Hyperglycaemic Hyperosmolar State (HHS) in children: a practical guide to management

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Abstract

Hyperglycaemic Hyperosmolar State (HHS), also known previously as Hyperosmolar Hyperglycaemic Non-Ketotic Coma (HONK) is a life-threatening but preventable acute metabolic complication of diabetes. It is becoming more common in childhood and optimal outcomes require a good understanding of the condition. It is very important that HHS is distinguished from DKA, as the management differs significantly, and HHS has a high morbidity and it can prove fatal. This review discusses the pathophysiology, how to make the diagnosis and the recommended treatment of this condition in children. The best clinical management of HHS in childhood involves careful correction of fluids and biochemical status of the patient and identification of precipitating causes whilst carefully monitoring for complications.

Keywords children; complication; diabetes; HONK; hyperosmolar hyperglycaemic syndrome; management

Introduction

Hyperglycaemic Hyperosmolar State (HHS), also known previously as Hyperosmolar Hyperglycaemic Non-Ketotic Coma (HONK), is a life-threatening condition that occurs in some forms of uncontrolled diabetes mellitus. HHS is characterized by severe hyperglycaemia, a marked increase in serum osmolality and severe dehydration *without* significant ketoacidosis. It is very different from the usual form of acute decompensation in Type 1 diabetes, diabetic ketoacidosis (DKA), which presents with a triad of hyperglycaemia, ketonaemia and acidosis. Levels of altered mental status can vary in both DKA and HHS, and either disorder can present with coma. It is very important that HHS is distinguished from DKA, as the management differs significantly, and HHS has a high morbidity and a mortality rate.

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Hospitalizations for HHS in children and young people have increased significantly in recent studies as obesity and Type 2 diabetes are increasing in prevalence.

There are no prospective studies currently to guide treatment of children and young people presenting with HHS and current recommendations are based on studies in adult populations and an understanding of the pathophysiology of HHS. Current studies of HHS in children are limited to case series or single-centre reviews and are mainly described in children with Type 2 diabetes. The International Society for Pediatric and Adolescent Diabetes (ISPAD) has recently written guidelines for the recognition and management of HHS, which are a useful reference source for anyone treating children and young people with this condition (see Further reading).

Pathogenesis

In contrast to diabetic ketoacidosis, in HHS there is enough circulating insulin to prevent excessive fat lipolysis and subsequent ketogenesis. HHS can occur with acute stress or sepsis, trauma or substance abuse, which can result in increased gluconeogenesis and glycogenolysis and hyperglycaemia from a relative deficiency of insulin or insulin resistance. Severe hyperglycaemia results in a rise in plasma osmolality in the extracellular fluid, which causes a shift of water from the intracellular to the extracellular space. Hypovolaemia from severe depletion of body water and excess sodium result in hypertonic dehydration. The stress of severe hyperglycaemia, hyperosmolality and severe dehydration, contributes to an increased production of counter-regulatory hormones like cortisol, catecholamines and glucagon. The increased secretion of the counter-regulatory hormones further accentuates the degree of hyperglycaemia (see Figure 1).

Children and young people who present with signs of severe dehydration and altered consciousness will continue to have increased urine output and are at increased risk of developing rhabdomyolysis and malignant hyperthermia.

Epidemiology

Whilst HHS may occur in young patients with Type 2 diabetes, Type 1 diabetes, and in infants, especially those with 6q24-related transient neonatal diabetes mellitus it is more commonly seen in elderly patients with Type 2 diabetes. It may occur as a complication in those without diabetes following severe burns, peritoneal dialysis, or haemodialysis. Patients taking certain drugs such as methadone, diuretics, corticosteroids, beta-blockers, phenytoin and diazoxide are also at increased risk of developing HHS. HHS appears to be on rise in adolescents with Type 2 diabetes, and extreme obesity (body mass index more than 30), as obesity in childhood grows in prevalence.

If children present with HHS at the diagnosis of diabetes, they will sometimes turn out to have Type 2 diabetes, although not always. A recent survey of hospital admissions with HHS in the US has suggested that as many as 70% had Type 1 diabetes. As dehydration is a main factor in HHS, children and young people developing diabetes who have learning difficulties and who are unable to ask for drinks are particularly susceptible.

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Pathophysiology of HHS

Stress/precipitating event i.e. infection, trauma, substance abuse, undiagnosed diabetes

↓

Insulin deficiency/ resistance + rise in counter-regulatory hormones (cortisol, glucagon, epinephrine, growth hormone)

↓

Extreme hyperglycaemia with minimal/absent ketogenesis

↓

Hyperosmolality

↓

Prolonged osmotic diuresis

↓

Volume depletion leading to severe dehydration + electrolyte depletion

Figure 1 Pathophysiology of HHS.

