CASE REPORT

Case of steroid-responsive encephalopathy from hypoglycaemia

Jay L Mathur,¹ Fereshteh Rajabi,¹ Allison Schroeder,² Torben K Becker³¹Department of Internal Medicine, UPMC Mercy, Pittsburgh, Pennsylvania, USA²Department of Physical Medicine and Rehabilitation, UPMC Presbyterian, Pittsburgh, Pennsylvania, USA³Department of Critical Care Medicine, UPMC Presbyterian, Pittsburgh, Pennsylvania, USA**Correspondence to**Dr Jay L Mathur,
JLMathur@gmail.com

Accepted 16 August 2017

SUMMARY

Hypoglycaemic encephalopathy is a feared complication in the management of patients with diabetes mellitus. We report on a 73-year-old woman with type 1 diabetes managed with an insulin pump who presented unresponsive after an inappropriate insulin bolus. The patient had minimal improvement in her neurological status over 8 days. After administration of 1 g intravenous methylprednisolone, she had dramatic neurological improvement including successful extubation and discharge from the intensive care unit. Steroid responsive encephalopathy is increasingly recognised in practice and literature. However, to the best of our knowledge, this is the first case of hypoglycaemic encephalopathy that responded to high-dose steroids.

BACKGROUND

Steroid-responsive encephalopathy (SRE) describes encephalopathies that improve, often dramatically, after exposure to steroids. This phenomenon has been increasingly recognised in clinical practice and medical literature over the past 10 years. SRE is often categorised as either vasculitic or non-vasculitic.¹ SRE has been observed in or associated with a growing number of non-vasculitic cases such as SRE associated with autoimmune thyroiditis (SREAT), Alzheimer's disease, Creutzfeldt-Jakob disease and cholesterol emboli.^{1–3} In patients with SREAT, case reports and case series have reported substantial improvement with steroid administration.⁴ Based on our review of the medical literature, this effect has not been previously described in patients with hypoglycaemic encephalopathy. Hypoglycaemia is a common medication-induced adverse effect in the management of insulin-dependent patients with diabetes, and hypoglycaemic encephalopathy is a feared complication. We report the case of a patient with protracted hypoglycaemic encephalopathy that rapidly improved after administration of high-dose steroids.

CASE PRESENTATION

A 73-year-old Caucasian woman with a medical history of type 1 diabetes mellitus (DM) managed with an insulin pump presented obtunded from hypoglycaemia. The patient had well-documented poor hypoglycaemic awareness, with symptoms occurring near blood glucose (BG) levels of 70 mg/dL (3.9 mmol/L), which had required rescue glucagon therapy and admission on one occasion before. She improperly scheduled insulin bolus

for a >100 g carbohydrate meal at 4:00 the day of presentation. The patient's husband awoke around 8:00 to find his wife unresponsive. He checked her BG, which was near 20 mg/dL (1.1 mmol/L), and administered rescue subcutaneous glucagon with no improvement. He requested emergency medical services (EMS). On their arrival, the patient was haemodynamically stable, and BG was found to be 90 mg/dL (5.0 mmol/L). She was given an ampule of dextrose 50% with no improvement.

On arrival to the emergency department (ED), the patient was obtunded with a Glasgow Coma Scale (GCS) of 5. Vital signs were remarkable for hypertension with an initial systolic blood pressure of greater than 200 mm Hg and tachycardia with a heart rate of 120. Her brainstem reflexes were diminished, and she exhibited a flexure posture in the upper extremities. Teeth clenching was observed with blood in her mouth. The remainder of her exam was non-contributory. The patient was intubated in the ED for airway protection. Her initial BG was 313 mg/dL (17.4 mmol/L). A depiction of the patient's hospital course can be found in [figure 1](#).

From presentation to day 6, the patient's GCS minimally improved from 5 to 7. The patient had few indicators of good neurological outcome, and her overall prognosis was thought to be poor.⁵ This led to a family discussion with a decision to not escalate care in addition to an observational period of 72 hours.

INVESTIGATIONS

Magnetic resonance imaging (MRI) without contrast demonstrated periventricular areas of white matter with T2 prolongation which, compared with imaging 8 years prior, had not significantly changed. This was thought to represent mild chronic vascular changes. There was no evidence of restricted diffusion or low gradient signal involving the brain parenchyma. Magnetic resonance angiography (MRA) without contrast showed patent large vessels without abnormalities including vasculitis or stenosis, although smaller vessels were not visualised. Serial electroencephalograms (EEG) demonstrated changes consistent with metabolic or anoxic encephalopathy without evidence of seizure activity or tendency. Endocrinological and neurological evaluations were both consistent with hypoglycaemic encephalopathy and likely induced seizure activity that resolved. Hypoxic injury was unlikely given the patient's haemodynamic stability seen in the field and on arrival without evidence of vessel

CrossMark

To cite: Mathur JL, Rajabi F, Schroeder A, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221262

Figure 1 Timeline of patient's course in the ICU with relevant diagnostic information, interval management, interventions and neurological examination.

disease on MRA or ischaemic changes on MRI. On hospital day 6, repeated neurological evaluation, including MRI and EEG, was unchanged.

