CASE REPORT

Forgetting to remember: hypoglycaemic encephalopathy

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SUMMARY

A 37-year-old woman with a history of poorly controlled type 1 diabetes presented acutely with a decreased Glasgow Coma Scale and a diagnosis of hypoglycaemic brain injury. Her MRI highlighted bilateral hippocampi diffusion restriction and T2 hyperintensity. Clinically, she had a marked cognitive deficit, particularly of short-term, anterograde amnesia. She was managed conservatively and with intensive rehabilitation.

BACKGROUND

1. This report examines a case of decreased Glasgow Coma Scale in a patient using excessive insulin. It highlights the importance of early management of hypoglycaemia and the long-term cognitive effects of bilateral hippocampal involvement.
2. It highlights the importance of requesting the appropriate investigations in a timely fashion. In this particular case, the MRI was crucial for the diagnosis.
3. It describes the 'hippocampal amnesic syndrome', which is characterised by anterograde and autobiographical amnesia.

CASE PRESENTATION

A 37-year-old woman with a background of poorly controlled type 1 diabetes and depression presented to the emergency department after being found unresponsive by her partner. After a night apart, her husband awoke to find her slumped in the living room. On arrival of the ambulance crew, a capillary glucose of 2.4 mmol/L was detected and also signs of recent subcutaneous insulin use were noted.

On arrival, a formal Glasgow Coma Scale (GCS) was recorded as 11/15 (E4V1M6). Baseline biochemical investigations were normal; venous glucose was recorded as 5.8 mmol/L. She had a pH value of 7.4 and a bicarbonate value of 21.3 mmol/L. Her blood alcohol level and toxicology tests were normal.

History from the family revealed a slowly progressive mood disorder associated with increased alcohol intake and weight loss over 1 year. She was known to mental health services and had recently started an antipsychotic. Previous suicidal ideation was unknown.

On examination at 12 hours postadmission she was agitated, pulling at her mask and nasal cannula. She had no motor or sensory neurological deficit; however, she was only able to answer in short,

one-word comments. No other abnormalities to bodily systems were detected.

A CT head was performed on arrival (figures 1 and 2). It was reported as normal; however, on further evaluation, it showed a subtle left hippocampal hypodensity. Since the patient continued to be unwell, an MRI was performed, clarifying the diagnosis. It revealed a symmetrical, bilateral T2 and T2 FLAIR hyperintensity within the postero-medial hippocampi associated with partial diffusion restriction (figures 3–5). She was diagnosed as having hypoglycaemic encephalopathy (HE) with bilateral hippocampi involvement secondary to profound hypoglycaemia.

Approximately 1 week after admission, formal examination revealed a marked cognitive deficit, particularly of short-term, anterograde amnesia. Formal Abbreviated Mental Test Score (AMTS) was

Figure 1 CT shows a subtle hypodensity in the left hippocampal area (most likely the initial oedema secondary to hypoglycaemia).

Figure 2 CT shows a subtle hypodensity in the left hippocampal area (most likely the initial oedema secondary to hypoglycaemia).

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Figure 3 MRI demonstrates bilateral, symmetrical hippocampi involvement secondary to profound hypoglycaemia.

Figure 4 MRI demonstrates bilateral, symmetrical hippocampi involvement secondary to profound hypoglycaemia.

Figure 5 MRI demonstrates bilateral, symmetrical hippocampi involvement secondary to profound hypoglycaemia.

recorded as 4/10. She became easily disoriented when mobile. Her speech had returned to baseline, and she was able to follow multiple stage commands and converse with complex language.

On the basis of her presenting symptom, paramedic findings and MRI results, her diagnosis was consistent with hypoglycaemic brain injury, with bilateral involvement of the hippocampi. She was managed conservatively with intensive rehabilitation and a change in her insulin regime from a basal bolus to a twice-daily regime. Her antidepressive and antipsychotic medications were

increased. During her admission, she steadily improved, but continued to present severe anterograde amnesia.

INVESTIGATIONS

- ▶ MRI head
- ▶ Blood glucose levels (capillary, venous)
- ▶ Arterial blood gas
- ▶ Toxicology screen

DIFFERENTIAL DIAGNOSIS

- ▶ Insulin overdose
- ▶ Drug/alcohol toxicity
- ▶ Intracerebral event
- ▶ Traumatic brain injury
- ▶ Suicide attempt

TREATMENT

- ▶ Continuous cognitive-behavioural therapy
- ▶ Occupational therapy and physiotherapy on a daily basis on the ward
- ▶ Change of insulin regime and review by diabetic specialist nurse and endocrinology

OUTCOME AND FOLLOW-UP

Currently, she receives on-going rehabilitation but remains to have a cognitive deficit. She has on-going input from mental health and remains on appropriate medication. Her blood sugars remain well managed on her new insulin regime, and no further hypoglycaemic events have occurred.

