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Overview of Cerebral Edema During Correction of Hyperglycemic Crises

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: **Male, 31**
Final Diagnosis: **Mixed diabetic ketoacidosis and hyperglycemic hyperosmolar state**
Symptoms: **Acute encephalopathy and motor polyneuropathy**
Medication: **Normal saline boluses followed by half-normal saline infusion • insulin drip**
Clinical Procedure: —
Specialty: **Critical Care • Endocrine • Nephrology • Neurology**

Objective: **Unusual or unexpected effect of treatment**

Background: Hyperglycemic crises can cause severe neurologic impairment. One of the most dreaded consequences of hyperglycemic crises is cerebral edema, a rare complication seen during the treatment of hyperglycemic crises resulting from overly-aggressive fluid resuscitation and rapid correction of hyperglycemia and hyperosmolarity.
Case Report: We present a case of profound hyperglycemic crisis with blood glucose greater than 2000 mg/dL, complicated by the development of new neurologic deficits after rapid correction of hyperglycemia. Brain imaging failed to reveal a diagnosis of cerebral edema or other acute intracranial process. However, the deficits did not resolve by the time of discharge, raising concern that the neurologic impairment may have been the consequence of overly-aggressive treatment of the hyperglycemic crisis.

Conclusions: Neurologic status must be monitored closely, with frequent re-examination, in patients who present with hyperglycemic crises. Care should be taken to prevent over-correction of hyperglycemia and hyperosmolarity following initial fluid resuscitation of these patients to prevent cerebral edema or other significant neurologic impairment.

MeSH Keywords: **Brain Edema • Diabetic Ketoacidosis • Hyperglycemia • Hyperglycemic Hyperosmolar Nonketotic Coma • Hyponatremia**

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/908465>

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Background

Diabetes mellitus is a chronic medical condition that causes vascular and neuronal injury and can lead to long-term neurologic complications, such as peripheral neuropathy, compression neuropathy, cranial nerve palsy, autonomic dysfunction, and stroke. Additionally, uncontrolled diabetes can cause acute, life-threatening hyperglycemic crises, including diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). Both conditions can present with sudden, severe neurologic impairment. DKA may cause confusion or coma, while HHS can result in the same symptoms as well as seizures or stroke-like symptoms. The correction of hyperglycemia can result in absolute or relative hypoglycemia, which may cause headaches, confusion, syncope, seizure, or stroke-like symptoms (with relative hypoglycemia being particularly hard to diagnose, as blood glucose can be at near normal levels). One of the most dreaded consequences of hyperglycemic crises is cerebral edema, a rare complication with an incidence rate of 0.7–1.0% [1] and which may occur after overly-aggressive fluid resuscitation and rapid correction of hyperglycemia and associated electrolyte abnormalities. We present a case of severe HHS complicated by the development of new neurologic deficits following rapid correction of hyperglycemia, which required additional investigation to rule out cerebral edema. This case highlights the importance of monitoring the rate of correction of hyperglycemia and hyperosmolality and serves as an opportunity to review strategies to avoid the overly-rapid correction of these metabolic derangements.

Case Report

A 31-year-old man with no prior medical history was brought to the hospital with acute encephalopathy and shock following 1 week of worsening thirst, anorexia, and diffuse myalgias. On admission, he was altered to the point of near unconsciousness, such that he required intubation and mechanical ventilation in the Emergency Department. The patient was afebrile, but vital signs were notable for both tachycardia and hypotension. Admission labs were remarkable for a blood glucose of 2065 mg/dL, lactate of 8.5 mmol/L, pH of 7.03, HCO₃ of 10 mmol/L, and anion gap of 32. He also demonstrated renal impairment with a BUN of 77 mg/dL and a creatinine of 4.98 mg/dL (there was no lab work prior to admission to differentiate acute versus chronic kidney injury); urinalysis showed glucosuria and only minimal ketonuria and proteinuria. Later in the patient's hospital stay, anti-islet cell antibodies and anti-glutamic acid decarboxylase antibodies came back negative, supporting a diagnosis of type 2 diabetes mellitus. The remainder of the admission lab work was unremarkable, including serum creatine kinase, blood and urine toxicology (including toxic alcohol levels), hepatitis serologies, and HIV studies.

A lumbar puncture was attempted on admission but failed to yield any cerebrospinal fluid.

