The clinical outcome and neuroimaging of acute encephalopathy after status epilepticus in Dravet syndrome

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AIM To analyze the clinical outcome and neuroimaging over a long duration follow-up in the currently largest series of acute encephalopathy after status epilepticus in patients with Dravet syndrome.

METHOD Clinical and neuroimaging data of patients with Dravet syndrome with a history of acute encephalopathy (coma >24h) after status epilepticus from February 2005 to December 2016 at Peking University First Hospital were reviewed retrospectively.

RESULTS Thirty-five patients (15 males, 20 females) with a history of acute encephalopathy were enrolled from a total of 624 patients with Dravet syndrome (5.6%). The median onset age of acute encephalopathy was 3 years 1 month. The duration of status epilepticus varied between 40 minutes to 12 hours. Thirty-four patients had a high fever when status epilepticus occurred, and only one had a normal temperature. Coma lasted from 2 to 20 days. Twelve patients died and 23 survived with massive neurological regression. The median follow-up time was 2 years 1 month. Neuroimaging of 20 out of 23 survivors during the recovery phase showed diverse degrees of cortical atrophy with or without subcortical lesions.

INTERPRETATION Acute encephalopathy after status epilepticus is more prone to occur in patients with Dravet syndrome who had a high fever. The mortality rate is high in severe cases. Survivors are left with severe neurological sequelae but often with either no seizure or low seizure frequency.

Dravet syndrome is a severe, intractable epilepsy syndrome that occurs in the first year of life, characterized by fever-sensitive, multiple seizure types, and psychomotor developmental delay after seizure onset. A variety of complications and a burden on quality of life are associated with the seizure disorder.1–3 Status epilepticus occurs commonly in patients with Dravet syndrome, especially those with fever, and are usually followed by recovery to their previous condition.4,5 However, some patients may have acute encephalopathy after status epilepticus, characterized by non-inflammatory cerebral edema, followed by prolonged consciousness disturbance, and is usually preceded by infection, often followed by severe neurological sequelae.6,7 The occurrence of acute encephalopathy in Dravet syndrome has been reported sporadically.8,9 Because of the poor outcome, the need for research on this topic has been advocated. We performed a retrospective study of our series of Dravet syndrome patients who had a history of acute encephalopathy and summarized their clinical outcome and neuroimaging features.

METHOD Six hundred and twenty-four Dravet syndrome patients were collected in the Pediatric Department of Peking University First Hospital from February 2005 to December 2016. The SCN1A gene mutation was searched in all patients using Sanger sequencing and multiple ligation-dependent probe amplification. All patients or their legal representatives provided informed consent before their inclusion in the study. The study was approved by the Ethics Committee of Peking University First Hospital. Thirty-five patients who met the following inclusion criteria were recruited: a clinical diagnosis of Dravet syndrome and a history of acute encephalopathy after status epilepticus.

The clinical diagnosis of Dravet syndrome was made if the patients had the following features: (1) a prolonged unilateral or bilateral clonic or tonic-clonic seizure onset in the first year of life, often triggered by fever (average age at onset 6mo); (2) the appearance of afebrile seizures such as focal seizures, atypical absence, or myoclonic seizures after 1 year of age; (3) frequent seizures provoked by...
fever; (4) usual occurrence of status epilepticus; (5) normal early development and subsequent delay in psychomotor development, ataxia, and pyramidal signs; (6) normal interictal electroencephalography in the first year of life followed by generalized, focal, or multifocal discharges; and (7) seizures are refractory to antiepileptic drugs. Status epilepticus was diagnosed if a seizure persisted for 30 minutes or longer. Acute encephalopathy was defined as a condition with decreased consciousness with or without other neurologic symptoms, such as seizures, lasting for less than 24 hours in association with infectious symptoms. For patients who may have suffered barbiturate coma or used continuous intravenous midazolam, acute encephalopathy was diagnosed when prolonged coma was observed after the discontinuation of these drugs. Coma caused by sedative drugs, head trauma, poisoning, central nervous system infection, and metabolic disorders have been excluded.

The medical data of the patients with Dravet syndrome with acute encephalopathy were collected, and the clinical outcome and brain magnetic resonance imaging (MRI) results were followed-up by telephone interview every 6 months. The frequency of seizures before and after the acute encephalopathy at our last visit was recorded as daily, weekly (defined as >3/mo), monthly (1–3/mo), yearly (<1/mo), and none (defined as no seizure observed after the acute encephalopathy) by the patient’s seizure diary recorded by their parents. The seizure frequency was comprised of all the seizure types. Psychomotor development was assessed by medical appreciation.

RESULTS

Thirty-five patients (15 males, 20 females) with acute encephalopathy were recorded among 624 patients with Dravet syndrome (5.6%), of which 32 cases had SCN1A mutations, including 15 missense mutations, seven nonsense mutations, five frameshift mutations, four splice site mutations, and 1 with a SCN1A fragment deletion. The remaining 3 did not carry SCN1A mutations.

The clinical features of 35 patients with Dravet syndrome before the onset of acute encephalopathy are shown in Table I. Before the onset of acute encephalopathy, the frequency of seizures was weekly in four cases, monthly in 26 cases, and yearly in five cases. Thirty-two patients had a history of one or more episodes of status epilepticus, while the remaining three never experienced status epilepticus before the onset of acute encephalopathy. The baseline brain MRI examinations of all patients were normal. Psychomotor development was mildly delayed in 30 patients and normal in five.

