Dravet syndrome: The long-term outcome
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SUMMARY
Few studies focused on the long-term outcome of Dravet syndrome in adulthood are available in the literature, but all are concordant. In this article, we consider the outcomes of 24 patients followed at the Centre Saint-Paul, Marseille, up to the age of 50, and compare them to the patients reported in the literature. Five patients (20.8%) died, at a mean age of 24.8 years, one by status epilepticus, three by sudden unexpected death in epilepsy (SUDEP), and one of unknown cause. Epileptic seizures tend to become less frequent and less severe after childhood. Fever sensitivity (temperature variations) persists throughout the clinical course of DS, but its impact on seizure frequency and severity is milder than in infancy. Generalized convulsive seizures, mostly reported as generalized tonic–clonic seizures (GTCS), were the only seizure type observed in almost all of the patients, often with a focal onset. They are less frequent than in childhood and mostly nocturnal. Some of these major convulsive seizures have less typical aspects, for example, bilateral or asymmetric tonic posturing, followed in some cases by a tonic vibratory state or clonic movements (Oguni et al., Brain Dev 2001;23:736–748; Akiyama et al., Epilepsia 2010;51:1043–1052). Other seizures like myoclonic seizures, atypical absences, and complex partial seizures (CPS) are less common in adulthood: Among our 24 patients, only 6 had atypical absences, and one myoclonic and one complex focal seizures. Electroencephalography (EEG) also changes with age but is still multiple and heterogenous, interictally and ictally. Photosensitivity and pattern sensitivity also showed a tendency to disappear before the age of 20. Motor abnormalities are common. Cerebellar features, including ataxia, dysarthria, intention tremor, and eye movement disorder, become more prominent. Walking is markedly impaired, often due to orthopedic signs such as kyphosis, kyphoscoliosis, flat feet, or claw feet. This symptomatology was minor during childhood and worsened during and after adolescence, despite physiotherapy. Mental retardation ranged from moderate to severe, with predominance of language impairment, and some patients had a major personality disorder, labeled autistic or psychotic. Dependency in adulthood is nearly constant: Only 3 of our 24 adult patients lived independently.

KEY WORDS: SMEI, Long-term outcome, Mortality, Seizures, Adults.

Severe myoclonic epilepsy of infancy (SMEI) was first described by C. Dravet (1978) as a well-characterized condition. The existence of borderline forms with similar clinical characteristics but without marked myoclonus (Ogino et al., 1988; Hattori et al., 2008) caused the condition to be named “Dravet syndrome” (DS). The range of clinical pictures widened further after the description of the SCN1A mutations that underline a majority of cases with DS. However, the long-term outcome of the DS has been considered to be fairly homogenously poor (Ohtsuka et al., 1991; Fujiwara et al., 1992; Oguni et al., 2001; Jansen et al., 2006), but the recent description of various types of epileptic encephalopathies associated with SCN1A mutations has slightly challenged this view (Harkin et al., 2007). The long-term outcome of patients with DS has been described in several recent studies (Jansen et al., 2006; Dravet et al., 2009; Akiyama et al., 2010).

In DS, the long-term perspective, which is the subject of this review, is dominated by a high mortality rate, persistence of a fairly typical epileptic encephalopathy, and by an unfavorable cognitive and a poor social outcome.
The overall picture seems unique, even among epileptic encephalopathies. Recently diagnosed cases seem to enjoy a slightly less severe evolution, perhaps as a consequence of more efficient treatment options and better global care. Our review is based on the study of a cohort of 24 patients followed beyond the age of 20 at our center (Dravet et al., 2009): 14 male and 10 female patients, aged 20–50 at last evaluation, first referred between 1970 and 1992.

**Mortality**

DS is associated with a significant mortality, and death may occur at any age, but more frequently during childhood; however, studies limited to childhood may have underestimated the incidence of early death in DS. Conversely, studies of DS in adults deal with survivors. In our recent series of 24 cases of DS, 5 patients (20.8%) died in adulthood, at ages 18, 20 (2), 30, and 31. In their 1992 review, Dravet et al. noted that 16% among 63 patients died at a mean age of 11 years. Akiyama et al. (2010) reported 12 deaths among 84 patients, at a mean age of 65 months, including 7 deaths in 38 with typical SMEI versus 5 deaths in 45 with “borderline” SMEI. Numerous other authors have reported early death in patients with DS, including four of eight patients (Miyake et al., 1991). The causes of death quoted in the larger series have been reported on Table 1: They are dominated by status epilepticus (SE) and its consequences in the younger patients, and by sudden unexpected death in epilepsy (SUDEP) in older children and also beyond the pediatric age.

Preventive measures have not been discussed in the literature, but one can assume that better management of acute seizure situations and SE may decrease the mortality linked to SE; we have introduced in our practice the avoidance of soft pillows in patients with DS at any age, in order to try and minimize the consequences of respiratory depression, one of the putative contributors to SUDEP. Our recent experience has taught us that SUDEP is now more frequent than death caused by SE, even in the younger patients.

**Epilepsy**

Epileptic seizures tend to become less frequent and less severe after childhood.

