Clinical commentary

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Hemiconvulsion-Hemiplegia-Epilepsy in a girl with cobalamin C deficiency

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ABSTRACT – Hemiconvulsion-Hemiplegia-Epilepsy initially involves an infantile presentation of febrile focal motor status epilepticus, with subsequent hemiplegia of the initially affected side. Months to years later, affected children go on to develop a chronic epilepsy with recurrent focal seizures which are often refractory to treatment. This uncommon paediatric epilepsy syndrome is poorly understood, with only a very small minority of cases associated with an underlying genetic or metabolic abnormality.

We present a four-year-old girl with genetic cobalamin C deficiency who had a dramatic presentation with Hemiconvulsion-Hemiplegia-Epilepsy. She had febrile focal status epilepticus, with right hemiconvulsive seizures for nearly 10 hours, ultimately requiring a midazolam infusion. Over subsequent days, she developed progressively worsening cerebral oedema, leading to herniation and requiring a craniectomy to relieve pressure.

This girl's presentation is the first association of cobalamin deficiency with hemiconvulsion-hemiplegia-epilepsy; and illustrates the importance of considering this entity when patients with this metabolic disorder present with acute deterioration. More importantly, the case also raises the possibility that derangements of cobalamin metabolism could be a contributing factor in cases of hemiconvulsion-hemiplegia-epilepsy, as well as febrile seizures in general.

Key words: cobalamin C deficiency, Cblc, cobalamin, B12, Hemiconvulsion-Hemiplegia-Epilepsy, status epilepticus, febrile, HHE

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Hemiconvulsion-Hemiplegia-Epilepsy (HHE) is a paediatric epilepsy syndrome characterized by a dramatic infantile presentation of hemiconvulsive febrile status epilepticus, which is refractory to medical therapy and may last many hours, or even days (Gastaut *et al.*, 1960). Patients subsequently develop a persistent hemiparesis. The characteristic imaging findings involve diffuse restricted diffusion in the affected hemisphere, which later evolves to atrophy. Months to years later, patients develop a chronic epilepsy. At first, seizures are focal, originating from the initially affected region, however, seizures from the contralateral hemisphere may later develop, including a hemi-Lennox Gastaut-like syndrome from the originally unaffected hemisphere (Saito *et al.*, 2013; Myers *et al.*, 2018).

At present, the underlying aetiology of HHE remains poorly understood. In most cases, the cause is unclear, though there are individual reports of associations with several genetic/metabolic conditions, including congenital adrenal hyperplasia, 1q43-q44 deletion, 16p13.11 deletion, L-2-hydroxyglutaric aciduria, protein S deficiency, factor V Leiden, and mutations in *SCN1A* and *CACNA1A* (*see references in supplementary material*). Here, we present a dramatic HHE presentation, occurring in a girl with cobalamin C deficiency (cblC).

Case study

A four-year-old girl with cblC had a complicated past medical history. During the pregnancy, she was noted to have *in utero* growth retardation. She was born at 38 weeks gestation by Caesarian section due to breech presentation. As a neonate, she had hypotonia, microcephaly, pancytopenia, and congestive heart failure; the latter improved following surgery for correction of ventricular septal defect, atrial septal defect, and patent ductus arteriosus. Hydrocephalus was diagnosed at age 2.5 months on a head ultrasound performed for apnoeas and seizures. A right ventriculoperitoneal (VP) shunt was placed, but apnoea and seizures did not immediately improve.

Due to her multiple medical issues, a broad metabolic work-up was undertaken at two months of age, revealing a combined methylmalonic acidaemia and hyperhomocysteinaemia. CblC was subsequently confirmed with molecular genetic testing revealing homozygous c.271dupA (p.Arg91Lysfs*14) mutation in *MMACHC*. Other genetic testing, including traditional karyotyping, comparative genomic hybridization microarray, and Prader-Willi/Angelman methylation testing, was all normal. Prior charts were reviewed, but results of new-born screening could not be located. She was treated with betaine, intramuscular hydroxocobalamin injections, and folic acid. She had moderate global developmental delay. She was the only child of French-Canadian parents, with no known consanguinity. There was no known family history of seizures or developmental impairment.

