Recurrent hypoglycaemia and cognitive impairment: a 14-year follow up

Introduction

Acute amnesia in association with episodes of hypoglycaemia is well recognized, presumably reflecting the vulnerability of normal hippocampal function to low blood sugar. Whether this contributes to chronic cognitive impairment in people with diabetes is uncertain, few cases with long-term follow up having been reported (Chalmers et al, 1991; Holemans et al, 2001; Kirchhoff et al, 2013). This article presents 14-year follow up on a diabetic patient with amnesia associated with hypoglycaemia, previously reported only in abstract (Larner et al, 2003).

Discussion

Profound hypoglycaemia may cause acute amnesia (Fisher, 2002), but few reports of diabetic patients with hypoglycaemia-associated amnesia with longitudinal neuropsychological assessment have appeared (e.g. Chalmers et al, 1991), some with acute bilateral hippocampal lesions (Holemans et al, 2001). Kirchhoff et al (2013) reported a patient with multiple hypoglycaemic episodes over many years whose neuropsychological assessment showed anterograde amnesia; volumetric magnetic resonance brain imaging showed atrophic change including loss of subcortical grey matter volume including the hippocampus.

When initially reported (Larner et al, 2003), hippocampal vulnerability to acute neuroglycopaenia was suggested to account for the selective deficit of anterograde memory and learning in this patient which reversed gradually although incompletely over months. It seems likely that his subsequent cognitive decline was also a consequence of repeated hypoglycaemic episodes, in view of the temporal association of marked cognitive decline with repeated episodes over 8 months, the relative stability of cognitive function over subsequent years free of hypoglycaemic episodes, and the similarities with the patient of Kirchhoff et al (2013).

Another possibility meriting consideration is autoimmune encephalitis. Autoantibodies to various pancreatic islet cell autoantigens may be detected in patients with type 1 diabetes; glutamic acid decarboxylase (GAD65) antibodies are present in 70–90% of newly diagnosed patients. Anti-GAD antibodies have also been associated with neurological syndromes, including limbic encephalitis causing profound anterograde amnesia (e.g. Bonello et al, 2014). A report of limbic encephalitis and type 1 diabetes associated with anti-GAD antibodies (Lopez-Sublet et al, 2012) described a 27-year-old woman with drug-resistant epilepsy who developed anterograde amnesia after repeated admissions for ketoacidosis and severe hypoglycaemia. She had temporal lobe signal hyperintensity on magnetic resonance brain imaging and high serum and CSF titres of anti-GAD antibodies, with evidence of intrathecal synthesis. Intravenous immunoglobulin treatment over 8 months lead to remission of seizures (Lopez-Sublet et al, 2012). Anti-GAD antibodies were never assayed in this patient, although the absence of epileptic seizures argues against their possible pathogenic significance.

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CASE REPORT

A 61-year-old man who had had insulin-dependent diabetes mellitus type 1 since the age of 12 years was found collapsed. Because of suboptimal glycaemic control, his diabetes was being treated with continuous subcutaneous insulin infusion. At presentation his blood glucose was 1.0 mmol/litre.

After correction of hypoglycaemia, he noted difficulty remembering the names of friends and the content of recent conversations, and needed external memory aids. He scored 27/30 on the Mini-Mental State Examination (MMSE) (Folstein et al, 1975) and 82/100 on the Addenbrooke's Cognitive Examination (ACE) (Mathuranath et al, 2000). Formal neuropsychological assessment showed normal attention, concentration, language and working memory functions, but impaired verbal and visual immediate and delayed recall (Wechsler Memory Scale III and Camden Memory Tests). Magnetic resonance brain imaging performed within a few days was normal.

He had gradual improvement in memory function: at 4 months his short-term verbal memory and learning was still impaired but his visual memory was improved. Sequential scores on MMSE were 28/30 and 30/30 (*Figure 1*) and on ACE were 93/100 and 93/100 at 4 and 10 months respectively.

The patient was then lost to follow up until he was re-referred aged 75 years, by which time he had been living in a nursing home for 3 years with a diagnosis of dementia. Review of medical records showed repeated hospital admissions for hypoglycaemia before nursing home placement. MMSE scores of 25/30 and 17/30 had been recorded at ages 65 years and 67 years, the latter dip coinciding with eight admissions for hypoglycaemia in 8 months. There was no history of epileptic seizures. Exposure to hyperglycaemia appeared limited: there was no history of diabetic ketoacidosis or record of retinopathy, nephropathy, or peripheral neuropathy. Where recorded, the level of glycated haemoglobin (HbA_{1c}) was around 10%. Hypoglycaemic episodes essentially ceased after nursing home placement when the patient no longer administered his own insulin.

At 75 years of age, he was evidently amnesic, alluding to the same piece of information three times in 10 minutes. MMSE score was 19/30 (*Figure 1*). His magnetic resonance brain imaging showed global brain atrophy (*Figure 2*) including medial temporal lobe structures, but there was only minor periventricular ischaemic change with no infarcts or microhaemorrhages.

Figure 1. Sequential Mini-Mental State Examination (MMSE) scores over the 14-year period of follow up.

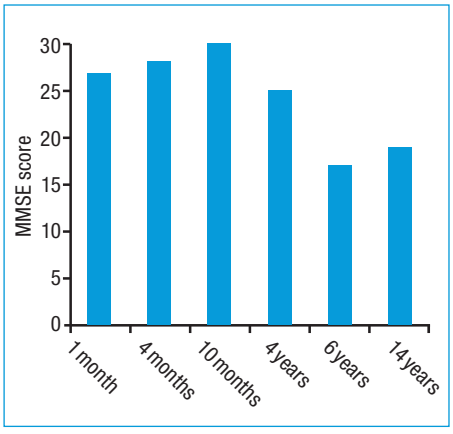
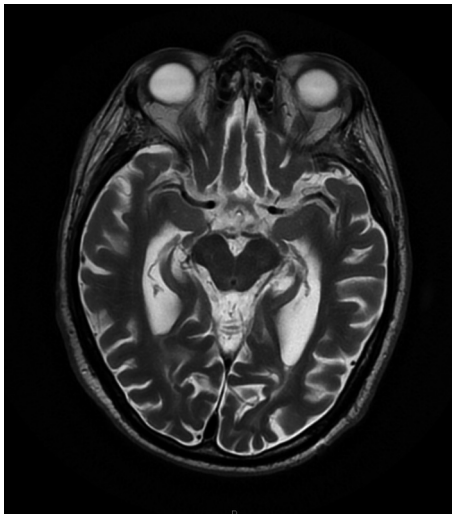


Figure 2. Magnetic resonance brain imaging (axial, T2-weighted) at level of the midbrain showing diffuse brain atrophy.



LEARNING POINTS

- There is an increased prevalence of cognitive impairment and dementia in people with diabetes.
- Few cases of diabetic people with amnesia associated with episodes of recurrent hypoglycaemia and with long-term follow up have been reported.
- Recurrent hypoglycaemia may be associated in the long term with cognitive decline and brain atrophy in the absence of significant cerebrovascular disease.
- It remains to be examined whether shared autoimmunity to islet cell and neuronal antigens such as GAD65 may contribute to hypoglycaemia-associated amnesia in diabetic patients.

Nevertheless, the authors suggest that diabetic patients with acute hypoglycaemia-associated amnesia should have anti-GAD antibodies assayed, as well as magnetic resonance brain imaging (both conditions may show hippocampal imaging changes), since this might indicate treatment options with immunomodulatory therapy. **BJHM**

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