The patient was placed on an insulin drip at 0.1 units/kg/hr and given intravenous (IV) fluids: 4 L normal saline (NS) on admission, followed by 0.45% NS at 200–250 mL/h (Figure 1). Over the course of the first 24 h, the patient's glucose decreased from 2065 to 122 mg/dL and his sodium increased from 138 to 172. Taking into account the patient's profound hyperglycemia, this corresponds to a corrected admission sodium of 170, which increased to 173 at the 24-h mark, a significantly smaller increase than was suggested by his uncorrected sodium values. The patient's serum osmolality of 446 mOsm/kg on admission decreased to 401 mOsm/kg in the first 12 h, and to 360 mOsm/kg 24 h after admission (Table 1). We started 5% dextrose in water (D5W) at 150 mL/h in response to his rising sodium levels, but was subsequently discontinued after it caused an acute drop in sodium from 172 to 165 in only 4 h. Eventually, once the patient's hyperglycemia, acidosis, and dehydration had all resolved, he was switched from 0.45% NS back to just D5W running at 150 mL/h for correction of his lingering hyperglycemia (his sodium had gone unchanged for 24 h following initial discontinuation of the D5W). Once the D5W was resumed, the patient's sodium began to drop back towards normal. Over the next several days, his encephalopathy improved, and he was successfully extubated without complication on hospital day 3. As his mental status began to recover, he was noted to have a right-sided facial nerve palsy, mild pupil asymmetry, and weakness during finger abduction and adduction, right wrist extension, and left foot dorsiflexion. Concerns arose that the rapid shifts in blood glucose, sodium, and osmolality might be the cause of his neurologic deficits.

An MRI brain was performed to evaluate for demyelination or edema. Due to concerns for possible facial nerve involvement, the MRI was performed using the FIESTA protocol, a technique that allows for better identification of cranial nerves lesions. This study did not show any evidence of demyelination or cerebral edema.

The patient's neurologic deficits improved during his hospital course but did not completely resolve by the time of discharge, and he was referred for follow-up in an outpatient neurology clinic to assess for clinical improvement and for consideration of a repeat MRI to look for late manifestations of suspected cerebral edema. Unfortunately, the patient was lost to follow-up and further attempts to contact him were unsuccessful.

Discussion

The patient presented with focal neurologic deficits of unclear etiology, for which there was significant concern for cerebral