The clinical features of the 23 survivors with acute encephalopathy are shown in Table II. The median age of the onset of acute encephalopathy was 3 years 1 month (range 6mo–10y). Thirty-one patients were under 5 years of age, while the remaining four patients were older (7y 8mo, 8y, 10y, and 5y 2mo respectively). All patients experienced status epilepticus (lasting from 40min to 12h) followed by coma (lasting 2–20d). During the status epilepticus, 34 patients had a high fever (39.0–42.0°C), while only one patient had a normal temperature. Twenty-five patients manifested as generalized tonic-clonic status and 10 manifested as unilateral clonic onset evolving into bilateral tonic-clonic status. The drugs to terminate ongoing status epilepticus included diazepam, midazolam, clonazepam, phenobarbital, and chloral hydrate. Twelve patients died between 2 and 9 days after the onset of acute encephalopathy, because of multiple organ dysfunction syndromes, such as respiratory failure and/or circulatory failure during acute encephalopathy (Table SI, online supporting information). All twelve deceased patients had SCN1A mutations, including six missense mutations, four nonsense mutations, one splicing site mutation, and one frameshift mutation.

The 23 surviving patients had massive neurological regression in the early recovery phase that manifested as lack of eye contact, dysarthria, hypotonia or spastic tetraplegia, and involuntary movements, and five manifested hemiplegia. The median follow-up time was 2 years 1 month (range 5mo–4y 4mo). Sixteen of the 23 survivors had variable improvement in motor, language, and cognition. Among them, 10 patients could walk without support, two could sit without help but could not walk alone, and four could hold their heads up but could not sit on their own. Eleven patients were able to say two or more words, even up to 4 years after the acute episode. The remaining seven patients had no significant improvement, after a follow-up time of 5 months to 3 years 10 months. After the acute encephalopathy, the seizure frequency was reduced in most survivors compared with that before the onset of acute encephalopathy. Ten patients had no seizure after the recovery (the follow-up time varied from 5mo to 4y 4mo), eight had reduced seizures (7 yearly and 1 monthly, a follow-up time of 1y 5mo–4y 3mo), and the remaining five showed no change in seizure frequency (4 monthly and 1 weekly, a follow-up time of 7mo–3y). Among the five patients, three had no change in seizure types, epileptic spasms occurred in two (Patients 1 and 10) after the acute encephalopathy, associated in one with focal seizures.

In 16 of the 23 survivors, electroencephalography was performed at 3 weeks to 9 months after acute encephalopathy (Table SII, online supporting information). All showed diffuse slow waves (bilateral in 9 and unilateral in 7) and interictal diffuse or multifocal epileptic discharges. In Patient 1, the electroencephalography performed 4 months after acute encephalopathy showed diffused slowing with multifocal spike activity and asymmetric epileptic spasms were recorded (Fig. S1, online support information). All showed diffuse slow waves (bilateral in 9 and unilateral in 7) and interictal diffuse or multifocal epileptic discharges. In Patient 1, the electroencephalography performed 4 months after acute encephalopathy showed diffused slowing with multifocal spike activity and asymmetric epileptic spasms were recorded (Fig. S1, online supporting information).

What this paper adds

- Acute encephalopathy is more prone to occur in patients with Dravet syndrome with a high fever.
- The mortality rate is high for acute encephalopathy after status epilepticus in patients with Dravet syndrome.
- Survivors have neurological sequelae.
Table I: The clinical features of 35 Dravet syndrome patients before the onset of acute encephalopathy

