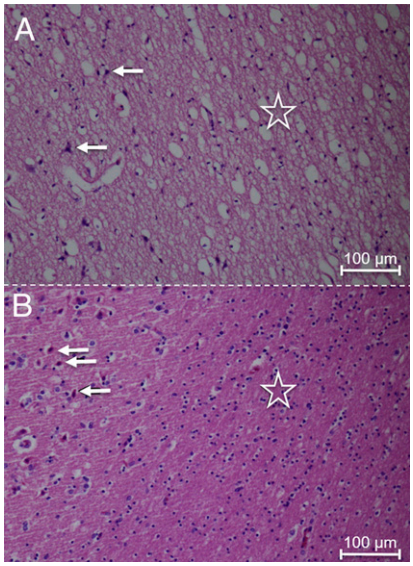

FIGURE 2
Cerebral pathology sections from postmortem examination: hematoxylin and eosin stained sections. A, Left parietal lobe from case 5 (died 12 hours after clinical signs of herniation); cortex is on the left and subcortical white matter on the right. Arrows indicate examples of pyknotic neurons consistent with recent anoxic-ischemic injury. Markedly edematous white matter is seen on the right (star). B, Inferior parietal lobe from case 3 (died 3 days after clinical signs of herniation), with cortex on left and subcortical white matter on right. Necrotic "red" neurons are seen (arrows indicate examples) with no significant white matter edema (star). This is the expected evolution of cerebral edema on histopathologic analysis.

Acute Presentation

All children had fever-associated convulsive status epilepticus (temperature 40–43.7°C) with suspected or confirmed viral infection. Status duration was 75 minutes to 4 hours despite early initiation of home rescue benzodiazepine, timely involvement of emergency medical personnel, and initiation of routine status epilepticus protocols in hospital. All children required intubation and ventilation, and multiorgan dysfunction was apparent within 24 hours in 4 cases (Table 2).

All children developed signs of brainstem dysfunction consistent with herniation, typically on days 3 to 5 after their initial status presentation, but as early as 28

hours in case 5. Interventions aimed at reversing increased intracranial pressure including mannitol (3), hypertonic saline (1), cooling (3), hyperventilation (2), and external ventricular drainage (1) were unsuccessful, though case 2 showed transient clinical improvement. Supportive care was withdrawn 8 to 9 days after status epilepticus in 4 cases and at 36 hours in case 5; all children died within 24 hours of withdrawal of intensive care.

Interestingly, case 3 had a similar, but less severe, presentation with status epilepticus lasting an estimated 6 hours at 9 years of age, requiring an 8-week hospital stay. MRI acutely revealed bilateral restricted diffusion, primarily in the frontal lobes. After status, she developed right hemiparesis, cognitive regression, and behavioral change, but returned to premorbid function in 8 months.

Neuroimaging

Early neuroimaging studies were ordered to investigate persistent decreased level of consciousness, while later studies were for prognostication including decisions regarding withdrawal of supportive therapies. Three children had computed tomography (CT) on day 2, which was normal or revealed only mild edema. Later studies (days 4–7) revealed diffuse edema with tonsillar herniation, often with the cerebellar reversal sign (hyperdense cerebellum relative to cerebrum), indicating severe irreversible brain injury.

Three MRI studies on days 6 to 9 demonstrated severe cerebral and cerebellar edema with uncal and tonsillar herniation resulting in brainstem compression (Fig 1). Subcortical white matter demonstrated more extensive diffusion restriction than cortex with variable involvement of deep white matter. Magnetic resonance angiography was normal in 2 cases; however, the day 9 study of case 1 revealed absence of intracerebral arterial flow. Magnetic resonance spectroscopy was performed in 2 cases, and revealed increased lactate and decreased N-acetylaspartate peaks.

Case 1 had 2 MRI studies during the acute presentation, revealing a distinctive pattern of evolution (Fig 1A). On day 4, focal bilateral symmetric perirolandic and left medial parietal cortical restricted diffusion was observed. Follow-up study on day 9 revealed resolution of cortical diffusion changes, and development of severe diffuse cerebral edema with tonsillar and uncal herniation. The subcortical and deep white matter revealed severe diffusion restriction. The latter pattern is mirrored in the later images of patients 3 and 4 (Fig 1 C and D).

Postmortem Analysis

Postmortem analysis revealed widespread anoxic-ischemic neuronal injury in all 4 cases examined (Fig 2). Case 5, who died 12 hours after brainstem signs were apparent, had severe white matter edema, transtentorial herniation, and associated uncal grooving. Significant edema was not observed in the other 3 cases, who had much longer intervals between herniation and death. Cortical zones of laminar and border zone infarction were noted in case 3. The same patient had postmortem liver and muscle biopsies, which revealed normal respiratory chain enzyme activity. Extensive bilateral hippocampal damage was noted in 2 cases.