Diagnosis

The relative lack of ketones in a child with hyperglycaemia and dehydration should alert the clinician to the possibility of HHS. DKA usually occurs in lean, younger patients with Type 1 diabetes and develops within hours to days while HHS is more likely to occur in older, obese patients with Type 2 diabetes and can take days or weeks to fully develop. Both DKA and HHS may present with polydipsia and polyuria and both conditions may cause abdominal pain with nausea and vomiting due to the acidosis. Dehydration is often more pronounced in HHS but Kussmaul respiration (rapid and deep respiration) with acetone breath is generally absent. A definitive diagnosis of HHS should be confirmed through laboratory investigation (see Box 1).

There can be overlap between HHS and DKA, complicating diagnosis and management. Mild acidosis may occur in HHS but is due to lactic acidosis resulting from severe dehydration. There may also be extreme hyperglycaemia in DKA resulting in hyperosmolality, particularly if high glucose drinks have been used to quench thirst.

The ISPAD consensus guideline criteria for HHS

- Plasma glucose concentration >33.3 mmol/litre
- Venous pH > 7.25; arterial pH > 7.30
- Serum bicarbonate >15 mmol/litre
- Small ketonuria, absent to mild ketonaemia
- Effective serum osmolality* > 320 mOsm/kg
- Altered consciousness (e.g., obtundation, combativeness, seizures)

*Serum osmolality = 2 × serum sodium + serum glucose + serum urea (all in mmol/litre).

Box 1

Although children and young people with HHS are severely dehydrated their hyperosmolality ensures that intravascular volume is relatively maintained, leading to fewer clinical signs. Furthermore, urinary losses continue to be large during treatment and so replacement of fluid quickly is required to prevent shock.

Management

HHS is a medical emergency. Prompt treatment of HHS is directed at general resuscitation (see Box 2), rapid restoration of the intravascular volume, replacement of fluid and electrolyte deficits and correction of hyperglycaemia and hyperosmolality (see Box 3). Whenever possible, all children and young people should be admitted to a high dependency or paediatric intensive

General resuscitation

Airway

- Ensure that the airway is patent and if the child is comatose, insert an airway
- If consciousness reduced or child has recurrent vomiting, insert nasogastric tube, aspirate and leave on open drainage

Breathing

- Give 100% oxygen by face-mask

Circulation

- Insert IV cannula and take blood samples (glucose, sodium, potassium, urea, blood gas)
- Cardiac monitor for T waves (hypokalaemia is common)
- Measure blood pressure and heart rate
- Start resuscitation fluid urgently

Box 2

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Fluid management strategy in HHS

- Administer bolus of 20 ml/kg of 0.9% sodium chloride solution if shocked.
- Repeated boluses as required to restore peripheral perfusion.
- Once vital signs have stabilized, give 0.45—0.75% sodium chloride solution over 24—48 hours, assuming fluid deficit of 12—15% body weight. It may be necessary to continue with 0.9% sodium chloride solution if intravascular volume remains depleted.
- Aim for a gradual decline in plasma sodium of 0.5 mmol/litre per hour by adjusting sodium concentrations in fluids.
- Plasma glucose should decrease by around 4—6 mmol/litre per hour with adequate rehydration. Failure of expected fall in plasma glucose should prompt reassessment of renal function.
- If there is continued fall in plasma glucose of more than 5 mmol/litre per hour after the first 4 hours, consider adding 5% glucose to the rehydration fluids.
- Replace urinary losses with 0.45—0.9% sodium chloride solution because of the high risk of circulatory collapse.

Box 3

care unit for frequent monitoring as they require a high level of nursing care and complications are common.

Fluid management

Patients usually present following a prolonged phase of osmotic diuresis leading to severe dehydration. Losses of water exceed those of sodium resulting in hypertonic dehydration. The principal goal of therapy must be restoration of the intravascular volume using isotonic fluid (0.9% sodium chloride solution) until there is haemodynamic stabilization followed by rehydration with more variable (0.45—0.9%) sodium chloride solutions (see Box 3).

Think about precipitating causes

Once the initial resuscitation is underway, precipitating or initiating causes of HHS such as infection must be identified and treated. Infection remains the most important precipitating factor in the development of HHS. Other precipitating causes of HHS are undiagnosed diabetes and substance abuse. A full clinical assessment should be carried out, including possible risk factors:

- renal function assessment
- mental state
- neurological state
- history from parents
- family history
- physical examination looking for acanthosis nigricans, obesity

Consider whether other investigations are indicated e.g. full blood count, CXR, CSF, throat swab, blood culture, urinalysis. Commence intravenous antibiotics if infection is presumed or suspected, as mortality rates remain high with HHS.

Monitoring

Careful monitoring is essential in order to replace fluid and electrolytes adequately and prevent complications. One-to-one nursing is crucial in this regard. The following should be meticulously documented in the medical notes:

- volume of fluid administered hourly
- urine output hourly
- blood glucose concentrations hourly
- plasma electrolytes (sodium, potassium, chloride, magnesium, calcium, phosphate, urea, creatinine) 2—3 hourly
- hourly blood pressure and basic observations of vital signs, neuro observations
- hourly level of consciousness initially, using the modified Glasgow coma score
- ECG monitoring, for potassium changes

Team members should be asked to report immediately to the medical staff any symptoms of headache, slowing of pulse rate, or any change in either conscious level or behaviour, which may indicate cerebral oedema, and any changes in the ECG trace, especially signs of hypokalaemia (flattened T waves, ST segment depression and prominent U-waves).