| Patient | Sex | SCN1A mutation | Age at onset of DS (mo) | Seizure types | SE before | Seizure frequency | AEDs | Brain MRI (examination age) | Development |
|---------|-----|----------------|-------------------------|---------------|-----------|------------------|------|---------------------------|-------------|
| 1       | F   | R1645X         | 6                       | GTCS, FS      | 1-2/y     | Monthly          | VPA+LEV | Normal (9mo)               | Mild delay  |
| 2       | F   | V1390L         | 10                      | GTCS, FS      | 5-6/y     | Monthly          | VPA+LEV | Normal (1y)                | Mild delay  |
| 3       | F   | IVS18+2T>A     | 4                       | GTCS, aTAS, MS| 2-3/y     | Monthly          | VPA+LEV | Normal (1y 4mo)            | Mild delay  |
| 4       | F   | C927F          | 8                       | GTCS, FS, MS  | 5-7/y     | Monthly          | VPA+LEV+TPM | Normal (2y)               | Mild delay  |
| 5       | F   | M1424R         | 6                       | GTCS, FS, MS  | 8-10/y    | Monthly          | VPA+LEV+TPM | Normal (10mo)              | Mild delay  |
| 6       | M   | E22-26del      | 4                       | GTCS, FS      | 2-3/y     | Weekly           | VPA+TPM  | Normal (1y 1mo)            | Mild delay  |
| 7       | F   | S994fsX        | 8                       | GTCS, FS, MS  | 0         | Monthly          | VPA+LEV | Normal (2y 5mo)            | Mild delay  |
| 8       | M   | S1666fsX       | 3                       | GTCS, FS      | 4-5/y     | Monthly          | VPA+TPM  | Normal (4mo)               | Mild delay  |
| 9       | M   | R222X          | 11                      | GTCS, FS      | 1         | Yearly           | VPA+TPM+CPZ | Normal (5y)               | Mild delay  |
| 10      | M   | c.4477-3T>C    | 7                       | GTCS, FS, MS  | 1-2/y     | Weekly           | VPA+TPM  | Normal (7mo)               | Normal     |
| 11      | M   |               | 3                       | GTCS, FS      | 0         | Yearly           | LEV+TPM | Normal (3mo)               | Normal     |
| 12      | F   |               | 5                       | GTCS, FS, MS  | 1         | Monthly          | VPA+LEV  | Normal (6mo)               | Normal     |
| 13      | F   |               | 4                       | GTCS, FS      | 0         | Monthly          | TPM+LEV  | Normal (4mo)               | Normal     |
| 14      | M   | c.602+1G>A     | 7                       | GTCS, FS      | 1-2/y     | Monthly          | VPA+LEV+CLB | Normal (1y 3mo)           | Mild delay  |
| 15      | F   | S1666F         | 8                       | GTCS, FS      | 2-3/y     | Monthly          | VPA+LEV  | Normal (1y 2mo)            | Mild delay  |
| 16      | M   | R946C          | 6                       | GTCS, FS, aTAS, MS | 1-2/y | Monthly | VPA+LEV+TPM | Normal (1y)     | Mild delay  |
| 17      | M   | D955RfsX971    | 7                       | GTCS, FS      | 2         | Monthly          | VPA+LEV+TPM | Normal (2y 3mo)           | Mild delay  |
| 18      | F   | A1783V         | 3                       | GTCS, FS, MS  | 1-2/y     | Weekly           | VPA+TPM  | Normal (1y 9mo)            | Mild delay  |
| 19      | F   | S1328P         | 4                       | GTCS, FS, MS  | 1-2/y     | Monthly          | VPA+LEV+TPM | Normal (2y 5mo)           | Mild delay  |
| 20      | F   | G329VfsX       | 6                       | GTCS, FS      | 1/y       | Monthly          | VPA+LEV+TPM+LEV | Normal (3y 1mo) | Mild delay  |
| 21      | F   | R1213X         | 7                       | GTCS, FS, aTAS, MS | 2     | Yearly           | VPA+LEV  | Normal (6y 3mo)            | Mild delay  |
| 22      | M   | A1510V         | 4                       | GTCS, FS      | 1         | Weekly           | VPA+LEV  | Normal (11mo)              | Mild delay  |
| 23      | M   | A1620C         | 3                       | GTCS, FS, MS  | 3-4/y     | Monthly          | VPA      | Normal (4mo)               | Normal     |
| 24      | F   | R101W          | 5                       | GTCS, FS, MS  | 2-3/y     | Monthly          | VPA+LEV  | Normal (1y 3mo)            | Mild delay  |
| 25      | M   | V422A          | 2.5                     | GTCS, FS, MS  | 3-4/y     | Monthly          | VPA+LEV  | Normal (2y)                | Mild delay  |
| 26      | M   | L556fsX        | 5.5                     | GTCS, FS, aTAS, MS | 4-5/y | Monthly | VPA+TPM | Normal (2y 4mo)            | Mild delay  |
| 27      | F   | R612X          | 5                       | GTCS, FS, aTAS | 1-2/y | Monthly | VPA+LEV+CPZ | Normal (5y 7mo) | Mild delay  |
| 28      | F   | W1286X         | 4                       | GTCS, FS, MS  | 4-5/y     | Monthly          | VPA+LEV  | Normal (2y 2mo)            | Mild delay  |
| 29      | F   | A1783T         | 5                       | GTCS, FS, MS  | 2-3/y     | Yearly           | VPA+TPM  | Normal (3y 8mo)            | Mild delay  |
| 30      | M   | c895-1G>A      | 2                       | GTCS, FS, aTAS | 1-2/y | Monthly | VPA+TPM+CPZ | Normal (3y 2mo) | Mild delay  |
| 31      | F   | R1892X         | 4                       | GTCS, FS      | 2-3/y     | Monthly          | VPA+TPM  | Normal (4y)                | Mild delay  |
| 32      | M   | F1699S         | 5                       | GTCS, FS, aTAS, MS | 2-3/y | Monthly | VPA+LEV  | Normal (2y 9mo)            | Mild delay  |
| 33      | M   | Q1904X         | 5                       | GTCS, FS      | 2-3/y     | Yearly           | VPA+TPM  | Normal (7mo)               | Mild delay  |
| 34      | F   | S243Y          | 3                       | GTCS, FS, aTAS | 1-2/y | Monthly | CZP+LEV+ZNS | Normal (1y 2mo) | Mild delay  |
| 35      | F   | I1810N         | 4.5                     | GTCS, FS, aTAS, MS | 1-2/y | Monthly | VPA+LEV  | Normal (2y 6mo)            | Mild delay  |

DS, Dravet syndrome; SE, status epilepticus; AEDs, anti-epileptic drugs; MRI, magnetic resonance imaging; GTCS, generalized tonic-clonic seizure; FS, focal seizure; aTAS, atypical absence seizure; MS, myoclonic seizure; VPA, valproate; LEV, levetiracetam; TPM, topiramate; CZP, clonazepam; CLB, clobazam; ZNS, zonisamide.

supporting information). The electroencephalography of Patient 4 showed widespread low voltage suppression both in the acute phase and 5 months after the acute encephalopathy.