Urine drug screen was positive for benzodiazepines only, which she received on arrival in the ED for presumed seizure activity. Acetaminophen, salicylate and ethanol levels were negative. Family and outpatient physicians familiar with the patient stated she did not exhibit abuse or suicidal behaviour. Further testing such as autoimmune/vasculitic, oncological or prion evaluation did not seem prudent given clear presenting history of hypoglycaemia.

DIFFERENTIAL DIAGNOSIS

Given the patient's history of DM managed with an insulin pump, inappropriately programmed insulin bolus and history of well-documented poor hypoglycaemic awareness, the leading explanation for her acute change in mental status was prolonged hypoglycaemia.

Other causes of acute neurological deterioration such as cerebrovascular accident, delirium and intoxication were ruled out. The patient remained haemodynamically stable with no evidence of vessel stenosis or ischaemic changes on neuroimaging. Seizure likely did occur and was induced by hypoglycaemia that abated soon after admission, as evidenced by EEG monitoring with no ongoing epileptiform activity. Other steroid-responsive disease processes were also considered, including autoimmune thyroiditis given patient's history of hypothyroidism, inflammatory processes including vasculitis or infectious encephalitis, adrenal insufficiency and multiple sclerosis. Causes of rapid onset dementia such as Lewy body dementia, amyloid deposition and Creutzfeldt-Jakob disease, which may present as SRE, seemed unlikely.¹⁶ Given the patient's degree of hypoglycaemia before arrival, it is possible some anoxic injury occurred that neuroimaging could not detect; however, this

effect would be mild compared with the insult of hypoglycaemic encephalopathy.

TREATMENT

On presentation, she received doses of lorazepam and levetiracetam and was initiated on a propofol infusion for presumed seizure activity with no response. Antiepileptic drugs were discontinued as continued seizure activity was ruled out. The patient maintained a liberalised blood sugar from 150 to 250 mg/dL (8.3 to 13.9 mmol/L) after admission with no significant neurological improvement over 7 days. She remained haemodynamically stable with no episodes of hypotension.

Based on previously documented neurological improvement from reports of SRE, we elected a trial of high-dose steroid administration consisting of 1 g methylprednisolone intravenous after obtaining verbal informed consent from the family.

OUTCOME AND FOLLOW-UP

Approximately 18 hours after administration, the patient had a dramatic improvement in mental status. For the first time since presentation, she was able to follow commands, open eyes spontaneously and communicate discomfort. Based on this unexpected response, treatment with 1 g intravenous methylprednisolone continued for a 3-day course. The patient continued to have significant neurological improvement. Approximately 48 hours after initiation of steroid therapy, the patient was successfully extubated with a GCS of 15. Seventy-two hours after initiation, the patient was discharged from the ICU with preemptive plans for neurorehabilitation.

The patient's post-ICU course was complicated by posterior glottic stenosis, which required two sessions of

microlaryngeal surgery and balloon dilatation by otolaryngology within a 1-week period. After the second procedure, she developed respiratory distress and was briefly transferred back into the ICU for closer monitoring. In the following weeks, her mentation and neurological exam remained stable, although fluctuant, with episodes of alternating alertness and drowsiness. Unfortunately, the patient suffered from a significant aspiration event in rehabilitation about 6 weeks after discharge from the ICU. Since her wishes obtained after extubation indicated she did not wish to escalate care further, no further curative treatment attempts were sought, and she subsequently died.

DISCUSSION

This case describes a case of hypoglycaemic encephalopathy that did not respond to glucose correction alone but was responsive to high-dose methylprednisolone. There is strong evidence to suggest the aetiology of the encephalopathy was from hypoglycaemia. Her type 1 DM was managed with an insulin pump for which the patient inappropriately scheduled a >100 g carbohydrate meal. She was found unresponsive by her husband 4 hours after. There was well-documented poor hypoglycaemic awareness requiring glucagon rescue therapy and hospitalisation on one occasion before this episode. Given the patient's history of hypoglycaemia, brain adaption to low glycaemic states could be considered. However, given her prolonged hypoglycaemia with severely low BG, this seems unlikely.⁷ Although no definitive neuroimaging findings have been associated with hypoglycaemic encephalopathy, reports have described some consistent findings, such as diffuse cortical lesions not within vascular distribution.^{8–11} Our patient did not exhibit such findings on neuroimaging.

SRE has been well documented in cases of vasculitic as well as non-vasculitic disease processes, such as autoimmune or inflammatory encephalopathy, including SREAT.^{2,4} Other non-vasculitic instances of SRE are rare but have been reported in association with Alzheimer's disease, Creutzfeldt-Jakob disease and cholesterol emboli.^{1,3,6} Hypoglycaemic encephalopathy, another form of non-vasculitic encephalopathy, has not been described to be steroid responsive.