EEG at 2.5 months showed a severely abnormal pattern with marked discontinuity and multifocal epileptiform discharges, at times reminiscent of burst suppression. Over a 24-hour period, approximately 50 focal electrographic seizures were captured, originating from many different foci over both hemispheres. The majority were subclinical, however, rhythmic eye and mouth movements were seen with some events. Brain MRI at this time showed a thin corpus callosum, severe hydrocephalus, and unusual appearance of the pons and cerebellum; a repeat study at 26 months showed considerable interval improvement in the latter two abnormalities (*see supplementary material*).

The girl was treated with phenytoin which controlled seizures, and this medication was later weaned. At 2.5 years, she presented with episodes of falling; the EEG correlate of these events showed that they were focal seizures, likely originating from the left frontocentral region. Levetiracetam was started and reduced seizure frequency. At 3.5 years, she was diagnosed with myoclonic seizures; the interictal EEG now showed generalized epileptiform discharges, with multifocal epileptiform discharges still present. Valproic acid was added and seizures were eventually completely controlled. The valproic acid was subsequently weaned by parents because of the good seizure control, but she remained on levetiracetam.

Days after her fourth birthday, she presented acutely with refractory hemiclonic febrile status epilepticus. Her fever was 40.5°C on presentation to the emergency department, and she was found to have decreased awareness, left-deviated gaze and left head version, and non-suppressible movements of the right arm. Her seizures continued for approximately 10 hours despite treatment with phenobarbital, phenytoin, and a midazolam infusion. EEG recording did not begin until just under 10 hours after her initial presentation; at that point, she had left-hemisphere periodic lateralized epileptiform discharges (PLEDs) which correlated with jerks of her right arm (*figure 1A*). The jerks stopped with increase of the midazolam infusion, but the EEG did not significantly change.

Brain CT on Day 1 of admission showed diffuse hypodensity and loss of grey-white differentiation over the left hemisphere. Brain MRI on Day 2 showed diffuse cytotoxic oedema over the entire left hemisphere (*figure 2A-C*), with normal arterial appearance on magnetic resonance angiography. Over the following three days, the left hemisphere PLEDs resolved but high-amplitude diffuse slowing appeared over the right hemisphere (*figure 1B*), raising suspicion that the right hemisphere was becoming compromised.