Insulin

Adequate fluid rehydration in HHS is essential before giving any insulin. Over-aggressive insulin treatment can lead to a rapid fall in plasma glucose leading to circulatory collapse and thrombosis if fluid replacement is inadequate, because a high glucose contributes to the maintenance of intravascular volume, so should not be changed rapidly. Insulin is given at much lower rates than in DKA because there is minimal ketosis. The optimal approach is summarized in Box 4.

Electrolytes

HHS also presents with significant depletion of potassium, phosphate and magnesium.

Potassium

Before insulin is started, potassium replacement is only needed if plasma potassium concentration is less than around 5.5 mmol/litre. When it is required give potassium chloride 40 mmol in 500 ml of replacement fluids once renal function has been assessed. During insulin treatment and hydration, serum potassium levels rapidly fall; therefore, it is recommended that potassium replacement should be initiated before insulin is started, with the goal of maintaining a plasma potassium concentration in the range of 4—5 mmol/litre. Monitor potassium

Insulin therapy in HHS

- Insulin treatment should be started when plasma glucose is no longer falling at a rate of at least 3 mmol/litre per hour.
- Consider starting insulin treatment earlier in patients with more severe ketosis or acidosis (a mixed DKA/HHS picture).
- Start continuous insulin infusion at approximately 0.025—0.05 U/kg/hour, and aim to achieve a fall of glucose of 3—4 mmol/litre per hour.
- Do not give insulin boluses or subcutaneous insulin.

Box 4

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levels 2–3 hourly with blood gases and continuous ECG monitoring is helpful.

Phosphate

Phosphate should be monitored 2–3 hourly as severe hypophosphatemia can lead to rhabdomyolysis, haemolytic uraemia, muscle weakness and paralysis. There are no studies on the use of phosphate therapy for HHS and the beneficial effect of phosphate therapy is purely theoretical.

If replacement is required, give a 50:50 mix of potassium phosphate and potassium chloride or potassium acetate in the IV fluids. Be aware that phosphate administration can lead to a risk of hypocalcaemia, tetanus and soft tissue calcification.

Magnesium

Magnesium levels are important because of the role magnesium deficiency in both exacerbating potassium loss and decreasing cellular uptake. Hypomagnesemia increases distal potassium secretion and impairs sodium–potassium–adenosine triphosphatase (Na-K-ATPase), which consequently decreases cellular uptake of potassium ions. Magnesium replacement should be considered in patients with low potassium levels and severe hypomagnesaemia and/or hypocalcaemia. The dose of magnesium is 25–50 mg/kg per dose for 3–4 doses given every 4–6 hours with a maximum infusion ate of 150 mg/min and 2 g/hour. It is important to monitor blood pressure. There is no evidence in HHS of whether magnesium replacement is beneficial.

Bicarbonate

Bicarbonate therapy is contraindicated in HHS owing to the risk of severe hypokalemia and bicarbonate therapy may also adversely affect oxygen delivery.

Outcomes and complications

Several complications have been reported in children and young people with HHS.

Delay in diagnosis is common and morbidity and mortality from complications of HHS in children are significant. Venous thrombosis can occur, especially when central venous catheters are used. In adults, low molecular weight heparin has been recommended, but it is not advised as a routine in children. It should be considered if the risks are very high on an individual basis.

In children, rhabdomyolysis has been reported in several cases. A picture of malignant hyperthermia, compartment syndrome and ventricular arrhythmias has also been reported in several children, and has a high mortality rate. Rapid correction of hyperglycaemia and hyperosmolality can result in cerebral oedema as a result of an osmotic gradient between brain and plasma.

Other fatal complications of HHS have also been reported such as acute renal failure, arrhythmias, and cerebral and systemic vascular accidents.

As soon as there is any suspicion of any of these complications, the child should be discussed with a paediatric intensivist. The mortality rate associated with HHS is reported to be considerably higher in adult patients, ranging from 10% to 20%, compared with 1%–5% in diabetes ketoacidosis.

Subsequent progress

Following recovery many patients presenting will require insulin treatment only for a short while, and many can be managed effectively with diet or oral agents. Patients should be given close follow up after discharge.

Conclusions

The recognition and management of HHS in children and young people with diabetes requires a high degree of awareness and suspicion by healthcare professionals. Meticulous care with fluids during management is essential to prevent complications and reduce mortality. The success of HHS management depends on careful and adequate correction of dehydration, hyperglycaemia and electrolyte deficits. Any comorbid precipitating event should be identified and treated appropriately. Improving patient education, regular follow up and easy access to healthcare resources are important in preventing this potentially fatal complication. ◆

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Practice points

- Management of HHS and diabetic ketoacidosis is different
- A definitive diagnosis of HHS should be confirmed through laboratory investigation
- Treatment of HHS requires rapid correction of fluids, electrolyte deficits, and hyperosmolality
- Morbidity and mortality from complications of HHS in children are significant

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