ACADEMIC: CLINICAL PEARL

A rare complication of hyperosmolar hyperglycaemic state in the intensive care unit

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Introduction

Diabetic ketoacidosis (DKA) and Hyperosmolar Hyperglycaemic State (HHS) are common presentations to the Intensive Care Unit (ICU) and represent a spectrum of pathology which encompasses well understood biochemistry. There are well established management processes and guidelines for DKA and HHS. This clinical pearl discusses these pathologies in the context of a patient with severe metabolic derangement who developed a rare complication.

Case presentation

GS, a 28-year-old male, was transferred, intubated and ventilated from a rural centre with a blood sugar level (BSL) in excess of the bedside glucometer available at the presenting site, a pH of 7.29, and a bedside ketone reading of 1.7 mmol/L. There was a relatively short prodrome of eight days of progressive drowsiness and fatigue, and he presented to the referring centre with confusion. At the referral site, the patient's Glasgow Coma Scale prior to intubation had dropped to six (E1, V1, M4). Available past history was only significant for illicit drug use.

He was given two litres of 0.9% normal saline between presentation at the referral site and admission to the ICU. Formal BSL testing following arrival showed a value of 75 mmol/L, with a sodium on the initial bloods of 162 mmol/L (corrected 192 mmol/L). The patient was given a diagnosis of HHS, however, due to the degree of derangement in his metabolic state, standard management was supplemented to slowly decrease serum osmolality over days.

HHS and DKA

HHS and DKA exist on a spectrum of presentations. Differentiation is based on the dominant features in history, examination, and investigations.

DKA is a rapidly evolving (<24 hours) state in which the relative insulin deficiency with respect to glucagon results in a shift in metabolic substrate utilisation from glycolysis towards gluconeogenesis.[20] The most notable of these from a definitional perspective is a transition of hepatic lipid metabolism to ketogenesis. Patients present with a mild degree of hyperosmolality due to hyperglycaemia and a high anion gap metabolic acidosis (normally >20). DKA is more common in younger patients with a known diagnosis of type 1 diabetes, and a brief history of either illness or non-compliance with their usual insulin therapy. Systemic symptoms are common in DKA and include polyuria, polydipsia, and weight loss with gastrointestinal (GI) symptoms of nausea, vomiting, and abdominal pain. These GI symptoms are characteristic of DKA, and are considered to occur secondary to the degree of electrolyte derangement in DKA and the significant degree of acidosis in this condition.[1,2] Beyond initial fluid resuscitation, management is focused on supplementation of insulin in order to restore the utilisation of glucose. Progress is monitored through the reversal of ketosis and the correction of glycolysis.

HHS commonly presents with a longer prodrome over several days to a week, as was the case for GS. Patients are usually older, and more often have a diagnosis of type 2 diabetes without compliance difficulties. Episodes are usually in the context of a physiological stressor or concurrent illness. There is a higher frequency of neurological symptoms when compared with DKA, and these may present as drowsiness, delirium, seizures, and even coma.[2,3] The preponderance of neurological symptoms is thought to be due to the significant elevation of serum osmolality seen in HHS, which is normally greater than 320 mOsm/L. These neurological symptoms start to emerge in DKA as the osmolality rises to beyond this level. The high anion gap metabolic acidosis seen in DKA is not usually a presenting feature of HHS.

Aside from the extreme hyperglycaemia, the case of Mr GS is particularly notable for the fact that there was no pre-existing history of diabetes mellitus and the patient was relatively young. Acidosis was not the dominant feature of his admission and there was minimal ketosis, therefore, clinically, the presentation is more in keeping with a diagnosis of HHS.

Management of HHS and DKA

Fluid resuscitation is a cornerstone of management of both DKA and HHS. There is variation between institutional and consensus guidelines regarding the specific type and volume of fluid used during the resuscitation phase of management. In general, this involves rehydration with a mix of isotonic and hypotonic fluids. One reasonable approach would be to proceed along the lines of the American Diabetes Association[21]:

- 1 L 0.9% normal saline solution in the first hour (and use colloid if they are shocked)
- If Na^+ >145 mmol/L, 4–14 mL/kg of 0.45% normal saline, depending on hydration state.
- Once the BSL is <16.7 mmol/L, the fluid may be switched to 5% dextrose with 0.45% saline.
- Half of the total deficit should be given in the first 18 to 24 hours (usually ~9 L), and the remainder given over the next 24 hours.

In this case, the estimated fluid deficit was closer to 18 L based on the measured Na^+ of 162 mmol/L.[4,5] The use of unbalanced isotonic fluids such as 0.9% saline in the setting of DKA may be considered controversial. The arguments centre on the potential to exacerbate the narrow strong ion difference acidosis present in DKA through the introduction of large volumes of unbalanced crystalloid.[6–8] This discussion aside, continual electrolyte monitoring and replacement is required in both cases, because during the resuscitative phase, metabolic derangements may include hypokalaemia, hypophosphataemia, hypomagnesaemia, hypoglycaemia, and hyperchloraemia.

