Clinical and Genetic Risk Factors for Acute Neurological Deterioration in Children with Dravet Syndrome

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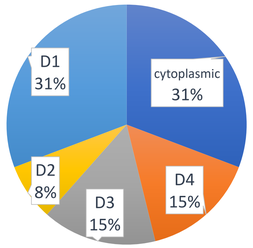
INTRODUCTION: Episodes of acute neurological deterioration, often precipitated by status epilepticus, have been reported in children with Dravet syndrome[1-4]. These may be associated with severe brain injury and cerebral oedema [4] which can prove fatal. Amongst survivors, a sustained developmental regression and/or emergence of new movement disorder may occur[1-3]. Despite the high morbidity and mortality associated with these episodes, little is understood about the risk factors for their occurrence. This case series explores clinical and genetic features of acute deterioration with resulting death or sustained neurological regression in 18 children with Dravet syndrome from 2 tertiary paediatric neurology centres in London.

METHODS: Retrospective case note review.

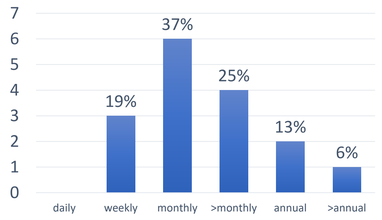
RESULTS:

Baseline Characteristics: 18 patients (11 male, 7 female) were identified. At deterioration, mean age was 59 months (range 5-129 months), 10/18 (55%) were under 5yrs, 6/18 (33%) were 5-10yrs and 2 were>10yrs (11%). 13 had genetics reports available for us to review; 12 mutations were missense and 1 truncating. At baseline, development was delayed in 14/18 (78%) whilst 4/18 (22%) had a movement disorder.

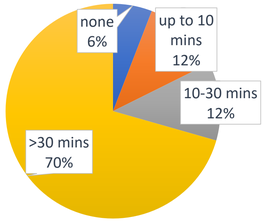
SCN1A variant location



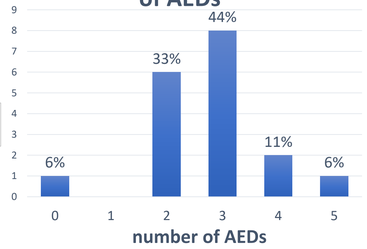
baseline convulsive seizure frequency



history of prolonged seizures

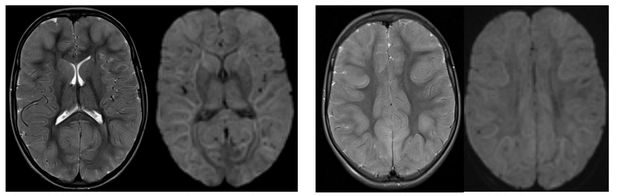


baseline number of AEDs

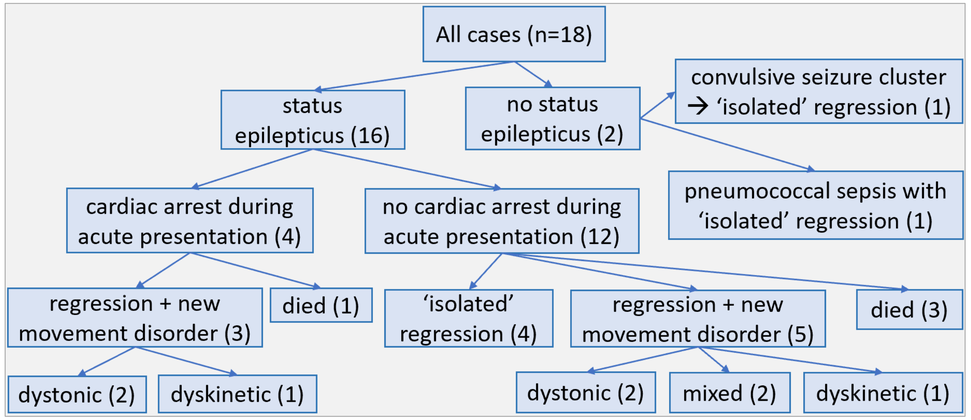


Details of Acute Deterioration: 17/18 (94%) cases had seizures as part of their acute deterioration (1 had pneumococcal sepsis without seizures and regressed with a new mixed dystonic dyskinetic movement disorder). 1/17 had a seizure cluster whilst 16/17 had convulsive status epilepticus. 4 (22%) children died; 1 had a cardiac arrest at presentation. Mean status epilepticus duration was 50 minutes (range 18-60). 9/18 (50%) were given phenytoin loading whilst 4/18 (22%) were on maintenance lamotrigine (2 of which were also given phenytoin loading). Fever occurred in all cases. 8/18 (44%) were positive for a respiratory virus and 2/18 (22%) had positive bacteriology (no CNS infection). Acute neuroimaging was normal in 2/18 (22%) cases and cerebral oedema was reported in 6/18 (66%). Signal change and/or diffusion restriction was reported in 14/18 (77%); this was global in 8/14 (57%) and bilateral but more localised in 4/14 (29%). Isolated acute cerebellar findings were reported in 2/18 cases. 16/18 had acute EEG, all reporting slowing/encephalopathy. Mean PICU admission duration was 8.8 days (range 2-23).

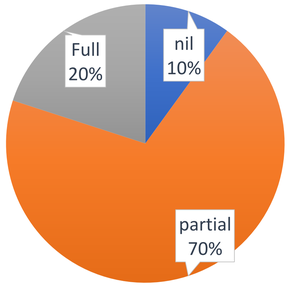
Follow-up: Median follow-up was 57 months (range 0-25yrs). Follow-up information was available in 10/14 survivors, of whom 1/10 (10%) had a sustained regression, 7/10 (70%) made a partial recovery and 2/10 (20%) recovered to baseline (both later had further deteriorations). All repeat MRI (n=5) showed cerebral atrophy/volume loss.



T2 and DWI images of a patient showing cerebral oedema with abnormal T2 signal of the cortex and subcortical white matter with diffusion restriction of the subcortical white matter



recovery at follow-up



DISCUSSION:

- Acute deteriorations in Dravet Syndrome occurred at a range of ages and prior seizure burdens
- 50% had phenytoin loading
- 6 had no cardiac arrest or inotropic requirement but had prolonged status epilepticus
- Majority of patients had febrile status epilepticus with respiratory viruses rather than severe sepsis
- Deterioration included developmental regression +/- movement disorder; isolated dystonic, isolated dyskinetic or mixed

CONCLUSION:

- Acute neurological deterioration in Dravet syndrome results in significant and usually permanent neurological deficit
- No variables were strongly predictive of an acute decompensation and death or persisting neurological regression
- Possible association between maintenance therapy and/or acute status epilepticus treatment with a sodium channel blocker
- All patients had prolonged (>30 min) seizures and/or significant haemodynamic compromise with cardiac arrest and/or requirement for inotropic support suggesting that adverse cerebral blood flow is likely to play a role
- More research is required to understand this uncommon but devastating phenomenon

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