Brain MRI results are summarized in Table SII (online supporting information). We failed to obtain the MRI data of the 12 deceased patients. In 11 patients who all survived the acute encephalopathy, MRI was performed in the first week of acute encephalopathy and showed bilateral (six cases) or unilateral (five cases) cerebral hemisphere edema (Figs. 1 and 2). In three cases it was associated with subcortical white matter hyper-intense signal in T1 and T2 weighted images. In Patient 3, the right hemisphere edema was associated with bilateral cortical atrophy (Fig. 2). This patient had several episodes of status epilepticus previously, but no MRI was performed after these status epilepticus. MRI was performed in 20 survivors during the recovery phase (25d to 3mo after the acute encephalopathy). It demonstrated diverse degrees of either bilateral or unilateral cortical atrophy in all, often associated with other abnormalities: cerebellar atrophy, right pontine atrophy, signal abnormalities in subcortical and periventricular white matter, right hippocampal sclerosis, signal abnormalities in bilateral basal ganglia, and basal ganglia atrophy (Fig. S2, online supporting information). In Patient 3, the cerebral atrophy observed at 7 days was exacerbated at 30 days. In the other three survivors brain MRI was not performed after the acute encephalopathy.

DISCUSSION

Dravet syndrome is an intractable epileptic encephalopathy in which seizures are pharmacoresistant and episodes of status epilepticus occur repeatedly. Despite postictal motor deficits after status epilepticus, patients with Dravet syndrome usually recover within a few hours and are back to their previous condition in most instances. However, some patients may present with severe neurologic deterioration or even death if they have suffered acute encephalopathy after status epilepticus. This condition has been sporadically reported.7,12,14,15 In their series of 15 cases, Okumura et al.12 evaluated the rate of occurrence of acute encephalopathy in 170 patients with Dravet syndrome which was around 7.6%. In our larger cohort, the rate was...
| Patient | Age at onset of AE | Temperature (°C) | Duration of SE | Duration of coma | Follow-up period | Age at last visit | Seizure frequency before AE | Seizure frequency | Cognitive | Motor |
|---------|-------------------|------------------|----------------|-----------------|-----------------|------------------|-----------------------------|-----------------|-----------|-------|
| 1       | 2y                | 39.6             | 2h             | 3d              | 7mo             | 2y 7mo           | Monthly                     | No eye contact, no words | Cannot hold up head, spastic tetraplegia |
| 2       | 4y 2mo            | 40.2             | 5h             | 7d              | 4y 4mo          | 8y 6mo           | Monthly                     | Environmental interaction, simple words | Walks without help, spastic hemiplegic gait, left facial palsy, involuntary movement |
| 3       | 5y                | 39.3             | 3h             | 3d              | 4y 3mo          | 9y 3mo           | Monthly                     | Environmental interaction, two words | Cannot hold up head, involuntary movement |
| 4       | 3y 8mo            | 40.1             | 6h             | 20d             | 12mo            | 4y 8mo           | Monthly                     | No eye contact, no words | Cannot hold up head, involuntary movement, hypotonia |
| 5       | 2y 7mo            | 39.5             | 1h             | 4d              | 2y 6mo          | 5y 1mo           | Monthly                     | Environmental interaction, two words | Walks unsteadily without help, involuntary movement |
| 6       | 3y 6mo            | 39.4             | 8h             | 10d             | 1y 3mo          | 4y 9mo           | Weekly                     | Eye contact only, no words | Can hold up head but cannot sit without help, involuntary movement, hemiplegia |
| 7       | 3y 11mo           | 39.5             | 1h             | 2d              | 7mo             | 4y 6mo           | Monthly                     | No eye contact, no words | Can hold up head but cannot sit without help, involuntary movement, hypotonia |
| 8       | 11mo              | 39.3             | 9h             | 3d              | 3y 3y 11mo      | Monthly          | Yearly                     | Environmental interaction, two words | Walks unsteadily without help, hemiplegic gait, involuntary movement, hemiplegia |
| 9       | 7y 8mo            | 42.0             | 40min          | 2d              | 7mo             | 8y 3mo           | Yearly                     | No environmental interaction, no words | Walks unsteadily without help, involuntary movement |
| 10      | 10mo              | 39.3             | 1h             | 3d              | 7mo             | 1y 5mo           | Weekly                     | No eye contact, no words | Cannot hold up head, involuntary movement, hemiplegia |
| 11      | 6mo               | 39.5             | 3h             | 2d              | 2y 3mo          | 2y 9mo           | Yearly                     | None                        | Sits without help, involuntary movement, hemiplegia |
| 12      | 8mo               | 39.7             | 6h             | 3d              | 2y 4mo          | 3y               | Monthly                     | Environmental interaction, two words | Walks unsteadily without help, hemiplegia |
| 13      | 6mo               | 39.4             | 7h             | 2d              | 3y 10mo         | 4y 4mo           | Monthly                     | No eye contact, no words | Cannot hold up head, involuntary movement, hemiplegia |
| 14      | 3y 1mo            | 41.2             | 1.5h           | 10d             | 6mo             | 3y 7mo           | Monthly                     | None                        | Can hold up head but cannot sit without help, involuntary movement, hypotonia |
| 15      | 2y 2mo            | 39.8             | 8h             | 2d              | 4y 2mo          | 6y 4mo           | Monthly                     | Environmental interaction, two words | Walks unsteadily without help, hemiplegia |
| 16      | 1y 7mo            | 40.4             | 5h             | 2d              | 2y 10mo         | 4y 5mo           | Monthly                     | Environmental interaction, two words | Cannot hold up head, involuntary movement, hemiplegia |
| 17      | 4y 6mo            | 39.5             | 7h             | 15d             | 2y 1mo          | 6y 7mo           | Monthly                     | No eye contact, no words | Cannot hold up head, spastic tetraplegia |
| 18      | 2y 2mo            | 39.6             | 11h            | 7d              | 2y 5mo          | 4y 7mo           | Weekly                     | Eye contact only, no words | Walks without help, spastic hemiplegic gait, left facial palsy, involuntary movement |
| 19      | 2y 9mo            | 39.7             | 6h             | 5d              | 1y 5mo          | 4y 2mo           | Monthly                     | No eye contact, no words | Cannot hold up head, hypotonia, involuntary movement |
| 20      | 3y 6mo            | 39.3             | 3h             | 10d             | 5mo             | 3y 11mo          | Monthly                     | No eye contact, no words | Cannot hold up head, hypotonia, involuntary movement |
| 21      | 8y                | 39.9             | 4h             | 5d              | 5mo             | 8y 5mo           | Yearly                     | None                        | Walks unsteadily without help, hemiplegia |
| 22      | 1y 5mo            | 39.0             | 5h             | 2d              | 6mo             | 1y 11mo          | Weekly                     | Environmental interaction, two words | Sits without help, involuntary movement, hemiplegia |
| 23      | 9mo               | 41.2             | 1h             | 3d              | 3y              | 3y 9mo           | Monthly                     | Environmental interaction, two words | Walks unsteadily without help, hemiplegia |