Management of Mr GS

In the case of Mr GS, acidaemia was not the dominant feature, and hyperglycaemia was in excess of the levels normally seen in DKA. Corrected sodium using the equation above was 192mmol/L, with a corresponding measured osmolality of 440 mOsm. Calculated osmolality was 400 mOsm. Management proceeded down the HHS pathway. For this patient, all normal resuscitation fluids in the algorithm are significantly hypotonic relative to his serum osmolality. In order to control the reduction rate in osmolality, 3% saline was infused in addition to the regime above, with a targeted fall in serum osmolality of less than 10 mOsm. Glucose supplementation was added after the first 24 hours to balance the fall in osmolality with the fall in sodium. Insulin was added on day two, as there was a persistently low level of ketosis in keeping with HHS, and within the spectrum of illness between DKA and HHS.

In this case, management was complicated by the degree of derangement of the osmolality, and despite the adjustment in the normal resuscitative algorithm, significant drops in osmolality of up to 20–30 mOsm/hr occurred in the first six hours after presentation to the peripheral centre. After this early phase of resuscitation, osmolality fall was controlled to less than 10 mOsm/h with an associated fall in Na^+ of less than 10 mmol/day. By day three, the patient had normalised electrolytes and serum osmolality, and was weaned from sedation. However, following a further observation period of 48 hours, he failed to demonstrate signs of neurological recovery. Cerebral venous thrombosis was ruled out with a venous phase computed tomography brain scan. Magnetic resonance imaging found symmetrical hyperintense T2-weighted imaging in the pontine region, in keeping with either pontine infarction or osmotic demyelination (Figure 1). He remained in ICU for a further 60 days, predominantly due to slow neurological recovery.

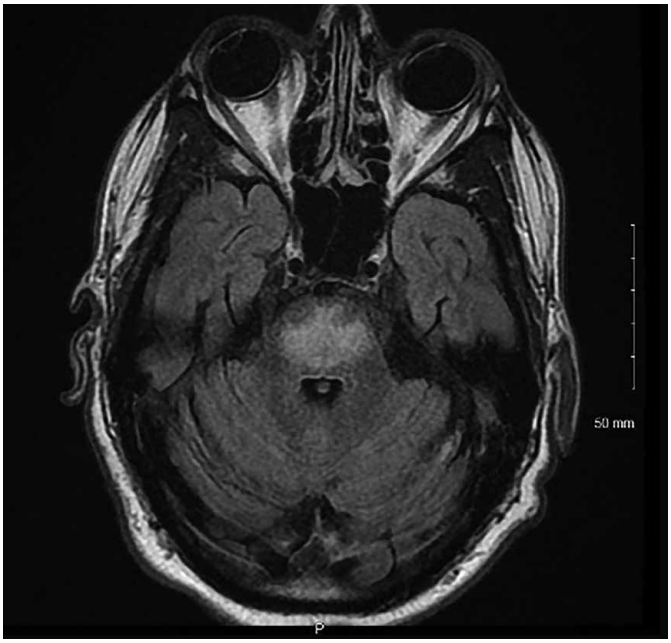

Figure 1. Magnetic Resonance Imaging demonstrating pontine infarction or osmotic demyelination. This scan represents a similar scan to the one obtained in the patient above.[22]

Pontine infarction and osmotic demyelination syndrome

Pontine infarction is a relatively rare complication of HHS, but is thought to be secondary to hyperviscosity and the proinflammatory state seen in the context of elevated glucose.

Central Pontine Myelinolysis is a separate condition more commonly seen in the setting of rapid correction from hyponatraemia. Osmotic demyelination results from direct injury to astrocytes and subsequent disruption of the blood-brain barrier, which leads to injury of oligodendrocytes from cytotoxic processes.[9] In normal physiology, hyponatraemia and a gradual decline in serum osmolality are compensated for by the neuronal cells via the loss of idiogenic osmoles (glycine, taurine, glutamine, sorbitol, and inositol).[10] These molecules are generated under normal circumstances to balance the intracellular and extracellular tonicity, and as relatively large, non-diffusible molecules, contribute to the Gibbs-Donnan equilibrium. During the development of hypernatraemia, the neuronal intracellular fluid sheds these idiogenic osmoles over time to prevent the development of cerebral oedema.[1,2] In the early phases of rapid correction of hyponatraemia, high extracellular sodium concentration and low intracellular osmolarity results in an efflux of water and an influx of sodium. This process occurs faster than the neuronal cell's ability to reduce idiogenic molecular concentrations, and results in protein aggregation, deoxyribose nucleic acid fragmentation, and eventually results in apoptosis.[13–15]

In hypernatraemia, there are case reports of patients developing osmotic demyelination syndrome.[16–19] The mechanism in these instances is thought to be related to the fluctuations in serum sodium and osmolality during either the development of HHS or the treatment phase, rather than to the relative degree of hypernatraemia. This case adds to that small literature base. It highlights the complexities of managing patients at the extreme end of physiological derangement and the emergence of unexpected sequelae during successful implementation of a well-defined treatment protocol.

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Patient consent

Consent was obtained by the treating team from the patient for the use of clinical details only for the purposes of this publication. The use of patient images was not obtained, so similar imaging has been used as referenced in Figure 1.

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