Bristol Royal Hospital For Children

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Acute Liver Failure in the Context of Refractory Status Epilepticus and Devastating Neurological Injury: Three Cases.

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Introduction

Although rare, an association between refractory status epilepticus and liver injury has been reported. However, its mechanism is not fully understood and its prognostic implications are unknown (1, 2).

Case 1

Presentation

An 18-month-old presented with **febrile status epilepticus**. She had a neuronal sodium channelopathy (**SCN2A mutation**). Her phenytoin dose had recently been weaned due to a mild transaminitis.

She was **haemodynamically unstable** requiring adrenaline and noradrenaline infusions. She was **hypoglycaemic** and **coagulopathic**, INR 2.0. Initial CT head showed no acute abnormalities.

PICU Course

Haemodynamic status rapidly improved. She had further seizures, treated with a midazolam infusion.

Severe **transaminitis** became evident on day 4 (peak ALT 9808 U/L), with associated **coagulopathy** (INR 4.2). A liver USS showed acute inflammatory changes. Phenytoin and carbamazepine were discontinued due to hepatotoxicity.

Seizures recurred on attempts to wean sedation. An MRI head showed **widespread hypoxic-ischaemic insult**.

The patient developed heart rate and blood pressure instability of unclear cause. On day 7 there was a clinical **coning event**, confirmed radiologically. The decision was made to re-orientate care and the patient passed away.

Case 2

Presentation

A 15-month-old girl with **DiGeorge** syndrome presented with **low GCS, eye rolling and extensor posturing**. She was **hypoxic** (SpO2 54%) and **pyrexial**. She required IV dextrose and glucagon for **profound hypoglycaemia** (1.5mmol/L).

Following benzodiazepines and levetiracetam she was intubated due to persistent unresponsiveness.

PICU Course

During the first 24h she had ongoing seizures treated with phenobarbital and escalating midazolam infusion. She was **haemodynamically unstable** requiring adrenaline and noradrenaline infusions. She had a persistent **metabolic acidosis** and **hyperlactataemia**.

Inflammatory markers were significantly raised, with peak white cell count of $27.7*10^9$/L, CRP 105mg/L and procalcitonin 62.8ng/mL.

MRI head showed **diffuse injury affecting the entire supratentorial cortex** and deep grey nuclei.

Transaminitis developed on day six (Peak ALT 504U/L).

There were multiple unsuccessful attempts to wean anti-epileptic infusions. Repeat CT head on day 7 showed catastrophic progression of injury. Life-sustaining treatment was withdrawn and the patient passed away. Investigation results received post-mortem revealed a **TANGO-2** gene mutation, which can be associated with a metabolic encephalopathy.

References

1. Decell,M K et al. “Fulminant hepatic failure associated with status epilepticus in children: three cases and a review of potential mechanisms.” Intensive care medicine vol.20,5(1994):375-8. eMed 1994;20:375–8.
2. Sahin,M et al. “Outcome of severe refractory status epilepticus in children.” Epilepsia vol.42,11(2001):1461-7

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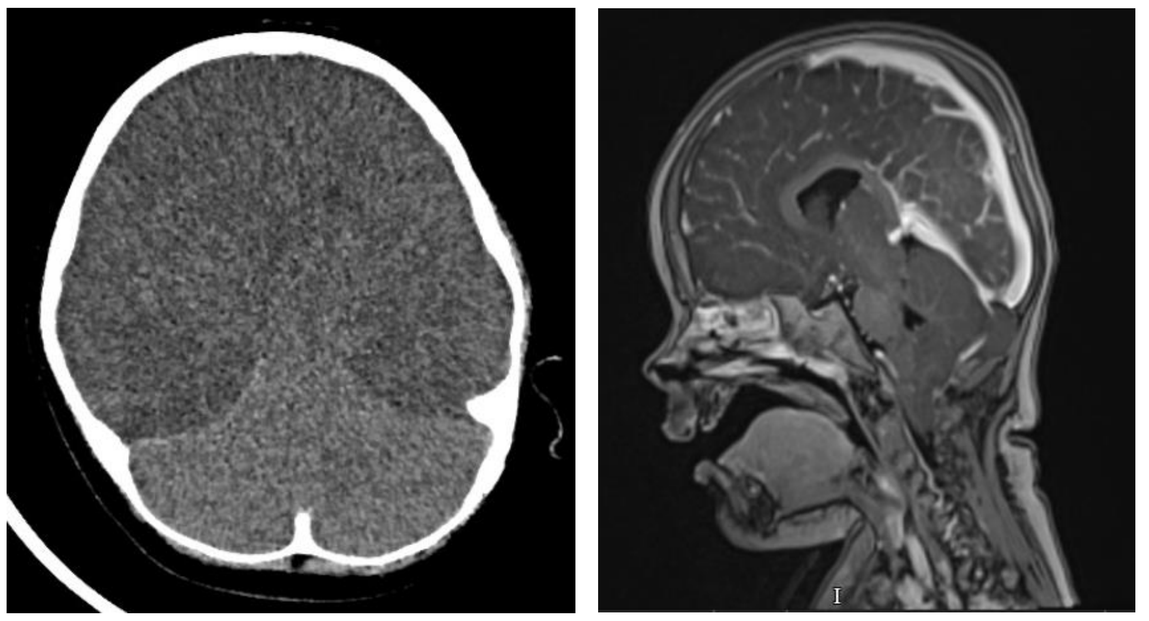