Fever sensitivity and sensitivity to increased body temperature persists throughout the clinical course of DS, but its impact on seizure frequency and severity is milder than in infancy: 12 of 24 adult patients in our series remained fever sensitive, whereas Akiyama et al. (2010) reported 30% with persisting fever sensitivity. Jansen et al. (2006) do not mention fever in their adult patients. Fever-related seizures in adults do not evolve into SE or seizure clusters (Akiyama et al., 2010), but this finding is not confirmed in our experience.

Generalized convulsive seizures, mostly reported as generalized tonic–clonic seizures (GTCS), were the only seizure type observed in almost all of the patients [Dravet et al., 2009: 24 of 24 (two of whom had been in remission for at least a year); Jansen et al., 2006: 14 of 14; Akiyama et al., 2010: 26 of 31]. They are less frequent than in childhood and mostly nocturnal. The move from major seizures occurring at awakening in the younger age classes to seizures occurring during sleep after age 5 years has been underscored (Fujitwara et al., 1992; Oguni et al., 2001). Among our 24 adult patients, 21 had GTCS during sleep: 7 while awake, 2 on awakening, 8 had a focal onset, and 4 had predominantly unilateral seizures. Unilateral convulsive seizures may indeed still be found in adults, but they do not tend to shift sides during the same seizure (Akiyama et al., 2010). Some of these major convulsive seizures have less typical aspects, for example, bilateral or asymmetric tonic posturing followed in some cases by a tonic vibratory state or clonic movements (Oguni et al., 2001; Akiyama et al., 2010).

Other seizures like myoclonic seizures, atypical absences, and complex partial seizures (CPS) are less common in adulthood. Among our 24 patients, only 6 had atypical absences, one myoclonic, and one complex focal seizures. Myoclonic seizures and atypical absences tended to disappear between the ages 15 and 120 months, with a mean of 62 ± 28 months in 28 patients who were followed up for 117 ± 61 months (Oguni et al., 2001),

**Table 1. Causes of death in SMEI**

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<tbody>
<tr>
<td>Study population</td>
<td>24 adults</td>
<td>63, 3–27 years</td>
<td>37, up to age 43</td>
<td>84, pediatric</td>
</tr>
<tr>
<td>Proportion</td>
<td>5 = 20.8%</td>
<td>10 = 16%</td>
<td>6 = 16.2%</td>
<td>12 = 14.3%</td>
</tr>
<tr>
<td>Mean age</td>
<td>24.8 years</td>
<td>11 years</td>
<td>Range 5–12 years</td>
<td>6 years</td>
</tr>
<tr>
<td>Status epilepticus and complications of SE</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>SUDEP</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia/infection</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Drowning</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>1</td>
<td>4</td>
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a finding coherent with the data reported by other authors (Giovanardi-Rossi et al., 1991; Ohtsuka et al., 1991; Maniwa, 1993; Ohki et al., 1997). Akiyama et al. (2010) reported the disappearance of the epileptic myoclonic and atypical absence seizures before the age of 20 in 93% (29 of 31) of the patients, Dravet et al. (2009) in 66% (16 of 24), and Jansen et al. (2006) in 57% (8 of 14). When the myoclonic seizures and atypical absences persist, they are usually grouped before or after the GTCS (Dravet et al., 2009). CPS persist in 22–50% of the patients (Jansen et al., 2006; Akiyama et al., 2010). Dravet et al. found only one of 24 with CPS (4%).

The incidence of convulsive SE (CSE) decreases markedly with age. In our series, three patients had SE at age 24, 26, and 28, whereas in the series of Akiyama et al. (2010), CSE completely disappeared after age 10. In patients who still experience myoclonic seizures and atypical absences, obtundation status may also occur: Two patients among 31, at the ages of 43 and 22 years (Akiyama et al., 2010), and 4 in our cohort of 24 patients experienced occasional nonconvulsive SE.

The overall frequency of seizures is much lower than in the young pediatric cases. Akiyama et al. (2010) reported five patients (16.1%) seizure-free for at least 1 year prior to the last follow-up. None had been seizure-free in the Australian patients’ group (Jansen et al., 2006). Two patients in our cohort were completely seizure-free for longer than 12 months (5 years in one). They achieved seizure freedom at age 30 and 31 years, respectively, and both following the addition of topiramate (TPM). Among the 22 other patients, five had one to several major seizures per year, 14, the majority, one to several per month, two several per week, and only one, one to several per day; seven patients still experienced seizure clusters.