AE, acute encephalopathy; SE, status epilepticus.
slightly lower at 5.6% (35/624). Acute encephalopathy after status epilepticus is a catastrophic, often fatal clinical condition. A multicentre study of early mortality in Japan showed that acute encephalopathy with status epilepticus was one of the main causes of death in Dravet syndrome patients (36%).16 Okumura et al.12 reported that 4 out of 15 patients died. Myers et al.14 reported five patients who died during acute encephalopathy. As the MRI showed brain herniation caused by cerebral edema in their patients, they have deemed that brain herniation could be a cause of

Figure 1: The neuroimaging evolution of Patient 2 before and after the acute encephalopathy. (a,b) The brain magnetic resonance imaging was normal before the acute encephalopathy. (c,d) Seven days after the onset of acute encephalopathy, marked edema in right cerebral hemisphere, left cerebellar atrophy. (e–h) Four months after the onset of acute encephalopathy, bilateral cerebral atrophy, right mainly, right pontine atrophy, cerebellar atrophy, and diffuse signal abnormalities in the right-side subcortical white matter.

Figure 2: The neuroimaging evolution of Patient 3 after the onset of acute encephalopathy. (a–c) Seven days after the onset of acute encephalopathy, marked edema in right cerebral hemisphere, bilateral cerebral atrophy. (d–f) One month after the onset of acute encephalopathy, bilateral cerebral atrophy, exacerbated than before. (g,h) Bilateral cerebellar atrophy.
death in patients with Dravet syndrome with status epilepticus, contributing to the early mortality in Dravet syndrome. Brain herniation was not reported by Okumura et al. Among our patients, 12 died after the acute encephalopathy because of multi-organ failure such as respiratory failure and/or circulatory failure, which might indicate brainstem dysfunction. However, as we did not have neuroimaging of these patients, we cannot know if this dysfunction was caused by brainstem herniation. In our series, it seems that there are no differences in seizure frequency before acute encephalopathy, temperature at the onset of acute encephalopathy, and the duration of status epilepticus between those who survived and those who died.

Febrile or afebrile status epilepticus often occurs in patients with Dravet syndrome. The frequency of status epilepticus may decrease with age, but febrile status epilepticus can still happen. In the 15 patients reported by Okumura et al., the median age at onset of acute encephalopathy was 3 years 8 months (range 8–180mo). Eleven children were younger than 5 years of age, whereas two were older than 10 years. The patients reported by Chipaux et al. were 13, 16, and 38 months, and 4 out of 5 reported by Myers et al. were older, from 5 to 11 years. In our 35 patients, the median age of the onset of acute encephalopathy was 3 years 1 month and most cases occurred under 5 years of age. So patients with Dravet syndrome under 5 years of age represent a high-risk population of acute encephalopathy but older patients are not excluded. Myers et al. reported five patients with Dravet syndrome died after acute encephalopathy; fever of 40°C or higher was measured in all. In our 35 patients, all but one had a high fever (>39°C) during the status epilepticus before the acute encephalopathy. Survivors suffered massive neurological regression such as lack of eye contact and hypotonia in the acute phase. During the recovery phase, some patients improved in cognition, language, and motor development after training, but most could not recover back to their previous condition, remaining with moderate or severe sequelae. Of 10 patients with hemi-clonic status, five developed hemiparesis after recovery. These findings are in line with those in the literature. In the Okumura et al. series, among 11 survivors, nine had severe sequelae and two had moderate sequelae. In the same study, the seizure frequency was reduced in most survivors after acute encephalopathy. This interesting phenomenon was confirmed in our study: 10 of the 23 survivors had no seizures after recovery and eight had reduced seizures. In addition, two patients had asymmetric epileptic spasms after the acute encephalopathy. Epileptic spasm is not a seizure type of Dravet syndrome, it may be caused by the reorganization of the neural networks after neuronal death because of necrosis or apoptosis caused by prolonged status epilepticus.