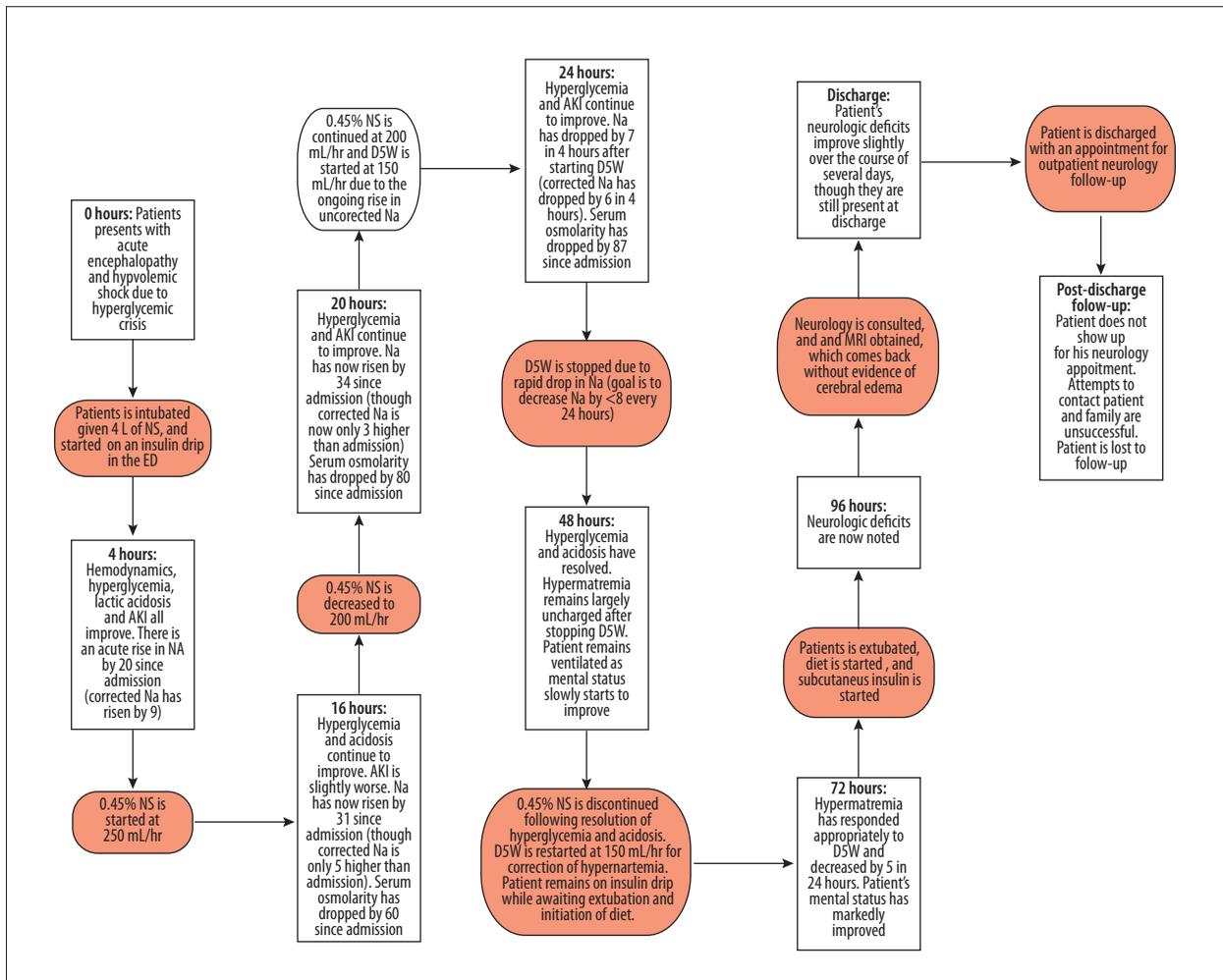


Figure 1. Timeline of patient's management and hospital course. White boxes represent patient's clinical status and response to treatment at various points in time. Red boxes represent the treatments instituted. AKI – acute kidney injury; D5W – 5% dextrose in water; ED – Emergency Department; Na – sodium; NS – normal saline; MRI – magnetic resonance imaging.

edema caused by rapid osmolar shifts during resuscitation. While cerebral edema was not detected on initial imaging, MRI is not always effective for early detection of cerebral edema or cerebral white matter lesions, which can result in significant delays in diagnosis [1]. Alternatively, the neurologic deficits may have been the result of severe hyperglycemia, which can manifest as either transient symptoms from the hyperglycemia itself or permanent symptoms as a consequence of hyperglycemic peripheral nerve infarcts, resulting in peripheral neuropathy. Because the patient was able to survive glucose levels greater than 2000 mg/dL, we suspect he had long-standing, undiagnosed diabetes. As a result, he may have had chronic undiagnosed diabetic motor polyneuropathy, which went unrecognized at home, and only came to light during medical evaluation.

Cerebral edema occurs when fluid moves from the extracellular to intracellular space faster than brain cells can adapt to

increased intracellular volume. This can happen when hypernatremia or hyperglycemia is corrected too rapidly, leading to a sudden and pronounced drop in serum osmolality. The exact mechanism of cerebral edema in hyperglycemic crises is not fully understood. The correction of hyperglycemia is usually accompanied by a concurrent rise in serum sodium, which “protects” against the rapid drop in serum osmolality that might ensue if blood glucose correction occurred in isolation [2]. It has been proposed that cerebral edema is more likely to occur when serum sodium rises at a disproportionately slow rate relative to the drop in glucose, which may occur with rapid infusion of hypotonic fluids. Similarly, cerebral edema may occur when insulin is infused too rapidly, causing glucose correction at a rate that is faster than the change in serum sodium [2]. One additional mechanism involves the production of osmotically-active substances within brain cells, called idiogenic osmoles [3]. These idiogenic osmoles are produced during periods of extracellular hyperosmolality to counteract osmolar

Table 1. Change in lab values in response to treatment of hyperglycemia.

	Admit labs	4 h after starting treatment	8 h	12 h	16 h	20 h	24 h	36 h	48 h	72 h	96 h
Na (mmol/L)	138	158	162	167	169	172	165	163	163	158	147
Na corrected for glucose (mmol/L)	170	179	177	177	175	173	167	164	163	158	147
K (mmol/L)	4.7	1.9	2.9	3.5	3.0	3.9	4.3	4.4	4.3	3.9	3.7
Cl (mmol/L)	96	121	132	139	144	147	145	141	139	127	115
HCO ₃ (mmol/L)	10	16	12	15	14	15	12	14	16	24	25
BUN (mg/dL)	77	69	65	60	62	60	54	45	43	36	27
Cr (mg/dL)	4.98	3.78	3.13	3.54	3.73	3.47	3.00	2.55	2.28	1.30	1.02
Glucose (mg/dL)	2065	1262	950	683	452	176	200	168	101	115	154
Anion gap	32	21	18	13	11	10	8	8	8	7	7
Serum Osmolarity (mOsm/kg)	446			401	388	367	360	350	346		
pH	7.03	7.14	7.37	7.31		7.31				7.50	

BUN – blood urea nitrogen; Cl – chloride; Cr – creatinine; HCO₃ – bicarbonate; h – hours; K – potassium; Na – sodium.

imbalance; they help the brain retain fluid and prevent brain shrinkage. However, as DKA or HHS is corrected and serum osmolality returns to normal, idiogenic osmoles are slow to clear, resulting in “extra” intracellular osmoles that are no longer needed to promote fluid retention and instead lead to potential influx of excess extracellular fluid into the intracellular space [3].

