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Short communication

Unusual consequences of status epilepticus in Dravet syndrome

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ABSTRACT

Although status epilepticus (SE) affects the course of Dravet syndrome (DS), it rarely alters dramatically psychomotor outcome. We report an unusual pattern in 3 patients who following refractory SE lasting respectively 2, 7 and 12 h experienced persistent and severe cognitive and motor deterioration. We compared these patients to published data and to personal experience in Necker hospital, to find links between severe outcome and clinical features such as treatment or duration of refractory SE. The key point was that anoxoischemic-like lesions appeared on MRI although cardiovascular function had remained stable. Therefore, neither hemodynamic failure, nor abnormalities of cardiac rhythm could explain the lesions and neurological worsening. For theoretical reasons the responsibility of therapy common for the 3 patients, e.g., barbiturates was suspected.

Introduction

Dravet syndrome (DS) is characterised by prolonged, often unilateral seizures triggered by fever in infants with previously normal psychomotor development, delayed occurrence of myoclonus and later various seizure types with psychomotor retardation. EEG and MRI show no specific pattern. High seizure frequency during the first 2 years is correlated with a worse cognitive outcome.[1] Prolonged seizures are frequent during the first three years of life, but they rarely last more than 2 h and are usually followed by recovery of the previous condition. They occurred in about 70% of the children.[1,2] Severe deterioration following SE is not usual.[2] We report 3 patients with severe neurological regression following SE, and compared them to reported data in order to consider risk factors for this severe event.

Patients and methods

Among the 103 patients followed for DS in our hospital, 92% experienced at least one SE. For the 70% of patients with available data regarding duration of status and drugs administered, SE lasted from 30 min to 8 h with recovery of the previous condition in most instances.

We, however, encountered 3 children with severe cognitive and motor deterioration following refractory SE (Table 1). None of the 3 patients presented a personal history and a familial history of febrile seizures was reported for patient 2. Molecular genetics showed SCN1A mutation in all 3. We analyzed their clinical characteristics, and family and personal histories. We also reviewed brain imaging and EEG recordings to identify risk factors for such poor motor and cognitive outcome.

Results

The 3 children had experienced 4 to 7 episodes of SE between 7 and 36 months of age. Cognitive development was as expected in DS. The first child had undergone psychomotor evaluation (Brunet-Lezine scale) at 9 months, with a score of 83, normal speech and lack of behavioural impairment, before the severe status occurred at 13 months. The second child had just begun to walk alone and communication was considered normal for the age, when the severe SE occurred at 16 months. The third patient had mild mental retardation at age 36 months when severe SE occurred, but no cognitive scale was performed as the diagnosis of DS had not yet been suspected. Severe status consisted of continuous, bilateral clonic movements with loss of consciousness lasting respectively

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Table 1
Demographic characteristics of the 3 patients.

Patients	D. L	H. C	M. V
Birth date	09/05/2006	12/09/2003	04/15/1997
Family history	No	Febrile seizures	No
Personal history	No	No	No
Mutation	C5341T>C	p.Ser1328Pro	C4720delT
Age at first seizure	2 months	6 months	9 months
Number of previous SE	4	5	7
Duration of previous SE	30–60 mn	30–60 mn	30 mn–2h30
Age at first SE	6 months	6 months	12 months

12, 7 and 2 h (Table 2). It occurred with fever in all of them. Cardiac rate, oxymetry and blood pressure were continuously monitored in the intensive care unit and remained normal. No abnormality of glycemia or natremia was noticed.

Clinical characteristics of SE, monitoring and treatment are given in Table 2. The first patient received a combination of benzodiazepines and phenytoin followed by phenobarbital. The second received thiopental responsible for suppression-bursts patterns on his EEG, after benzodiazepines, phenytoin and phenobarbital. The third was treated with high doses of phenobarbital after benzodiazepines. Before this SE, the 3 children had a combination of valproate and clobazam for the 2 first patients, clonazepam for the third one. Stiripentol was added to the AEDs in patients 1 and 2, during the 2 months preceding the refractory SE; The third one did not receive stiripentol.