The neuroimaging of patients with Dravet syndrome is usually normal; however, non-specific brain atrophy and hippocampal sclerosis have been described in some patients. Some studies considered a relation with repetitive fever-associated status epilepticus, probably caused by the damage of seizures and diffuse anoxo-ischemic brain lesions. Other studies reported that the MRI changes had no relation with the duration of epilepsy, age at seizure onset, or the frequency of episodes of status epilepticus. Whether hippocampal sclerosis is caused by febrile status epilepticus or prolonged status epilepticus remains unclear. In our study, the neuroimaging showed brain edema in the acute phase of acute encephalopathy. In the recovery phase, most survivors showed diverse degrees of brain atrophy. In some cases, they were associated with cerebellar or pontine atrophy. Two were with hippocampal sclerosis. Status epilepticus with persistent hemi-clonic seizures always led to hemispheric or predominantly hemispheric cerebral lesions, and generalized tonic-clonic status epilepticus resulted in bilateral cerebral lesions. Okumura et al. distinguished two patterns in the distribution of the observed brain lesions, one with cerebral cortex-dominant lesions with or without deep grey matter involvement and one with subcortical-dominant lesions. In the Myers et al. series, the neuroimaging of five deceased patients with acute encephalopathy revealed severe brain swelling with uncal, transtentorial, and inferior tonsillar herniation in the acute phase of acute encephalopathy. The neuroimaging of Patient 3 in our study showed brain atrophy and right hemisphere brain edema in the acute phase, but she had a history of episodes of status epilepticus before the acute encephalopathy. The brain atrophy observed during the acute phase was probably caused by status epilepticus previously. After 1 month of acute encephalopathy, the brain atrophy was exacerbated compared with the acute phase.

The risk factors for acute encephalopathy in Dravet syndrome are not yet clear. Some studies reported that patients with Dravet syndrome with acute encephalopathy are more likely to have a more severe phenotype, including an earlier age at onset, myoclonic seizures, and repeated episodes of status epilepticus compared with the overall population that have Dravet syndrome. In our study we also found a severe phenotype: the onset age of Dravet syndrome was earlier than 6 months in 22 out of 35 patients; 25 out of 35 had more than one status epilepticus each year; 18 out of 35 had myoclonic seizures. Interestingly this severe phenotype is most frequent in the patients who died: 12 out of 12 had Dravet syndrome onset before 6 months, 12 out of 12 had more than one status epilepticus per year, 7 out of 12 had myoclonic seizures. However, as in the series of Okumura et al., the seizure frequency was not high before the acute encephalopathy; it was weekly in only five cases in the entire group and in only one case in the deceased patients. Some other studies considered that SCN1A gene is a genetic predisposition for acute encephalopathy and patients with nonsense and frameshift mutation of SCN1A might have a poor outcome. In our patients, it seemed that the SCN1A mutation types were not related to the outcome of acute.
encephalopathy but we did not perform a statistical study. In the study by Okumura et al., all children had a febrile illness before the onset of acute encephalopathy, but the authors do not indicate the temperature level. Myers et al. reported that five patients with Dravet syndrome died after acute encephalopathy, and body temperature of 40°C or higher was measured in all. They explained that hyperthermia alone had a deleterious effect on sodium channel function in experimental animal studies and that extreme hyperthermia might explain the dramatic severity of acute encephalopathy in patients with Dravet syndrome. In our study, high fever was the obvious trigger of acute encephalopathy. All the patients but one had a high fever (>39°C) during the status epilepticus before the acute encephalopathy. This high temperature is unusual in patients with Dravet syndrome in whom the seizures are triggered by a minor change (around 38°C) in temperature. Thus it is possible that a high fever during seizures plays an important role in the severity of the episode.

Whether the medication administered in status epilepticus acute management influenced the outcome of acute encephalopathy is still unknown. Different studies held different opinions. Chipaux et al. and Gataullina and Dulac held that barbiturates had excellent efficacy against status epilepticus. However, Tanabe et al. identified that intravenous barbiturates had excellent efficacy against status epilepticus triggered by fever in patients with Dravet syndrome. Moreover, Gataullina and Dulac considered that the chronic treatment by benzodiazepines is a factor of status epilepticus refractoriness because it reduces the gamma-aminobutyric acid response to benzodiazepines and also the cerebral blood flow. However, in our patients, drugs used to terminate ongoing status epilepticus were mainly benzodiazepines, as the routine status epilepticus protocols.

