

# 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; Kirchoff 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). Kirchoff 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 neuroglycopenia 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 Kirchoff 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.

## 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<sub>1c</sub>) was around 10%. Hypoglycaemic episodes essentially ceased after nursing home placement when the patient no longer administered his own insulin.

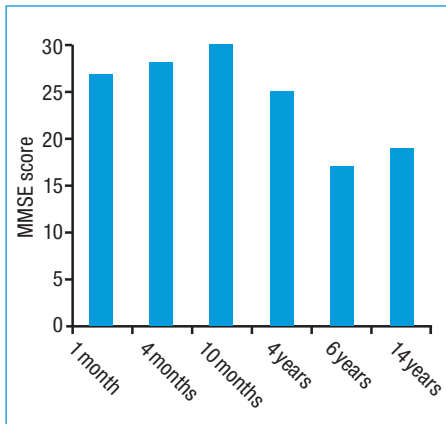
At 75 years of age, he was evidently amnesic, alluding to the same piece of information three times in 10 minutes. MMSE score was 19/30 (*Figure 1*). His magnetic resonance brain imaging showed global brain atrophy (*Figure 2*) including medial temporal lobe structures, but there was only minor periventricular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

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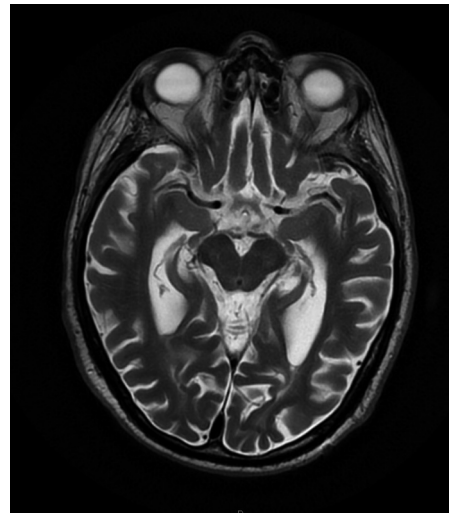
Figure 1. Sequential Mini-Mental State Examination (MMSE) scores over the 14-year period of follow up.



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**

Bonello M, Larner AJ, Marson AG (2014) Profound amnesia after temporal lobectomy: an autoimmune process resembling patient H.M.? *Case Rep Neurol* **6**: 251–5 (doi: 10.1159/000369058)  
 Chalmers J, Risk MT, Kean DM, Grant R, Ashworth B, Campbell IW (1991) Severe amnesia after hypoglycaemia. Clinical, psychometric, and magnetic resonance imaging correlations. *Diabetes*

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



Care **14**: 922–5  
 Fisher CM (2002) Unexplained sudden amnesia. *Arch Neurol* **59**: 1310–13 (doi: 10.1001/archneur.59.8.1310)  
 Folstein MF, Folstein SE, McHugh PR (1975) “Mini-Mental State.” A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**: 189–98 (doi: 10.1016/0022-3956(75)90026-6)  
 Holemans X, Dupuis M, Misson N, Vanderijst J-F (2001) Reversible amnesia in a type 1 diabetic patient and bilateral hippocampal lesions on magnetic resonance imaging (MRI). *Diabet Med* **18**: 761–3 (doi: 10.1046/j.1464-5491.2001.00481.x)  
 Kirchoff BA, Lugar HM, Smith SE et al (2013) Hypoglycaemia-induced changes in regional brain volume and memory function. *Diabet Med* **30**:

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.

e151–6 (doi: 10.1111/dme.12135)  
 Larner AJ, Moffat MA, Ghadiali E, Majid S, English P, Williams G (2003) Amnesia following profound hypoglycaemia in a type 1 diabetic patient. *Eur J Neurol* **10**(Suppl 1): 92 (abstract P1170)  
 Lopez-Sublet M, Bihan H, Reach G et al (2012) Limbic encephalitis and type 1 diabetes with glutamic acid decarboxylase 65 (GAD65) autoimmunity: improvement with high-dose intravenous immunoglobulin therapy. *Diabetes Metab* **38**: 273–5 (doi: 10.1016/j.diabet.2012.02.005)  
 Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR (2000) A brief cognitive test battery to differentiate Alzheimer’s disease and frontotemporal dementia. *Neurology* **55**: 1613–20

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Case Report

A feverish junior doctor with a diagnosis not to be missed

Introduction

The differential for a febrile patient with a non-specific focal lung shadow and elevated lactate is broad and for teaching, but it is an accurate and concise read, a useful first step in reaching a diagnosis. This is particularly important in preventing errors of the antibiotic disease setting. This case report is the abstracted learning point, hopefully decrease the likelihood of a missed diagnosis.

Discussion

This case highlights the importance of a thorough and considered search for any potential presenting with a fever of unknown origin. Common initial work-up for infectious aetiology can have two periods of several weeks, which is for health-care professionals to apply. This case report describes a 47-year-old woman who presented with acute febrile illness secondary to proton pump inhibitor (PPI)-induced acute interstitial nephritis. This case report was accepted by *BJHM* on 18/08/2016. It is available online at <http://dx.doi.org/10.1136/bjhm-2016-000000>. It is available in print in *British Journal of Hospital Medicine* September 2016, Volume 77, Number 9, pages 541–542.

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Case Report

Acute interstitial nephritis caused by two different proton pump inhibitors

Introduction

Acute interstitial nephritis is an important cause of acute kidney injury and diagnosis for about 40% of cases. Since 1992 it has been established that proton pump inhibitors can cause acute interstitial nephritis. This case report describes a 47-year-old woman who presented with acute febrile illness secondary to proton pump inhibitor (PPI)-induced acute interstitial nephritis. This case report was accepted by *BJHM* on 18/08/2016. It is available online at <http://dx.doi.org/10.1136/bjhm-2016-000000>. It is available in print in *British Journal of Hospital Medicine* September 2016, Volume 77, Number 9, pages 543–544.

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with a further episode of acute interstitial nephritis when rechallenged with a different proton pump inhibitor (esomeprazole). Previous case studies have shown that introduction of the same proton pump inhibitor caused recurrent worsening of renal function. This is the first report of acute interstitial nephritis occurring secondary to two different proton pump inhibitors in the same individual. This case highlights the importance of proton pump inhibitor-induced acute interstitial nephritis as a cause of acute kidney injury and the need for clinicians to consider acute interstitial nephritis when diagnosing acute kidney injury in patients taking proton pump inhibitors. This case report was accepted by *BJHM* on 18/08/2016. It is available online at <http://dx.doi.org/10.1136/bjhm-2016-000000>. It is available in print in *British Journal of Hospital Medicine* September 2016, Volume 77, Number 9, pages 545–546.

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