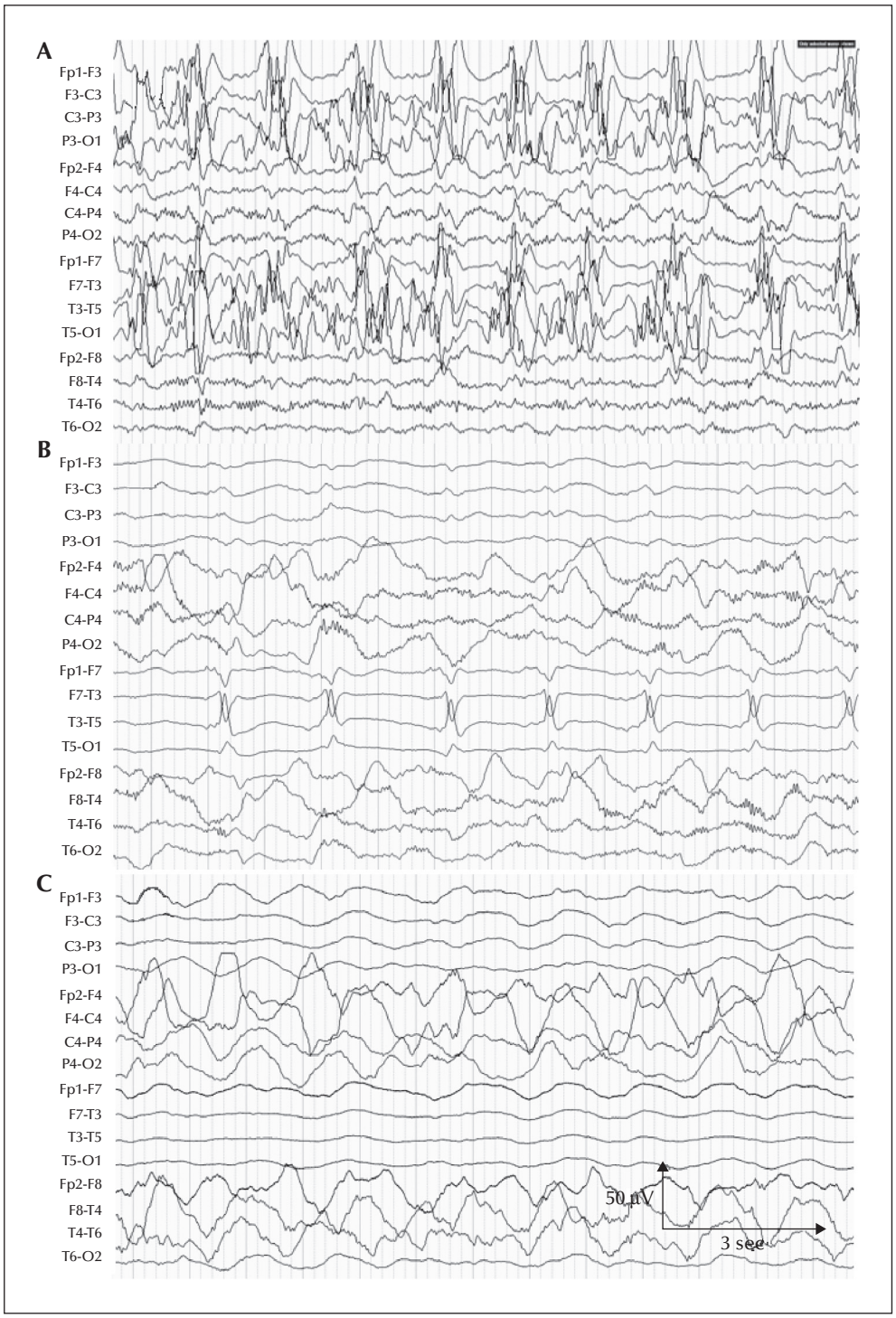

Figure 1. EEG following status epilepticus presentation. On Day 1 of acute presentation, EEG showed periodic lateralized epileptiform discharges (PLEDs) over the left hemisphere (A). By Day 3, the PLEDs were more localized over the left temporal region, and higher amplitude slowing had developed over the right hemisphere (B). By Day 4, left-sided PLEDs had resolved, replaced with diffuse suppression, and high-amplitude polymorphic slowing continued over the right hemisphere (C).

No electrographic seizures were seen. She remained intubated in the paediatric intensive care unit. Neurosurgery was consulted to sample CSF from the VP shunt reservoir to rule out VP shunt infection, and to consider inserting an intracranial pressure (ICP) monitor. The CSF did not show signs of infection. The ICP