Our study has limitations concerning the lack of information on MRI data in the patients who died, the lack of detailed information on the treatment of the entire episodes from onset, and the lack of statistical study allowing precise comparison between the deceased patients and the survivors. In fact, not all the patients were regularly followed-up directly in our hospital and it was not easy to get complete information by telephone every 6 months.

In conclusion, patients with Dravet syndrome can rapidly develop into refractory status epilepticus and evolve into prolonged coma when they have high fever caused by infection. It could result in acute encephalopathy and fatal outcome while survivors are left with severe neurological sequelae. Acute encephalopathy is a catastrophic complication of Dravet syndrome. We presumed that in patients who are at an early age at Dravet syndrome onset, repetitive status epilepticus, high fever, and under 5 years of age were potential risk factors of acute encephalopathy and we must be aware that acute encephalopathy can develop in patients with Dravet syndrome even if the seizures are well controlled by antiepileptic drugs. The caregivers should be educated on this and prevent high fever when the child has an infection, especially for patients under 5 years of age. It is also very important to establish a home rescue plan to prevent prolonged status epilepticus triggered by fever. Doctors in emergency settings should be familiar with status epilepticus management. When the postictal coma is unusually prolonged, neurological signs including brainstem reflexes should be closely monitored and brain MRI should be quickly performed. Even though the true cause of acute encephalopathy is still unknown, early aggressive intervention might be lifesaving.

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SUPPORTING INFORMATION
The following additional material may be found online:

Table S1: The clinical features and outcomes of 12 deceased Dravet syndrome patients with acute encephalopathy

Table SII: The EEG and brain MRI findings of the acute encephalopathy of 23 survivors

Figure S1: EEG findings of Patient 1 in 4 months after the acute encephalopathy.

Figure S2: The neuroimaging findings of Patient 5 and Patient 7.

REFERENCES
1. Lagae L, Brambilla I, Mingorance A, Gibson E, Battensby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol 2018; 60: 63–72.
2. Gataullina S, Dulac O. Is epilepsy the cause of comorbidities in Dravet syndrome? Dev Med Child Neurol 2018; 60: 8.
3. Lichten SH, Mcmahon JM, Schneider AL, Davey MJ, Scheff E. Sleep problems in Dravet syndrome: a modifiable comorbidity. Dev Med Child Neurol 2018; 60: 192–8.
4. Dravet C, Bureau M, Ogami H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy: Dravet syndrome. Adv Neural 2005; 95: 11–102.
5. Connolly MB. Dravet syndrome: diagnosis and long-term course. Can J Neurol Sci 2016; 43(Suppl. 3): S1–8.
6. Mizuguchi M, Yamanouchi H, Ichiyama T, Shiomi M. Acute encephalopathy associated with influenza and other viral infections. Acta Neurol Stand 2007; 115 (Suppl. 4): 45–56.
7. Do T, Huynh T, Le T. Acute encephalopathy in Dravet syndrome: case reports and literature review. Neuro Asia 2016; 21: 181–5.
8. Do T, Huynh T, Le T. Acute encephalopathy in Dravet syndrome: two case reports and discussion of risk factors. Ann Transl Med 2015; 3(Suppl. 2): AB041.
9. Tsuji M, Mazaki E, Ogawa I, et al. Acute encephalopathy in a patient with Dravet syndrome. Neuropediatrics 2013; 42: 78–81.
10. Dravet C, Bureau M, Oguni H, Cokar O, Guerrini R. Dravet syndrome (Severe myoclonic epilepsy in infancy). In: Bureau M, Genton P, Dravet C, et al., editors. Epileptic Syndromes in Infancy, Childhood and Adolescence. 5th edn. Paris: John Libbey Eurotext, 2012: 125–56.

11. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus – report of the ilae task force on classification of status epilepticus. Epilepsia 2015; 56: 1515–23.

12. Okumura A, Uematsu M, Imataka G, et al. Acute encephalopathy in children with Dravet syndrome. Epilepsia 2012; 53: 79–86.

13. De Liso P, Chemaly N, Laschet J, et al. Patients with Dravet syndrome in the era of stiripentol: a French cohort cross-sectional study. Epilepsy Res 2016; 125: 42–6.

14. Myers KA, McMahon JM, Mandelstam SA, et al. Fatal cerebral edema with status epilepticus in children with Dravet syndrome: report of 5 cases. Pediatrics 2017; 139:e20161933.

15. Chipaux M, Villeneuve N, Sabouraud P, et al. Unusual consequences of status epilepticus in Dravet syndrome. Seizure 2010; 19: 190–4.

16. Sakauchi M, Oguni H, Kato I, et al. Mortality in Dravet syndrome: search for risk factors in Japanese patients. Epilepsia 2011; 52(Suppl. 2): 50–4.

17. Ragone F, Grana F, Dalla Bernardina B, et al. Cognitive development in Dravet syndrome: a retrospective, multicenter study of 26 patients. Epilepsia 2011; 52: 86–92.

18. Oguni H, Hayashi K, Awa S, Y. Fukuyma Y, Osawa M. Severe myoclonic epilepsy in infants – a review based on the Tokyo Women’s Medical University series of 84 cases. Brain Dev 2003; 25: 736–48.