Following status epilepticus, all three patients experienced massive neurological regression, becoming hypotonic with spastic tetraplegia and loss of eye contact (Table 3). Six months after the status, at 19 months, the first child had moderately improved but remained hypotonic and could not walk; he said only 2–3 words and suffered from dystonia mainly in the face. Patients 2 and 3 had not recovered previous state several years later: both exhibited major hypotonia with poor eye contact, had totally lost speech, and remained dependent for feeding. Both had spastic tetraplegia, one had dystonia.

All 3 patients had previously normal brain MRI, confirmed on retrospective examination (Fig. 1). A second MRI was performed 3–8 weeks after the prolonged SE showed in all 3 patients major cortical and white matter but only slight atrophy of basal ganglia (Figs. 1 and 2). Perfusion CT scan performed for patient 1 two weeks after the status showed 30% reduction of cerebral blood flow

Table 2
Features of the complicated SE.

Age at complicated SE (CSE)	13 months	16 months	38 months
Duration of CSE	12 h	7 h	2 h
Hemodynamic failure	No	No	No
Cardio-pulmonary and oxymetry monitoring	Normal	Normal	Normal
Drugs given chronically	Valproate 30 mg/kg/d Clobazam 2 mg/kg/d Stiripentol 75 mg/kg/d	Stiripentol 62 mg/kg/d, started 2 months before Valproate 21 mg/kg/d Clobazam 1.4 mg/kg/d	Valproate 40 mg/kg/d Clonazepam 1 mg/kg/d
Drugs used for the previous status	6.5 months: (<1 h) Diazepam 2 mg/kg Phenytoin 15 mg/kg 7.5 months: (<1 h) Diazepam 2 mg/kg Phenobarbital 15 mg/kg 7.5 months: (<1 h) Diazepam 2 mg/kg Phenobarbital 15 mg/kg	(4 status <1 h) Diazepam and Clonazepam for status 1 and 2 Diazepam, Clonazepam and Phenobarbital 15 mg/kg for status 3 and 4	10 months: (1 h30) Diazepam 0.5 mg/kg Valproate 12 mg/kg Clonazepam 0.4 mg/kg/d Phenobarbital 15 mg/kg Phenytoin 15 mg/kg/d Fluid resuscitation and Dopamine 5 μg/kg/d 30 months: (2 h30) Diazepam 1.4 mg/kg Clonazepam 0.03/kg mg and 0.02 mg/kg/h Phenobarbital 20 mg/kg 4 others: (<1 h) Diazepam then clonazepam
Drugs used for the CSE	Diazepam 2 mg/Kg, Phenobarbital 20 mg/kg, Phenytoin 15 mg/kg, Clonazepam 0.3 mg/kg then 1.2 mg/kg/d	Diazepam 1 mg/Kg Phenobarbital 10 mg/kg Midazolam (1 dose), Clonazepam (1 dose), Phenytoine (1 dose) Pentothal 4 mg/kg, single dose	Diazepam 1 mg/kg Midazolam 0.3 mg/kg in 2 doses Phenobarbital 15 mg/kg then 1 mg/kg/h

Table 3
Outcome.

Clinical data after SE	Hypotonia, dystonia	Hypotonia, spastic tetraplegia	Hypotonia, dystonia, spastic tetraplegia
Cognitive data	Standing with help, voluntary grasping	No environmental interaction	Eye contact only
Speech	2–3 words	No	No
Age of 1st MRI	3 months	5 months	29 months
1st MRI findings	Normal	Normal	Normal
Age of last MRI	13 months	18 months	39 months
Last MRI findings	Cortical and sub-cortical atrophy, with reduced white matter	Cortical and sub-cortical atrophy, with diffuse anoxoischemic lesions	Cortical and sub-cortical atrophy, anoxoischemic lesions.