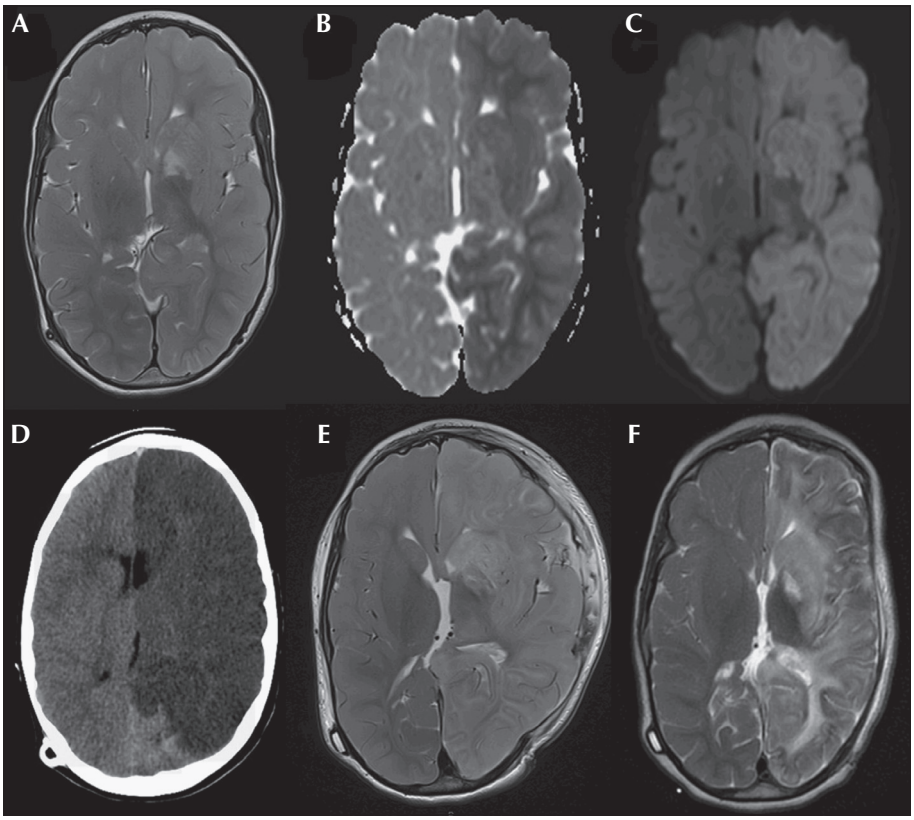

Figure 2. Neuroimaging following status epilepticus presentation. Brain MRI on Day 2 of acute presentation showed diffuse cytotoxic oedema of the left hemisphere, demonstrated by hyperintensity on T2-weighted sequences (A), hypointensity on apparent diffuse coefficient mapping (B), and hyperintensity on diffusion weighted imaging sequences (C).
Head CT on Day 5 demonstrated increased swelling of the left hemisphere, now with herniation causing mass effect on the right hemisphere (D). This pressure was partially alleviated by a left craniectomy (E). Repeat T2-weighted MRI, 39 days after initial presentation, showed resolution of the mass effect and early signs of left hemisphere atrophy (F).

monitor was not inserted due to concerns of introducing a shunt infection, and it was felt that her functioning VP shunt would protect her to some degree from any potential ICP increase. In addition, it was thought that she could be followed closely with repeat imaging and clinical examination despite sedation and intubation.
On examination, on Day 4, her pupils were equal and reactive, and she was spontaneously and purposefully moving the left arm and leg, such that she required more sedation to keep her calm. However, on Day 5, her left pupil became fixed and dilated and her spontaneous movements ceased. An urgent CT showed clear left-sided uncal herniation from progressive cerebral oedema of the affected hemisphere. As such, a large left-sided decompressive craniectomy was performed to relieve the pressure (*figure 2D-E*) and an ICP monitor was inserted for a brief period. Immediately postoperatively, she was more awake, her left pupil was reactive again, and her ICP was within the low-normal range.
At the time of her initial presentation with status, serum homocysteine was elevated at 37.0 μmol/L (reference range: 4.6-15.5), though this was not changed from her typical baseline levels. Nasopharyngeal swab viral polymerase chain reaction was positive for coronavirus 229E, thought to be the cause of her fever. Follow-up brain MRI, 39 days following initial presentation, showed early atrophy of the left hemisphere (*figure 2F*). Clinically, she had a persistent right hemiparesis affecting the arm and leg. Her bone flap was replaced one month after surgery and she continued to improve slowly with full rehabilitation services. She was seizure-free at discharge on levetiracetam and clobazam, but four months following her acute HHE presentation, she developed episodes of suspected focal impaired awareness seizures involving ~10 seconds of behavioural arrest with jerking movements of the left side of her body.