Neuroimaging from case 1 showing (a) global hypoxic ischaemic injury with "reversal sign" and (b) cerebellar tonsillar descent through the foramen magnum.

Case 3

Presentation

A 6-year-old with **chromosomal translocation t(2;8)** presented with a **generalised tonic-clonic seizure**, terminated with benzodiazepines, paraldehyde and phenytoin. Initial bloods and neuroimaging (CT and MRI) were unremarkable.

Over the following days there were concerns about **non-convulsive status epilepticus** due to **fluctuating GCS**. He was intubated and admitted to PICU.

PICU course

Seizures continued despite increasing midazolam infusion and levetiracetam.

Transaminitis developed on day 5 of admission: ALT 2792 U/L, AST 579 U/L, GGT 300 U/L. Liver synthetic function was unaffected.

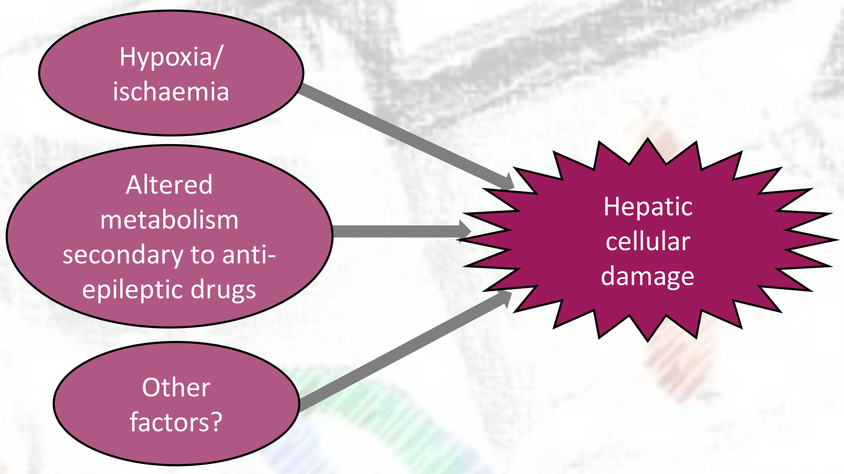
After initial reluctance to initiate additional anti-epileptics due to the transaminitis, phenobarbital ultimately achieved seizure control.

An MRI head performed 2 days after PICU admission showed appearances consistent with ischaemic leukoencephalopathy caused by a **diffuse severe hypoxic-ischaemic event**, felt to have been in evolution for a period of time, with grave prognostic implications. The decision was made for withdrawal of life-sustaining treatment and the patient passed away.

Discussion

- All three patients had underlying genetic abnormalities associated with seizures. However, none had a history of refractory seizures, and the degree of neurological injury was unexpected and devastating.
- For two patients, anti-epileptic choice was affected by the presence of liver dysfunction.
- Our patients had evidence of systemic metabolic compromise (hypoglycaemia, acidosis, hyperlactataemia).

- The association between refractory status epilepticus and liver dysfunction is likely due to the combined effect of multiple factors.



- A better understanding of this association may help to identify patients at risk and inform treatment decisions in refractory status epilepticus.