To decrease the risk of cerebral edema among patients with hyperglycemic crises, sources recommend slow glucose and serum osmolality correction following initial resuscitation efforts. Specifically, guidelines recommend aggressive resuscitation starting with 1–1.5 L of NS given in the first hour, and to continue until blood pressure stabilizes [2, 4]. It is vital that insulin is not started at this time, as addition of insulin during rapid fluid administration can cause unpredictable changes to blood glucose levels and serum osmolality [5]. Once the patient is adequately resuscitated, insulin should be started as a bolus of 0.1 units/kg followed by continuous infusion at 0.1 units/kg/h. NS should be continued at a rate of 4–14 mL/kg/h if the patient has a low corrected sodium, or the fluid can be switched to half NS at a rate of 4–14 mL/kg/h if the patient has a normal or elevated corrected sodium, with the goal of achieving a serum osmolality of 320 mOsm/kg and glucose of 250 mg/dL (for patients in DKA) or 300 mg/dL (for patients in HHS) [2,4]. When these goals have been met, 5% dextrose

can be added to the IV fluids and the rates of IV fluids and IV insulin can be adjusted as necessary to correct serum osmolality by 3 mOsm/kg/h [4] and glucose by 50–70 mg/dL/h [2,4].

Unfortunately, these recommendations are difficult to achieve in practice, because the administration of IV fluids and insulin both act to reduce blood glucose levels, and they do so in a synergistic and unpredictable manner [5] that cannot be reliably calibrated to ensure a steady and consistent correction rate for either hyperglycemia or hyperosmolality. Furthermore, these patients are often profoundly dehydrated and hypotensive at presentation, prompting blood pressure stabilization with rapid IV fluid infusion that takes precedence over slow, guideline-driven fluid administration. Finally, no study has shown that adhering to a strict guideline-driven approach to fluid administration with slow correction of hyperosmolality and hyperglycemia actually reduces the incidence of cerebral edema [6].

Reassuringly, cerebral edema is actually an extremely rare complication of hyperglycemic crises, with an incidence rate of less than 1% in children [1] and likely even lower in the adult patient population. It is more likely to occur in patients with newly diagnosed diabetes, and it is also more likely to occur as a consequence of DKA rather than HHS. During the first 12 h of treatment, hourly neurologic checks should be performed, and any changes in neurologic status should be evaluated

with a head CT. Symptoms of cerebral edema include headache, altered mental status, lethargy, seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest. If CT imaging reveals cerebral edema, or if the patient develops an unexpected deterioration in neurologic status following initial improvement, treatment should be initiated via mechanical intubation to prevent an acute rise in pCO₂, which can induce cerebral vasodilation and further increase intracranial pressure [7]. Mannitol can also be administered at 0.5 gm/kg to reduce intracranial pressure, and emergent neurosurgical evaluation should be requested.

In the case described, there was concern that the patient developed cerebral edema given the rapid correction of his hyperglycemia and hyperosmolality, and the development of new neurologic deficits following an initial improvement in mental status. The patient's new diagnosis of diabetes, severe acidosis (pH of 7.03), and significant dehydration (blood pressure of 87/50 and BUN of 77 mg/dL) put him at high risk for cerebral edema, but his older age placed him at lower risk [7,8]. While his MRI did not reveal cerebral edema, this case highlights the need to carefully monitor and evaluate patients for the development of neurological changes. These changes may be an early sign of cerebral edema, which carries a poor

prognosis and should be promptly treated to reduce mortality among patients in hyperglycemic crisis [6].

Conclusions

Cerebral edema is a rare yet devastating neurologic complication seen in hyperglycemic crises, which can occur when hypernatremia and hyperosmolality are corrected too rapidly. While cerebral edema results in severe neurologic impairment, concern for this condition should not take precedence over aggressive fluid resuscitation and hemodynamic stabilization; after this has been achieved, the focus can shift towards more careful and precise correction of hyperglycemia and electrolyte imbalances. Hourly neurologic checks should be performed during the first 12 h of treatment, and any changes in neurologic status should be evaluated with brain imaging. If cerebral edema is present, treatment should be initiated with mechanical intubation and IV mannitol while seeking prompt neurosurgical consultation.

Conflicts of Interest

None.

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