Discussion

The patient presented acutely with very prolonged, refractory hemiclonic febrile status epilepticus, unilateral cytotoxic oedema, and subsequent

hemiparesis; the classic features of HHE. Although a viral illness provoked the episode, premature weaning of valproic acid likely increased susceptibility. Her clinical course was severe in that she developed malignant cerebral oedema leading to herniation, requiring craniectomy to relieve pressure. This occurred despite her already having a shunt in place which should have allowed for some additional protection from increasing intracranial pressure. The patient had pre-existing epilepsy, so the presentation is not completely classic, as some authors feel the refractory febrile status epilepticus should be the initial seizure presentation (Panayiotopoulos, 2016), however, recent reviews have not outlined this as a mandatory criterion (Auvin *et al*., 2012).

This is the first report of HHE in cblC, a rare inborn error of metabolism in which patients have impaired conversion of dietary vitamin B_{12} into its metabolic active forms, methylcobalamin and adenosylcobalamin, resulting in combined methylmalonic acidaemia and hyperhomocysteinaemia. The overall frequency of epilepsy is approximately 25-50% (Wang *et al*., 2010; Weisfeld-Adams *et al*., 2013). The epilepsy phenotype is variable, with focal seizures being the most common presentation, occurring in ~70-80% of patients with epilepsy (Biancheri *et al*., 2002; Ma *et al*., 2011). Focal or generalized status epilepticus occurs in roughly a third of patients (Biancheri *et al*., 2002; Ma *et al*., 2011). Other seizure types reported less commonly in cblC are generalized tonic-clonic, myoclonic, tonic, and epileptic spasms (Biancheri *et al*., 2002; Ma *et al*., 2011; Weisfeld-Adams *et al*., 2013).

Despite the rarity of cblC, this patient's presentation may have broader implications for our understanding of the underlying pathophysiology of HHE. A study of febrile seizures found that serum B_{12} levels were lower in children with febrile seizures, with lower folic acid levels predicting febrile seizure recurrence (Ozkale *et al*., 2015). Exactly how abnormalities of the B_{12}/folate pathway would increase febrile seizure risk is unclear, however, B12 deficiency can lead to symptoms of dementia (Smith and Refsum, 2016), indicating that global cerebral dysfunction is a possible consequence of imbalances in this metabolic pathway.

More subtle derangements of the B_{12}/folate pathway may be a contributing factor in cases of HHE. Elevated serum homocysteine is a known risk factor for stroke, and can increase oxidative stress and cause endothelial dysfunction (Welch and Loscalzo, 1998). Post-ictal hypoperfusion is a well-recognized event following seizures (Farrell *et al*., 2017). In the context of already impaired blood flow, tissue damage may be exacerbated with hyperhomocysteinaemia, and could lead to the dramatic restricted diffusion seen in HHE. Of course, much more research is necessary to thoroughly explore this hypothesis.

Conclusion

We present a girl with cblC and epilepsy, who subsequently presented with HHE. This rare epilepsy syndrome has only been associated with a small number of genetic/metabolic anomalies, and cblC can now be added to this short list. All patients presenting with HHE should have a genetic and metabolic work-up; our case emphasizes that investigations should always include tests for cobalamin deficiency, including serum homocysteine and methylmalonic acid. □

Supplementary data.
Supplementary materials are available on the www.epilepticdisorders.com website.

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None of the authors have any relevant conflict of interest to declare.

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TEST YOURSELF

(1) The initial presentation of HHE is:
A. Progressive hemiplegia
B. Febrile hemiclonic status epilepticus
C. Multifocal myoclonic jerking
D. Developmental regression

(2) In HHE, chronic epilepsy most commonly:
A. Does not develop
B. Develops days after the initial acute presentation
C. Develops months to years after the initial acute presentation
D. Initially involves generalized seizure types

(3) Which of the following statements is false regarding HHE?
A. The acute HHE presentation may be confused with ischaemic stroke
B. The cytotoxic oedema seen during acute HHE presentation can lead to a mass effect and cerebral herniation
C. The acute HHE presentation is most often provoked by common viral illnesses
D. The majority of HHE cases are caused by *SCN1A* mutations

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".