The mechanism by which steroids modulate encephalopathy is also poorly understood. During prolonged and severe hypoglycaemia, neuroexcitatory transmitters such as aspartate and glutamate are released. These neurotransmitters induce glial and myelin oedema.^{11–13} Unlike anoxic injury, hypoglycaemia induces metabolic damage that does not lead to necrosis.¹² This allows the potential for reversibility. It may be hypothesised that oedema can be mitigated by the administration of high-dose steroids.

Hypoglycaemic encephalopathy is a feared consequence of diabetes management due to immediate and even permanent neurological complications. This case demonstrates a dramatic response in neurological outcome after administration of intravenous methylprednisolone to a patient with hypoglycaemic encephalopathy. Therefore, high-dose steroids can be considered in patients with hypoglycaemic encephalopathy refractory to standard and supportive therapies.

In a patient with prolonged hypoglycaemic encephalopathy that did not respond to standard therapy, dramatic neurological improvement was seen in short temporal association with administration of high-dose methylprednisolone.

Further research is warranted to examine potential beneficial effects of high-dose steroids in patients with severe and prolonged hypoglycaemic encephalopathy who show no to minimal improvement with BG correction and best supportive care practices.

Patient's perspective

We, the patient's husband, children and grandchildren, were with our loved one ('the patient') every day. We were able to closely observe the lack of improvement over the patient's hospitalisation prior to steroid administration. This was explained to us as something that, to the best knowledge of the treating physicians, had not previously been attempted, and thus our consent was sought. The medication was administered in the late afternoon, and the next morning, she opened her eyes and responded by blinking her eyes or nodding her head when we talked to her. She was given two more doses, and later was able to be extubated. We were amazed at how the patient had significant neurological improvement after steroid administration. During her hospital stay, her level of alertness would wax and wane. She received steroids again on the wards for a suspected upper airway constriction, and we again observed significant improvement in her level of alertness, demeanour and mood afterwards. When the patient was in rehabilitation, we felt that she was behaving as if she was depressed. We had requested the treating physicians there to consider a course of steroid therapy, but they did not feel that it would help her. Overall, we appreciated the extra time spent with our loved one thanks to the apparent improvement with steroid administration.

Learning points

- Steroid responsive encephalopathy (SRE) is increasingly recognized in medical practice and literature.
- Hypoglycaemic encephalopathy, a feared complication in management of diabetes mellitus, may be a new example of SRE.
- In patients with hypoglycaemic encephalopathy who have minimal neurological change with standard therapy, high-dose steroids may lead to significant neurological improvement.

Acknowledgements We would like to thank our patient's endocrinologist, Dr. Lauren Willard, for her continued help in our work.

Contributors All authors have seen and approve of the manuscript submitted and contributed greatly to it. Contributions are listed with specific authors that contributed. Conception and design of case report and manuscript, acquisition of data, analysis and/or interpretation of data, drafting the manuscript, revising the manuscript critically for important intellectual content, approval of the version of the manuscript to be published: all authors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Mateen FJ, Josephs KA, Parisi JE, *et al.* Steroid-responsive encephalopathy subsequently associated with Alzheimer's disease pathology: a case series. *Neurocase* 2012;18:1–12.

- 2 Castillo P, Woodruff B, Caselli R, *et al*. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol* 2006;63:197–202.
- 3 Laloux P. Steroid-responsive leucoencephalopathy due to cholesterol embolism. *J Neurol Neurosurg Psychiatry* 2007;78:112.
- 4 Laurent C, Capron J, Quillerou B, *et al*. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): characteristics, treatment and outcome in 251 cases from the literature. *Autoimmun Rev* 2016;15:1129–33.
- 5 Ikeda T, Takahashi T, Sato A, *et al*. Predictors of outcome in hypoglycemic encephalopathy. *Diabetes Res Clin Pract* 2013;101:159–63.
- 6 Santoro D, Colombo I, Ghione I, *et al*. Steroid-responsive Hashimoto encephalopathy mimicking Creutzfeldt-Jakob disease. *Neurol Sci* 2011;32:719–22.
- 7 van de Ven KC, Tack CJ, Heerschap A, *et al*. Patients with type 1 diabetes exhibit altered cerebral metabolism during hypoglycemia. *J Clin Invest* 2013;123:623–9.
- 8 Bathla G, Hegde AN. MRI and CT appearances in metabolic encephalopathies due to systemic diseases in adults. *Clin Radiol* 2013;68:545–54.
- 9 Kuriyama A, Sato K. Hypoglycemic encephalopathy. *CMAJ* 2015;187:E437.
- 10 Mahawish K. Hypoglycaemic encephalopathy. *BMJ Case Rep* 2016;2016:bcr2015214296.
- 11 Onder H. Reversible diffusion restriction in the splenium of the corpus callosum due to severe hypoglycemia: a case report and literature review. *J Neuroradiol* 2016;43:419–21.
- 12 Auer RN, Siesjö BK. Hypoglycaemia: brain neurochemistry and neuropathology. *Baillieres Clin Endocrinol Metab* 1993;7:611–25.
- 13 Butterworth RF. *Basic neurochemistry: molecular, cellular, and medical aspects*. 6th edn. Philadelphia: Lippincott-Raven, 1999.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow