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Practice Pearls

Acute Neurological Complications in Pediatric Diabetic Ketoacidosis

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Diabetic ketoacidosis (DKA) is an acute and serious complication of diabetes mellitus, mostly type one. It is associated with a high risk of morbidity and mortality if not treated promptly.[1] Several acute neurological complications may occur in DKA, with cerebral injury that may lead to cerebral edema, being the most common. Other less common and less known acute neurological complications include stroke and electrolyte derangements. The latter can lead to seizures or cardiac arrest with consequent brain hypoxic-ischemic injury.[1–8] In this article, we summarize the common and lesser-known acute neurological complications of DKA. Importantly, we emphasize that the clinical presentations of some acute neurological complications of DKA overlap, and thus the correct diagnosis may be overlooked. Prompt recognition of the various neurological complications and targeted treatment is essential for the successful management of these patients.

Although not the focus of this article, it is important to be aware that a mixed picture of DKA and hyperosmolar hyperglycemic state may also present with severe neurologic presentations and poor outcomes.

Cerebral injury and edema

This is the most common acute neurological complication of DKA. Cerebral edema, the most severe presentation of cerebral injury in DKA, occurs in about 1% of pediatric DKA. Risk factors include new-onset diabetes, longer duration of symptoms, young age (< 5 years), hypocapnia, severe acidosis and use of sodium bicarbonate boluses.[1] Mortality of fulminant cerebral edema in DKA is 20%–25%.[1] Presentation of cerebral injury varies from headache, irritability and altered mental status to abnormal respiratory pattern and cranial nerve palsy.[1] Patients can deteriorate rapidly. Although rapid fluid administration has been hypothesized as a mechanism for development of cerebral edema, this association has not been proven, with accumulating evidence against such a hypothesis.[1,2] Cerebral edema may occur prior to the administration of fluids, and more conservative fluid administration has not changed the rate of cerebral edema.[1,2] A randomized controlled trial in DKA management in children used neurologic outcomes (Glascow Coma Scale (GCS) and clinically apparent brain injury) to assess the selection of fluids and rate of administration.[2] Neither factors were found to significantly influence neurologic outcomes. The best-supported hypothesis for cerebral injury is cerebral ischemia and reperfusion injury.[9] If the patient has clinical features of cerebral edema (Table 1), the intravenous fluid rate should be decreased. Hypertonic saline or mannitol is critical to treat the increased intracranial pressure, and neuroimaging in this scenario is not usually indicated. Intracranial pressure monitoring can be employed for patients with more severe neurological impairment.[1]

Electrolyte abnormalities

Electrolyte abnormalities, particularly hyponatremia and hypokalemia, are seen almost universally in DKA.[1,2] There is typically no neurologic effect of hyponatremia because serum osmolality is elevated due to hyperglycemia.[2] However, severe hypokalemia, hypophosphatemia and hypomagnesemia can present with weakness that begins in the lower limbs and progresses upward. This weakness can involve the respiratory and gastrointestinal muscles, causing respiratory failure and ileus, respectively.[1–3] Calcium should be monitored as well. Cardiac arrhythmias may occur with severe hypokalemia, which can lead to hypoxic-ischemic encephalopathy as a consequence of cardiac arrest (Table 1).[1,2]

Stroke

DKA induces a pro-thrombotic state which increases the risk of cerebral and sinus venous thrombosis. Ischemic and hemorrhagic strokes occur rarely in DKA.[4] Presentations of strokes can include headache, nausea/vomiting, altered mental status, nuchal rigidity, seizures and focal neurological deficits. Cerebral edema may mask the presence of a stroke.[4] CT with CT venogram and brain MRI can help distinguish cerebral edema from the various causes of stroke. It is important to balance the need to hydrate stroke patients with the need to decrease fluids if cerebral edema is also present. Anticoagulation is typically recommended for cerebral and sinus venous thrombosis.

Extrapontine myelinolysis

Extrapontine myelinolysis is reported very rarely in children with DKA and involves symmetric demyelination of extrapontine sites. It is often, but not always, associated with rapid shifts in serum

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Table 1. Summary of the acute neurological complications of pediatric diabetic ketoacidosis

Complications	Neurological presentation	Diagnosis	Management
Cerebral edema	Altered mental status, bradycardia, incontinence, headache, vomiting, lethargy, hypertension, abnormal pain response, decorticate or decerebrate posturing, cranial nerve palsy, abnormal respiratory pattern	Clinical	Hypertonic saline or mannitol, maintain normal blood pressure and oxygen saturations, avoid intubation unless there is a concern for impending herniation, consider intracranial pressure monitoring
Electrolyte abnormalities	Weakness (hypokalemia, hypophosphatemia), seizures/paralysis (hypophosphatemia)	Serum electrolytes and extended electrolytes (Na, K, PO_4, Ca)	Avoid changes to Na >3 mmol/L/h. Replace potassium if <5 mmol/L and voiding. Replace phosphate if <0.5 mmol/L or symptomatic. Replace magnesium if severely low or symptomatic
Stroke (hemorrhage, ischemia, cerebral venous thrombosis and sinus venous thrombosis)	Headache, nausea/vomiting, altered mental status, nuchal rigidity, seizures, focal neurological deficits. Increased suspicion if symptoms do not improve with correction of DKA	CT ± CT angiogram/ venogram, MRI	Supportive measures, consult stroke service
Extrapontine myelinolysis	Altered mental status, focal neurological deficits	MRI	Clinical improvement with treatment of DKA
Posterior reversible encephalopathy syndrome	Headache, altered mental status, seizures, visual disturbance	MRI	No targeted therapy. Resolves with treatment of DKA
Acute peripheral neuropathy	Weakness, numbness	Nerve conduction studies	Alpha-lipoic acid
Cerebral mucormycosis	Headache, periorbital edema, proptosis, blindness, cranial nerve involvement, altered mental status	Fungal blood cultures, histopathology of affected tissues	Surgical debridement, IV amphotericin B with step-down to posaconazole

DKA = diabetic ketoacidosis.

osmolarity due to rapid correction of hyponatremia.[5] However, if cerebral edema is also present, then hypertonic saline should not be given slowly in DKA for fear of causing extrapontine myelinolysis, since extrapontine myelinolysis is rare and sodium is rarely actually low in DKA. The presentation can vary but typically includes altered mental status and focal neurological deficits.[5] Brain MRI is recommended for diagnosis.

Posterior reversible encephalopathy syndrome (PRES)

PRES is characterized by headaches, altered mental status, seizures and visual disturbance.[6] PRES may be triggered by various conditions, including hypertension, renal failure and autoimmune diseases. It has been reported to occur very rarely in DKA, likely secondary to several factors, for example, renal failure.[6] PRES generally resolves with treatment of the triggering insult.

Acute peripheral neuropathy

Acute peripheral neuropathy is extremely rare in DKA, and although it shares the presenting features of pain and decreased sensation to the extremities, it is distinct from chronic neuropathy.[7] Proposed mechanisms for acute neuropathy include rapid shifts in blood glucose and vascular endothelial dysfunction.[7] Symptoms can be treated with alpha-lipoic acid.[7]

Mucormycosis

DKA is an important risk factor for mucormycosis. Mucormycosis is a fungal infection caused by filamentous fungi of the Mucoraceae family. This infection carries high morbidity and mortality even with early diagnosis and treatment. Mucormycosis is a risk especially in patients with long-term poorly controlled diabetes rather than in patients with new-onset diabetes presenting with DKA. Symptoms are nonspecific and mostly respiratory in nature but can progress to a neurological presentation including altered mental status, blindness and cranial nerve palsy.[8]

Conclusions

Acute neurological complications of DKA can develop at any time, from onset of illness to treatment and anion gap closure.[1,2] Early symptoms of neurological complications can be subtle. Neurological monitoring should be performed at least hourly to determine the level of consciousness until the acidosis resolves.[1] Any worsening level of consciousness should prompt consideration of cerebral injury and possible edema. If clinical features for cerebral edema occur, treatment should be initiated rapidly. When the neurological status does not improve after DKA is corrected, an expeditious search for the lesser-known acute neurological complications and further testing, including neuroimaging, should be considered, since many of these complications share similar clinical features.[1,4–6,8] For example, cerebral injury, stroke, extrapontine myelinolysis, PRES and cerebral mucormycosis present with headache, altered mental status, irritability, seizures and focal neurological deficits.

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