**Supplementary information - Report of cases:**

Both cases fall within the general group of MEFS and this may be part of the clinical spectrum of disorders in which fever is associated with status epilepticus i.e. New-Onset Refractory Status Epilepticus (NORSE) or Febrile Illness Related Epilepsy Syndrome (FIRES)(1)

*Case 1:*

Case 1 was born at term, with a birth weight of 3kg. Developmentally he sat at 6-8 months, started walking at 13 months and by age 5 had learned to jump. He exhibited speech delay throughout and at the 2y 9-month assessment his language was at a 15-month level. At the age of 3, he presented with focal status epilepticus and continued to experience frequent partial seizures and a right hemiparesis. The initial presentation occurred 5 days after an influenza vaccination, whilst Case 1 was also experiencing a mild febrile illness. Initially he responded poorly to treatment with multiple antiepileptics, including thiopentone, methylprednisolone and IVIg, but was later treated with Co-Enzyme Q with reasonably good effect in that stopping the drug coincided with recurrence of on epilepsy one occasion.

Investigations revealed a transient left thalamic lesion on Magnetic Resonance Imaging (MRI) with subsequent progression of white matter T2 hyperintensity on repeat scans. An active left frontotemporal epileptogenic focus was identified on EEG. Blood lactate was 2.7mmol and blue native gel electrophoresis revealed borderline low complex IV activity. Muscle biopsy demonstrated variable muscle fibre size and type II atrophy and an increased lipid content, muscle mtDNA content being 33% of expected (borderline low). Mitochondria were prominent consistent with long mitochondria in fibroblasts. Neonatal and developmental myosins were negative and cardiac echocardiogram showed a grossly normal structural heart with a systolic ejection fraction of 53%.

Molecular genetic analysis of 17 genes implicated in autosomal disorders of mitochondrial DNA maintenance, *SCN1A* analysis and whole mitochondrial genome sequencing did not reveal any pathogenic variants. Subsequent whole exome sequencing and genetic analysis of family members was therefore undertaken, revealing a *de novo* heterozygous missense mutation in *DNM1L*, NM\_012062.4: c.1207C>T p.Arg403Cys.

In summary, Case 1 represents a case of severe frontotemporal epilepsy in childhood, in the context of a febrile illness, with persistent right hemiparesis, mild ptosis and mild learning and behavioural difficulties. Raised muscle lipid and reduced mitochondrial DNA content is seen, together with mild non-specific thalamic abnormalities, a *de novo* mutation in *DNM1L.* He was treated with carbamazepine and clobezam with reasonable therapeutic efficacy as well as Co-Enzyme Q. Ketogenic diet was not used (2, 3).

*Case 2:*

Case 2 was referred to a tertiary neurology service at the age of 7. He was born at term by normal delivery, but concerns were raised at a young age regarding his global development. Case 2’s speech and language was delayed, he walked only at 18 months and was later diagnosed with autistic spectrum disorder.

At the age of 5, he presented with infrequent asymmetric generalised tonic-clonic epileptic seizures [GTCS], provoked by febrile illness and exercise. EEG demonstrated age appropriate background activity and no epileptiform discharges. A year later he developed focal status epilepticus and suffered a further protracted episode of convulsive status epilepticus two days later that required intubation, ventilation and a three-week stay in intensive care. Following this admission, he demonstrated significant neurodevelopmental regression and was subsequently referred to local paediatric services when he failed to regain lost skills. Initially he was unable to walk, his swallow was impaired and he only regained speech six months later.

Epilepsia partialis continua [EPC], affecting the right side of the face, was effectively managed with a short course of clobazam. He continued to have brief, self-limiting, focal right-sided facial clonic seizures associated with left frontal ictal onset on EEG and developed non-convulsive status epilepticus, [NCSE], associated with bilateral slow spike waves. Both seizure types responded well to clobazam. Occasionally he suffered convulsive GTCS episodes, precipitated by fever, which were reasonably controlled with levetiracetam, carbamazepine and clobazam. Clinical examination revealed mild gait ataxia and slight upper limb spasticity, with restriction of saccadic and pursuit vertical eye movements. Cardiac and ophthalmological assessments were unremarkable.

Comparative brain MRI scans pre- and post- the protracted status epilepticus episode demonstrated normal morphology and myelination but evidence of global bilateral cerebral volume loss. Investigations initially tailored towards a mitochondrial disease or Niemann Pick C revealed a random plasma lactate of 2.5mmol/L., muscle biopsy showed mild type 2 fibre atrophy, prominent lipid in type 1 fibres and rare cytox-negative SDH positive fibres. Mitochondria were prominent consistent with long mitochondria in fibroblasts. Respiratory chain enzymes and oxysterol levels were normal and negative gene sequencing of *NPC1* and *NPC2*. *POLG* sequencing, biotinidase activity and very long chain fatty acid profile were also normal. Muscle mtDNA copy number was normal at 71% of expected. However, subsequent genomic testing and Sanger sequencing demonstrated a *de novo* heterozygous missense mutation in *DNM1L*, NM\_012062.4: c.1207C>T p.Arg403Cys.

In summary, Case 2 represents a case of global developmental delay, with early childhood onset focal epilepsy and an episode of febrile illness-induced status epilepticus. Bilateral cerebral volume loss and a raised lactate are seen with a normal muscle biopsy in the context of a *de novo* heterozygous *DNM1L* mutation.

**References**

1. Hirsch LJ, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia. 2018.

2. Nabbout R, Mazzuca M, Hubert P, Peudennier S, Allaire C, Flurin V, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). Epilepsia. 2010;51(10):2033-7.

3. Appavu B, Vanatta L, Condie J, Kerrigan JF, Jarrar R. Ketogenic diet treatment for pediatric super-refractory status epilepticus. Seizure. 2016;41:62-5.