19. Saito T, Saito S, Sugai K, et al. Late-onset epilepsy in children with acute febrile encephalopathy with prolonged convulsions: a clinical and encephalographic study. Brain Dev 2013; 35: 531–9.

20. Gally E, Anttonen AK, Valanne L, et al. Dravet syndrome: new potential genetic modifiers, imaging abnormalities, and ictal findings. Epilepsia 2013; 54: 1577–85.

21. Siegler Z, Barsi P, Neuwirth M, et al. Hippocampal sclerosis in severe myoclonic epilepsy in infancy: a retrospective MRI study. Epilepsia 2005; 46: 704–8.

22. Guerrini R, Striano P, Catarino C, Sidoliya SM. Neuroimaging and neuropathology of Dravet syndrome. Epilepsia 2011; 52(Suppl. 2): 38–4.

23. Saitoh M, Shinozuka M, Hoshino H, et al. Mutations of the SCN1A gene in acute encephalopathy. Epilepsia 2012; 53: 558–64.

24. Gataullina S, Dulac O. From genotype to phenotype in Dravet disease. Seizure 2017; 44: 58–64.

25. Tanabe T, Awaya Y, Matsuishi T, et al. Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome) – a nationwide questionnaire survey in Japan. Brain Dev 2008; 30: 629–35.
RESUMEN

EL RESULTADO CLÍNICO Y DE NEUROIMAGEN, DE LA ENCEFALOPATÍA AGUDA DESPUÉS DE UN ESTADO EPILEPTICO EN EL SÍNDROME DE DRAVET

OBJETIVO Analizar el resultado clínico y de neuroimagen después de un seguimiento de larga duración en la serie más larga actualmente de pacientes con encefalopatía aguda después de un estado epiléptico y afectos de síndrome de Dravet.

MÉTODO Se revisaron de forma retrospectiva datos clínicos y de neuroimagen de pacientes con síndrome de Dravet y con una historia de encefalopatía aguda (coma >24h) después de un estado epiléptico ocurrido desde Febrero del 2005 a Diciembre del 2016 en el Primer Hospital Universitario de Pekín.

RESULTADOS Treinta y cinco pacientes (15 varones y 20 mujeres) con una historia de encefalopatía aguda fueron enrolados de un total de 624 pacientes con síndrome de Dravet (5,6%). La media de edad de presentación de la encefalopatía aguda fue de 3 años y 1 mes. La duración del estado epiléptico varió entre 40 minutos a 12 horas. Treinta y cuatro pacientes tuvieron una fiebre alta cuando el estado epiléptico ocurrió y solamente uno tuvo temperatura normal. El coma duró de 2 a 20 días. Doce pacientes murieron y 23 sobrevivieron con una regresión neurológica masiva. La media de seguimiento en estos pacientes fue de 2 años y 1 mes. La neuroimagen de 20 de 23 sobrevivientes en la fase de recuperación mostró diversos grados de atrofia cortical con y sin lesiones subcorticales.

INTERPRETACIÓN La encefalopatía aguda después de un estado epiléptico es más propensa a ocurrir en pacientes con síndrome de Dravet y fiebre alta. La tasa de mortalidad es alta en casos severos. Los sobrevivientes presentan secuelas neurológicas severas, pero sin crisis epilépticas o una baja frecuencia de ellas.

RESUMO

O RESULTADO CLÍNICO E DE NEUROIMAGEM DA ENCEFALOPATIA AGUDA APÓS ESTADO EPILEPTICO EM SÍNDROME DE DRAVET

OBJETIVO Analisar o resultado clínico e de neuroimagem após um acompanhamento de longa duração na maior série da atualidade de encefalopatia aguda após estado epileptico em pacientes com síndrome de Dravet.

MÉTODO Dados clínicos e de neuroimagem de pacientes com síndrome de Dravet com uma história de encefalopatia aguda (coma > 24h) após estado epiléptico do First Hospital da Universidade de Pequim foram revisados retrospectivamente de Fevereiro de 2005 a Dezembro de 2016.

RESULTADOS Trinta e cinco pacientes (15 do sexo masculino, 20 do sexo feminino) com uma história de encefalopatia aguda foram recrutados de um total de 624 pacientes com síndrome de Dravet (5,6%). A idade mediana de início da encefalopatia aguda foi de 3 anos e 1 mês. Trinta e quatro pacientes tiveram febre alta quando o estado epiléptico aconteceu, e apenas uma teve temperatura normal. A duração do estado epiléptico variou entre 40 minutos e 12 horas. O coma durou de 2 a 20 dias. Doze pacientes vieram a óbito e 23 sobreviveram com regresseão neurológica masiva. O tempo mediano de acompanhamento foi 2 anos e 1 mês. A neuroimagem de 20 dos 23 sobreviventes durante a fase de recuperação mostrou diversos graus de atrofia cortical com ou sem lesões subcorticiais.

INTERPRETAÇÃO A encefalopatia aguda após estado epiléptico é mais provável de acontecer em pacientes com síndrome de Dravet que tiveram febre alta. A taxa de mortalidade é alta em vários casos. Os sobreviventes apresentam sequelas neurológicas severas, mas frequentemente sem convulsões, ou com baixa frequência de convulsões.