There were no signs of meningoencephalitis in any case. The postmortem examinations in cases 1, 4, and 5 revealed findings in keeping with multiorgan dysfunction including pneumonia/pneumonitis in all 3 children, renal tubular necrosis in 2, liver necrosis in 2, and focal adrenal hemorrhage in 1.

DISCUSSION

Five children with DS and *SCN1A* mutations presented with high fever (≥40°C) and status epilepticus complicated by severe brain swelling and death. All demonstrated dramatic cerebral and cerebellar edema, far more severe than imaging changes typically seen after convulsive status epilepticus,[10] suggesting this phenomenon may be specific to DS. Though focal and generalized cerebral edema have been previously reported after status epilepticus in DS,[2,8,9,12,13] these are the first cases demonstrating mass effect resulting in death.

The reason the children in our series developed such profound diffuse edema is unclear. Hypoxic-ischemic injury likely contributes to their presentation, supported by multiorgan failure in 4/5 cases and postmortem neuropathological analysis. However, the MRI patterns of restricted diffusion of cases 1, 2, and 4 are not consistent with the border zone (watershed) or basal ganglia patterns typical of global

FIGURE 1 Continued

restriction throughout the subcortical white matter with extension into the deep lobar white matter in the right frontal and bilateral occipital regions (left more than right). Restricted diffusion was also seen in the cerebellum (not shown). C, Case 3 (day 5). Sagittal T2 (i) reveals massive cerebral and cerebellar edema with uncal and tonsillar herniation and brainstem compression. Axial T2 (ii) reveals diffuse edema of the cortex and deep gray structures. DWI and ADC sequences (iii and iv) reveal diffuse restricted diffusion throughout the subcortical and deep white matter. ADC is low in the cortex and lower in the subcortical white matter. Bilateral thalamic restricted diffusion was also present (not shown). D, Case 4 (day 8). Coronal T2 (i) reveals marked cerebral edema with uncal herniation and compression of basal cisterns. Axial T2 (ii) reveals diffuse edema of the cortex and deep gray structures. DWI and ADC sequences (iii and iv) reveal diffuse restricted diffusion in the subcortical white matter, extending into the deep white matter and cortex of the left occipital lobe. This is likely an infarct resulting from compression of the left posterior cerebral artery secondary to uncal herniation.

hypoxic-ischemic injury. The cortical diffusion restriction and T1 and T2 signal change are in keeping with laminar cortical necrosis, confirmed on postmortem.

Extreme hyperthermia may explain the dramatic severity of presentation, given that all children presented with high fever. The impact of temperature on the $Na_V1.1$ channel has been clearly demonstrated in murine models of DS. Environmental hyperthermia is sufficient to increase frequency of epileptiform electroencephalography discharges and elicit seizures, indicating that elevated temperature alone has a deleterious effect on sodium channel function, independent of inflammatory processes accompanying fever.[16]

Ion channel dysfunction likely underlies development of severe cerebral edema, supported by observations in other genetic channelopathies. Mutations of *CACNA1A*, encoding the P/Q type voltage-gated calcium channel subunit α-1A can cause fatal cerebral edema in association with minor trauma or hemiplegic migraine (Online Mendelian Inheritance in Man #601011).[17,18] Hemiplegic migraine can also be caused by *SCN1A* mutations,[19] demonstrating the clinical overlap between *CACNA1A* and *SCN1A* phenotypes.

Mitochondrial dysfunction is another potential contributing factor, particularly as overlap of mitochondrial pathology with DS has been observed, including *POLG1* variants associated with acute MRI revealing cytotoxic edema.[2]

Although these are the first reports of fatal brain edema causing herniation after status epilepticus in DS, this entity may not be rare. An excellent article on acute encephalopathy in DS by Okumura et al[9] includes 3 children with brain edema who died; mass effect was not reported but may have developed later. Together with our series, we suggest that herniation may often be the mechanism of death in patients with DS who die of acute encephalopathy after status epilepticus.

As patients with DS present frequently with status epilepticus, brain imaging is often not performed at all. When CT is used, studies are frequently normal during the early stages of edema. Other cases may have been attributed to an unwitnessed severe hypoxic-ischemic event or septic shock.

In addition, children who die relatively young may not yet have a DS diagnosis or *SCN1A* testing performed. Within our cohort, cases 4 and 5 did not have their *SCN1A* mutation identified until after death. Given this, *SCN1A* testing should be considered in all children with fever-associated status epilepticus who go on to develop severe cerebral edema, even if the swelling is not fatal.