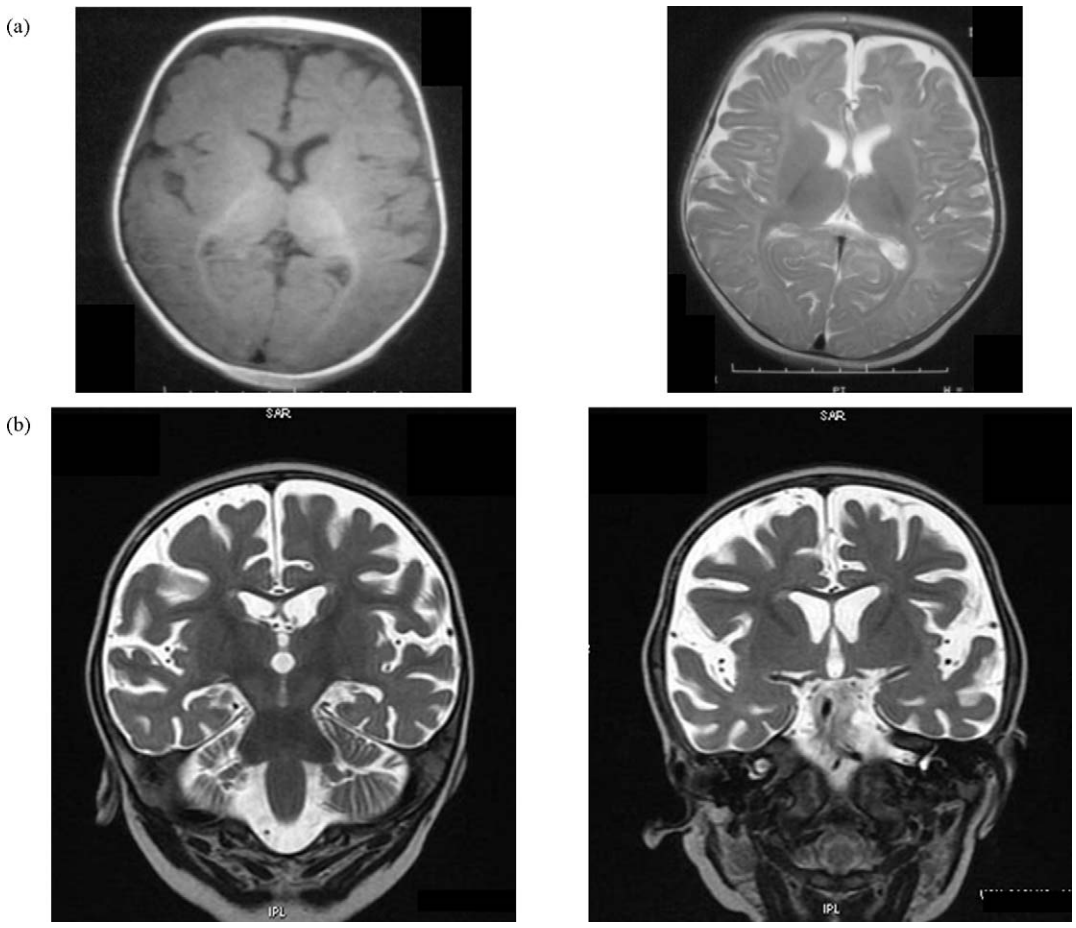

Fig. 1. MRI of patient 1 before (age 3 months) (a) and 2 months after complicated SE (age 13 months) (b).

in cortical areas and basal ganglia compared to normal control of the same age.

Discussion

Clinical characteristics of our 3 patients were initially typical for DS, but their evolution was unusual: sudden and severe worsening followed prolonged and drug resistant SE. Two of them had no improvement after several years of follow up, and although patient 1 slightly improved, she did not recover previous condition. Although Oguni et al. published 2 children with ''residual severe neurological deficits after prolonged SE'', this post-ictal deterioration is unusual in DS.[2] In our series, this deterioration encouraged search of an alternative diagnosis but molecular findings confirmed the diagnosis of DS and avoided useless further investigations.