EEG also changes with age. As in younger children, the EEG aspects are multiple and heterogenous, interictally and ictally. In our series, the background activity was normal or near-normal in 8, and slow/disorganized in 11. Paroxysmal changes were absent in 4, multifocal in 11, focal in 7, and associated with generalized changes in 6. Generalized changes were infrequent. Ictal recordings were obtained in five adult patients: Three had subclinical focal discharges during sleep, mostly temporal and temporooccipital; three had secondarily GTCS during sleep. In one, obtundation status associated with catatonia was recorded, with onset during an afternoon sleep period and persistence for >20 min after awakening (Fig. 1). Another patient had brief tonic-like seizures at sleep onset (Fig. 2). Among the 31 adult patients reported by Akiyama et al. (2010), 4 (12.9%) had generalized spike-waves and

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**Figure 1.**

EEG from a 42-year-old female patient with DS. Recording at awakening of an afternoon nap of an atypical absence state that began during sleep and persisted after awakening, ending spontaneously after a total duration of 70 min (30 min while sleeping and 40 after awakening). The patient was catatonic, and nearly unresponsive. Her behavior changed abruptly after the cessation of the abnormal EEG activity. The EEG shows a continued mixed slow activity with multifocal spikes. On the right, a brief abstract of the EEG after cessation of the status. Total duration of EEG represented here: 20 s.

*Epilepsia* © ILAE
multifocal spikes, 13 (41.9%) had multifocal spikes, 6 (19.3%) had only focal (frontal or temporal) spikes, and 8 (25.8%) had no spikes (age at the disappearance of spikes in these eight patients ranged from 8–23 years).

Photosensitivity and pattern sensitivity also showed a tendency to disappear before the age of 20 (Oguni et al., 2001; Akiyama et al., 2010). Some patients with DS may retain light sensitivity, the photoparoxysmal response depending on the quantity of light rather than on wavelength (Takahashi et al., 1999). Patients with this type of photosensitivity may represent the most resistant types of patients with DS (Oguni et al., 2001). Among our patients, one with persistent photoparoxysmal responses self-stimulated either by waving his hand in front of his eyes or repeatedly closing his eyes (Fig. 3).

Neurologic status: Motor abnormalities are common. Cerebellar features including ataxia, dysarthria, intention tremor, and eye movement disorder are most prominent. In our group, ataxia was present in 9, dysarthria in 8, and tremor in 7. Pyramidal symptoms were present in 4 and extrapyramid signs in 3. Walking was markedly impaired in 7. Fragmentary myoclonus was still seen in 12. Seven of twenty-four patients had orthopedic signs, such as kyphosis, kyphoscoliosis, flat feet, or claw feet. This symptomatology was minor during childhood and worsened during and after adolescence, despite physiotherapy. Two patients were operated on for kyphosis with a transient benefit. Five patients had a gross walking impairment and two used a wheelchair. Jansen et al. (2006) found marked cerebellar dysfunction in 28.5% (4 of 14),
extrapyramidal signs in 4.

**Cognitive/Behavioral and Social Outcome**

All adult patients had significant impairment. We did not perform specific quantitative assessment beyond childhood. The results of the cognitive studies performed in childhood are reported elsewhere in this volume. In our series, mental retardation ranged from moderate to severe. For Jansen et al. (2006), 5 of 11 patients were moderately retarded, and 6 severely (three deteriorated during adulthood). In our series, 6 patients of 24 had a major personality disorder, labeled autistic or psychotic. Language impairment was prominent (assessed in 21 patients): No language in three, noncommunicative language in four, poorly structured but communicative language in 7, and poor but communicative language in 7. In the Akiyama et al. (2010) series of 31 adults, 7 had no language, 9 could say only a few words, 9 could have a primitive conversation, 5 a simple conversation, and only one had a minimal language disability but developed psychosis.

Dependency in adulthood is a nearly constant feature of DS. Only 3 of our 24 adult patients lived independently (i.e., with external support); 8 were partly and 13 were totally dependent. Among the 14 patients reported by Jansen et al. (2006), 2 lived independently but were unemployed, 2 lived in supervised community accommodation, and 10 were relying on “considerable support.” In the Akiyama et al. (2010) series, only one patient could live independently.

**Conclusion**

The evolution of DS from early childhood into adulthood follows a fairly predictable pattern, and the range of situations found in adults is limited. All authors have stressed that no patient remains unscathed, in terms of cognition, behavior, and social life. However, this very severe picture was observed in patients with often delayed diagnosis and inadequate treatment. In our more recent observations, more efficacious drugs were used, and a better seizure control was obtained with considerable reduction of seizure duration and avoidance of SE. These patients have less severe cognitive impairment in their first years and their behavioral disorders are less severe. We may foresee that the long-term outcome, at least in some of them, will be much better. A good outcome was reported by Buoni et al. (2006) in a young man of 13 years with typical DS and truncating mutation, who had an IQ of 125. The factors that determine the degree of severity are not well understood. Genetic factors may play a major part, and the severity of epilepsy, including the number of episodes of SE and the frequency of major seizures, are probably significant determinants.

The major feature of DS remains the high risk of lethality: Although adequate medical intervention and management may reduce the risk of death due to seizures and SE, the high incidence of SUDEP, especially in older children and young adults, singles out DS among other epileptic encephalopathies. There is ample room for progress, and some improvements may already have occurred in the medical management. Much remains to be explained and understood and translated into efficient intervention for the benefit or our patients.

**Disclosures**

PG and RV do not have conflicts of interest. CD is member appointed by Biocodex as an occasional expert for clinical reports and advisory services, and as attendance at conferences as contributor.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**References**