Profound status-induced brain edema is a severe, previously unrecognized fatal entity in DS. Children with a history suggestive of DS and *SCN1A* mutation presenting in status epilepticus should be monitored closely for signs of catastrophic cerebral edema in the following days. Failure to awaken in a timely manner after status should not necessarily be attributed to medication effect or infection, when other causes may be present. Neurologic vital signs including brainstem reflexes should be closely monitored and imaging studies done emergently if recovery from status appears atypical. It remains to be proven whether early recognition of cerebral edema with aggressive intervention to counteract increasing intracranial pressure could be life-saving.

ABBREVIATIONS

CT: computed tomography
DS: Dravet syndrome

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REFERENCES

1. Dravet C. The core Dravet syndrome phenotype. *Epilepsia*. 2011;52(suppl 2):3–9
2. Gaily E, Anttonen AK, Valanne L, et al. Dravet syndrome: new potential genetic modifiers, imaging abnormalities, and ictal findings. *Epilepsia*. 2013;54(9):1577–1585
3. Chipaux M, Villeneuve N, Sabouraud P, et al. Unusual consequences of status epilepticus in Dravet syndrome. *Seizure*. 2010;19(3):190–194
4. Akiyama M, Kobayashi K, Yoshinaga H, Ohtsuka Y. A long-term follow-up study of Dravet syndrome up to adulthood. *Epilepsia*. 2010; 51(6):1043–1052
5. Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. *Epilepsia*. 2011;52(suppl 2):44–49
6. Camfield CS, Camfield PR, Veugelers PJ. Death in children with epilepsy: a population-based study. *Lancet*. 2002;359(9321):1891–1895
7. Sakauchi M, Oguni H, Kato I, et al. Mortality in Dravet syndrome: search for risk factors in Japanese patients. *Epilepsia*. 2011;52(suppl 2):50–54
8. Nishri D, Blumkin L, Lev D, et al. Hepatic coma culminating in severe

brain damage in a child with a SCN1A mutation. *Eur J Paediatr Neurol*. 2010;14(5):456–459

9. Okumura A, Uematsu M, Imataka G, et al. Acute encephalopathy in children with Dravet syndrome. *Epilepsia*. 2012;53(1):79–86
10. Kavuk I, Hufnagel A, Agelink MW, et al. MRI changes associated with partial status epilepticus. *Eur J Med Res*. 2005;10(6):243–246
11. Rennebaum F, Kassubek J, Pinkhardt E, et al. Status epilepticus: clinical characteristics and EEG patterns associated with and without MRI diffusion restriction in 69 patients. *Epilepsy Res*. 2016;120:55–64
12. Tang S, Lin JP, Hughes E, Siddiqui A, Lim M, Lascelles K. Encephalopathy and *SCN1A* mutations. *Epilepsia*. 2011;52(4):e26–e30
13. Takayanagi M, Haginoya K, Umehara N, et al. Acute encephalopathy with a truncation mutation in the SCN1A gene: a case report. *Epilepsia*. 2010;51(9):1886–1888
14. Kim YO, Bellows S, McMahon JM, et al. Atypical multifocal Dravet syndrome lacks generalized seizures and may show later cognitive decline. *Dev Med Child Neurol*. 2014;56(1):85–90
15. Harkin LA, McMahon JM, Iona X, et al; Infantile Epileptic Encephalopathy Referral Consortium. The spectrum of *SCN1A*-related infantile epileptic encephalopathies. *Brain*. 2007;130(pt 3):843–852
16. Oakley JC, Kalume F, Yu FH, Scheuer T, Catterall WA. Temperature- and age-dependent seizures in a mouse model of severe myoclonic epilepsy in infancy. *Proc Natl Acad Sci USA*. 2009;106(10):3994–3999
17. Chabriat H, Vahedi K, Clark CA, et al. Decreased hemispheric water mobility in hemiplegic migraine related to mutation of *CACNA1A* gene. *Neurology*. 2000;54(2):510–512
18. Kors EE, Terwindt GM, Vermeulen FL, et al. Delayed cerebral edema and fatal coma after minor head trauma: role of the *CACNA1A* calcium channel subunit gene and relationship with familial hemiplegic migraine. *Ann Neurol*. 2001;49(6):753–760
19. Dichgans M, Freilinger T, Eckstein G, et al. Mutation in the neuronal voltage-gated sodium channel *SCN1A* in familial hemiplegic migraine. *Lancet*. 2005;366(9483):371–377

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