The high frequency of uni- or bilateral SE triggered by fever in DS contrasts with the usual lack of lasting post-ictal motor deficit, and the severity of DS is mainly related to mental delay, not to gross motor defect.[1–3] Despite post-ictal motor defect, patients usually recover within a few hours. The three reported patients contrast by severe persistent neurological deterioration following prolonged SE. The combination of pyramidal and extrapyramidal signs is reminiscent of systemic hemodynamic failure, causing lesions in white matter and basal ganglia, as seen in ischemic encephalopathy (Fig. 2). Such cerebral abnormalities are distinct from those reported in DS. Early MRI of patients with DS, usually performed within the first 2 year of life, is normal.[1] Later in life, temporal sclerosis is occasionally reported, as well as non-specific atrophy.[2,4,5] Other reports mention atrophy and white matter T2 hyperintensities.[3,5] Diffuse cortico-sub-cortical atrophy with abnormal white matter signals has not been reported.

Three hypotheses may account for such deterioration: hemodynamic failure due to long duration of SE, cardiac rhythm abnormalities related to DS channelopathy, and reduced local cerebral blood flow related to drugs administered for SE.

Although following prolonged SE cognitive and behavioural troubles affect 20–79% of patients, motor troubles are usually mild.[6] Whether mortality or morbidity increases with the duration of SE remains unclear.[7] Patient 3 had previously suffered from prolonged seizures without similar consequences, as 92% of DS children followed in our institution. Age and duration of SE could be risk factor since most previous episodes of SE in these patients had occurred in the first year of life and had lasted for less than 1 h. However, for patient 3, a very similar episode had occurred in the same age range (30 months) and had lasted the same time (2.5 h) without such a dramatic outcome.

Energy needs of brain cells increase during seizures and blood flow increases by 2–3 folds (SPECT or PET), especially for long lasting seizures.[8] Prolonged seizures cause neuronal death due to necrosis or apoptosis, following oedema and blood-brain barrier lesions.[9] Anoxo-ischemic lesions could result from insufficient perfusion of discharging cells. However, systemic hemodynamic failure was not noticed for any of the 3 patients in intensive care unit.

Acute anoxo-ischemia could result from cardiac arrhythmia, possibly linked to sodium channel abnormalities of DS. This could