DISCUSSION

Profound hypoglycaemia can cause irreversible central and peripheral nervous system damage. The brain is very susceptible to hypoglycaemia; hence, damage can ensue even after short and severe hypoglycaemic episodes. In the central nervous system, damaged mitochondria, increased intracellular calcium, increased superoxide dismutase (free radical) production, increased release of aspartate and glutamate from the presynaptic terminal can all lead to neuronal death.¹

The blood-brain barrier (BBB) has limited glucose transport activity. Glucose levels in the brain interstitial fluid are only one-fifth of those in serum; therefore, the brain is especially vulnerable to hypoglycaemia. Any disruption in the BBB (eg, caused by hypoglycaemia) will lead to metabolic dysfunction.

Once it reaches 3.0 mmol/L, widespread EEG changes appear. At 2.8 mmol/L, cognitive decline ensues with inability to perform complex intellectual tasks and when <1.5 mmol/L (severe neuroglycopenia), consciousness is impaired and convulsions and coma may appear. With a glucose value of 2.4 mmol/L on arrival, the patient was clearly impaired, aggressively agitated and unresponsive to verbal interrogation. No seizures were witnessed. A full neurological examination was impossible. The first CT scan report did not mention ischaemic, haemorrhagic or metabolic injuries; however, on more detailed evaluation there was a subtle hypodense lesion in the left hippocampal region, which, in hindsight, most likely represents the initial stages of hypoglycaemic injury. No oedema or midline shift was noted. The MRI performed 2 days later revealed bilateral, symmetrical, hippocampal injury, most evident on T2-WI, corresponding to hypoglycaemic damage.

MRI is the most essential tool for diagnosing HE. Typically, reversible cytotoxic oedema is detected² (DWI/ADC) in the cerebral cortex,³ hippocampus,⁴ splenium,⁵ internal capsule⁶ and subcortical white matter; most hypoglycaemic lesions

correspond to areas of reversible cytotoxic oedema as seen on DWI, which can predict the prognosis according to the degree of lesion extent.⁷ T2 and T2 FLAIR symmetrical hyperintensities correlate with the areas of damage. DWI is very important to predict the outcome.^{8–10}

From a clinical perspective, the most disabling feature was anterograde amnesia, a common consequence of bilateral hippocampus lesions. The hippocampus is the 'gateway' through which new memories become permanent ones. The so-called 'hippocampal-amnesic syndrome' results in a reduced capacity to consciously (explicitly) recall facts and events (declarative memory). However, unconscious (implicit) memories such as well-known skills and tasks (procedural memories) are unaffected. Our patient, for example, was able to use a phone (procedural memory) but was incapable of remembering whom she needed to call (explicit memory). Or, she remembered having a 'sugar problem' but not that she required insulin to control it. She also had tremendous difficulty remembering certain important people and personal circumstances (and events) of her past life (autobiographical memory).

The most limiting factor of her anterograde amnesia was her inability to recall what she had eaten throughout the day and the fact that she required insulin to control her diabetes. She became increasingly frustrated with her own limitations. Approximately 15 min after being told that she must eat healthy, avoid dietary sugar and that she must consistently use her insulin, she was unable to recall that conversation. Unfortunately, due to the location of the cerebral damage, the severity of her amnesia is unlikely to improve with time. Hyperintensities detected in corpus callosum or internal capsule lead to a more favourable

outcome^{11–12} than lesions in cerebral cortex, basal ganglia or hippocampus^{13–16}

Recurrent episodes of hypoglycaemia affecting the brain have a multitude of effects. Among the most important, it can cause long-term cognitive dysfunction and hippocampal oxidative damage despite an enhanced expression of Nrf2. It has been suggested that hypoglycaemia induces an Nrf2-dependent anti-oxidant response in the hippocampus, which counteracts oxidative damage. However, in persons with type 1 diabetes, this neuroprotective mechanism is insufficient to prevent neuronal oxidative damage, resulting in chronic deficits in working and long-term memory.¹⁷

Contributors CC (neurologist and stroke consultant) and TDM (CMT1) dealt with the case. They admitted her from the AE/EADU and continued her care on their ward. They discussed her case on a daily basis and arranged for investigations together. They also had a daily ward round evaluating her progression. All the information regarding her medical care was obtained by them, with her permission, from their daily assessments and from her health records from their system and from her general practitioner. The discussion of the paper was carried out by CC and the clinical presentation by TDM.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- The posterior region of the brain lacks self-regulatory mechanisms to reduce the risk of hypertensive-bleeds (which can lead, eg, to PRES), and the anterior portions of the brain are more susceptible to metabolic derangements. In the latter, the cerebellum and brainstem remain unaltered because of the effectiveness of the glucose transport mechanisms.
- MRI is the essential tool when diagnosing hypoglycaemic encephalopathy (HE). It must show symmetrical involvement of the medial temporal lobe, hippocampi, caudate nucleus and/or putamen.
- DWI is very useful in the setting of HE: it detects brain regions of selective vulnerability to hypoglycaemia and regions of early (and subtle) involvement. Importantly, it heralds the overall prognosis in HE.
- Bilateral hippocampal damage can cause anterograde amnesia, mainly for explicit memory (with preservation of implicit memory).

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