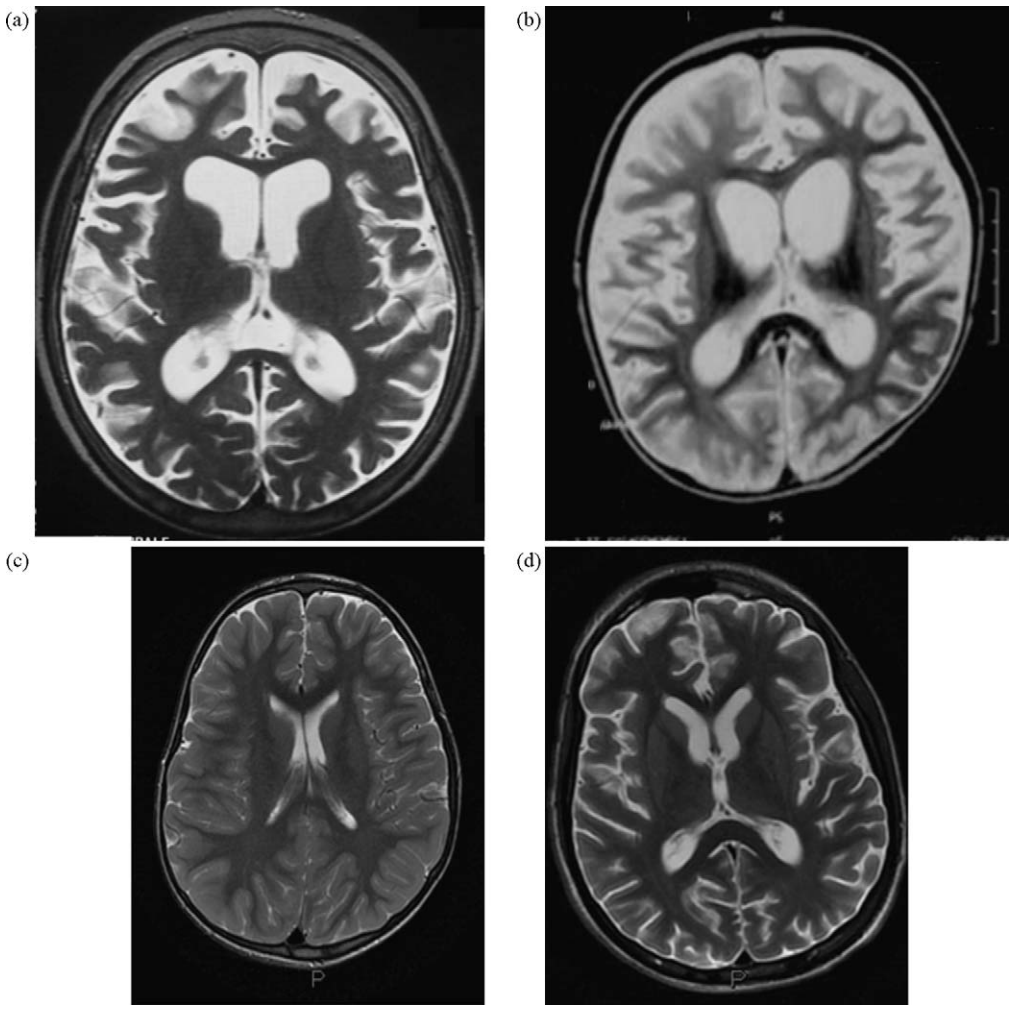

Fig. 2. MRI of patients 2 and 3 after complicated SE (a, b) on T2 weighted sequence compared to normal (c) and acute anoxic-ischemia at the same age (d). MRIs (a, b) were performed at mean 6 weeks after the event. The MRI of patients with DS (a, b) shared severe cortical atrophy similar to that of postanoxic-ischemic lesions but in addition dramatic loss of white matter with slight basal ganglia atrophy.

lower cardiac output and cerebral blood flow, and could therefore account for the higher incidence of sudden death in patients with DS.[10,11] In Dravet's series, two out of 63 children died suddenly[3] and 2 out of 41 in Chiron et al's series.[12] Our patients were, however, in ICU and no change of cardiac rhythms was identified despite continuous monitoring.

Brain damage could result from the medications administered: barbiturates and phenytoin. Phenytoin can produce cardiac dysrhythmia, but the compound was administered in the ICU without any impact on ECG monitoring. Barbiturates or its combination with stiripentol could have reduced local cerebral blood flow. Wada et al. showed that high doses of barbiturates decrease cerebral blood flow by over 25% ($p < 0.01$) during 3 h following the administration in animals.[13] This was confirmed in humans by transcranial Doppler measures.[14] When thiopental is used in paediatric SE, the mortality rate seems to be raised, compared with propofol.[15] Thiopental use in adult refractory SE has some rational because the mortality rate is 10 fold higher than in children.[6,16] Moreover, stiripentol inhibits P450 cytochrome metabolism, so blood levels of barbiturates could have been increased in the patients 1 and 2, especially following repeat barbiturate injections. Unfortunately, no blood levels were available. Patient 2 received one high dose of pentothal; patient 3 received a continuous high dose administration of phenobarbital. No published data compare the effects of different antiepileptic schedules for SE in patients with DS. In our retrospective series, data were missing for 30% of the DS patients, and for the remaining 70%, no blood levels were available. Unfortunately, for the 2 patients reported by Oguni et al. with residual severe neurological deficits after prolonged SE, no data is given regarding the treatment used for the SE.[2]

Conclusion

Refractory SE may dramatically alter neurological outcome in DS. SE is frequent in this disease but rarely causes anoxo-ischemic lesions. There are theoretical reasons to suspect that barbiturates in DS could contribute to such brain damage. It seems reasonable to suggest avoiding thiopental in SE occurring in patients with DS and restraining the administration of barbiturates to failure of alternative possibilities, with strict monitoring of AEDs blood levels, especially for patients who receive polytherapy including compound that reduce barbiturate clearance.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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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

1. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy (Dravet syndrome). In: Roger J, Bureau M, Dravet Ch, Genton P, Tassinari CA, Wolf P, editors. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. 3rd ed. London: John Libbey; 2002. p. 81–103.
2. Oguni H, Hayashi K, Awaya Y, Fukuyama Y, et Osawa M. Severe myoclonic epilepsy in infants–a review based on the Tokyo Women's Medical University series of 84 cases. *Brain Dev* 2001;**23**(November (7)):736–48.
3. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O, Severe myoclonic epilepsy in infancy: Dravet syndrome in Delgado.Escueta AV, Guerrini R, Medina MT, Genton P, Bureau M, Dravet C, editors. *Advances in Neurology*, vol. 95. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 71–102.
4. Siegler Z, Barsi P, Neuwirth M, Jerney J, Kassav M, Jansky J, et al. Hippocampal sclerosis in severe myoclonic Epilepsy in Infancy: a retrospective MTI Study. *Epilepsia* 2005;**45556**(5):704–8.
5. Striano P, Mancardi MM, Biancheri R, Madia F, Gennaro E, Paravidino R, et al. Brain MRI findings in severe myoclonic epilepsy in infancy and genotype-phenotype correlations. *Epilepsia* 2007;**48**(June (6)):1092–6.
6. Fountain N. Status epilepticus: risk factors and complications. *Epilepsia* 2000; **Suppl. 2**:S23–30.
7. Novorol CL, Chin RF, Scott RC. Outcome of convulsive status epilepticus: a review. *Arch Dis Child* 2007 Nov;**92**(11):948–51.
8. Wiest R, Von Bredow F, Schindler K, Schauble B, Slotboom J, Brekenfeld C, et al. Detection of regional blood perfusion changes in epileptic seizures with dynamic brain perfusion CT—a pilot study. *Epilepsy Res* 2006;**72**(December (2–3)):102–10.
9. Coulter DA, DeLorenzo RJ. *Basic mechanisms of status epilepticus Advances in Neurology*, vol. 79. Philadelphia: Lippincott Williams and Wilkins; 1999pp. 725–733.
10. Nabbout R. Can SCN1A mutations account for SUDEP? *Epilepsia* 2008;**49**(February (2)):367–8.
11. Hindocha N, Nashef L, Elmslie F, Birch R, Zuberi S, Al-Chalabi A, et al. Makoff A Two cases of sudden unexpected death in epilepsy in a GEFS+ family with an SCN1A mutation. *Epilepsia* 2008;**49**(February (2)):360–5.
12. Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. *Lancet* 2000;**356**(November (9242)):1638–42.
13. Wada DR, Harashima H, Ebling W, Osaki EW, Stanski DR. Effects of thiopental on regional blood flows in the rat. *Anesthesiology* 1996;**84**(March (3)):596–604.
14. de Bray JM, Granry JC, Monrigal JP, Leftheriotis G, et Saumet JL. Effects of thiopental on middle cerebral artery blood velocities: a transcranial Doppler study in children. *Childs Nerv Syst* 1993;**9**(July (4)):220–3.
15. Van Gestel JP, Blussé. van Oud-Alblas HJ, Malingré M, Versvers FF, Braun KP, et al. Propofol and thiopental for refractory status epilepticus in children. *Neurology* 2005;**65**(August (4)):591–2.
16. Tanabe T, Awaya Y, Matsuishi T, Iyoda K, Nagai T, Kurihara M, et al. Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy–a nationwide questionnaire survey in Japan. *Brain Dev* 2008;**30**:629–35.