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An Emerging Challenge in Paediatric Obesity: A 13-year-old Boy with Life-threatening Hyperosmolar Hyperglycaemic Syndrome

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Abstract Obesity is a pandemic health care issue that may cause not only morbidity but also mortality. We reported a case of a 13-year-old obese boy with newly diagnosed Type II diabetes mellitus presented with hyperosmolar hyperglycaemic syndrome (HHS) complicated by shock, acute renal insufficiency, acute pulmonary oedema and malignant hyperthermia-like syndrome. We alert practitioners for possible increasing incidence of HHS in obese adolescents in Hong Kong. Early recognition, aggressive fluid therapy, delay and insidious start of insulin, as well as use of dantrolene are possible strategies to reduce the morbidity and mortality of this syndrome.

Key words Hyperosmolar hyperglycaemic syndrome; Paediatric obesity

Introduction

Hyperosmolar hyperglycaemic syndrome (HHS) is a disorder of marked hyperglycaemia and hyperosmolality without severe ketosis. In the past, HHS has been seen most commonly in elderly patients with Type II diabetes mellitus (T2DM) . With the increasing incidences of obesity and T2DM in the paediatric population, more and more cases of HHS involving children and adolescents have been reported worldwide. We might expect more cases of HHS to be seen in our locality.

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Case Report

A previously healthy 13-year-old Sino-Thai boy presented to Accident and Emergency Department (AED) with a 3-day history of increasing lethargy. He had weakness, nausea, and feeling of "hotness" in his chest. He visited general practitioner who made the diagnosis of gastroesophageal reflux and gave him Losec (a proton-pump inhibitor) and antacid but provided no relief. On the next day, he visited the same general practitioner again and was given Pantoloc (a proton-pump inhibitor) and antacid. On the day of admission, his symptoms got worse; he became more fatigue and had marked decrease in activity. He had polyuria and polydipsia. He was very thirsty and drank 5.8 litres of soya bean milk (Vitasoy) and other herbal drinks. He had no vomiting, abdominal pain nor fever. He had significant family history of T2DM in his father, elder sister and paternal grandmother. On physical examination, his body mass index was 44 kg/m^2. He had cold extremities with capillary refill at 2 seconds. Pupils were equal and reactive. He was lethargic but still oriented, with spontaneous eye opening and obeyed verbal commands. He had extensive acanthosis nigricans. The initial vital signs recorded in AED were: pulse 179/min; blood pressure 106/48 mmHg; respiratory rate 18/min; temperature 36.8^{o}C, oxygen saturation 98%. The H'stix recorded was "HI".

However, the true blood glucose and urinalysis were not checked. Venous blood gas and electrolyte showed pH 7.108; bicarbonate 10.4 mmol/L; sodium 123 mmol/L; potassium 6.8 mmol/L. Electrocardiogram showed sinus tachycardia with tented T wave. He was given 10 ml/kg normal saline at full rate and 0.05 units/kg/h actrapid infusion at AED. There was response to the fluid challenge and the heart rate decreased to 135/min but the blood pressure remained low, 102/35 mHg. On-call paediatrician was consulted. Blood glucose was checked and he was transferred to intensive care unit (ICU). He was treated as diabetic ketoacidosis (DKA) and the rate of insulin drip was increased to 0.1 units/kg/h and was given normal saline at a rate of 220 ml/h. Catheterisation of bladder was done and urine dipstick showed ketone 1+ and glucose 3+. The alarming laboratory blood glucose result came back only five hours after admission. It was 105.4 mmol/L! Laboratory-determined chemistries showed serum sodium 123 mmol/L (132-145 mmol/L); corrected sodium after adjusting for hyperglycaemia was 170 mmol/L; potassium 7.3 mmol/L (3.5-5.1 mmol/L); urea 21.2 mmol/L (1.8-6.0 mmol/L); creatinine 314 mmol/L (50-77 mmol/L). The calculated osmolality was 375.6 mOsm/kg. The measured serum osmolality was 403 mOsm/kg (275-295 mOsm/kg). Cardiac enzyme, troponin T was 46 ng/L (<14 ng/L). Creatine phosphokinase (CPK) was 3688 U/L (<270 U/L). Blood and urine cultures were negative. Chest X-ray was normal.

In the first six hours after admission, there was a reciprocal relation between the blood glucose and the heart rate and patient's clinical status deteriorated. The blood glucose dropped sharply from 105.6 mmol/L to 64.7 mmol/L at a rate of 6.8 mmol/h. He became more tachycardiac and hypotensive as the blood glucose dropped. The urine output decreased from osmotic diuresis to oliguria. Approximately 2500 ml of fluid was given in the first six hour after admission. Central venous line was inserted to facilitate fluid replacement and monitoring. Shock was treated by aggressive fluid replacement up to 1000 ml/h normal saline. But at the same time, oliguria and acute renal insufficiency set in. Insulin was stopped and inotropes with dopamine and dobutamine were started to improve the renal perfusion.

The patient developed rhabdomyolysis evidenced by rising CPK and the positive urine myoglobin. A rising temperature was noted, though there was no evidence of infection. Malignant hyperthermia-like syndrome was suspected and dantrolene infusion was given. The fever came down and the CPK peaked at 7349 U/L. The patient then developed acute pulmonary oedema at around 17 hours after admission. While intubation and haemofiltration were anticipated for acute pulmonary oedema and acute renal insufficiency, the acute pulmonary oedema resolved gradually after multiple doses of diuretics. A total of approximately 19 litres of fluid was given in the first 24 hours after admission. He was haemodynamically more stable after the aggressive fluid replacement. 0.9% saline was changed to 0.75% saline in view of hypernatraemia. Phosphate and potassium were added to the intravenous fluid.

After adequate fluid replacement, insulin was restarted at low dose 20 hours after admission and the blood glucose gradually returned to normal. The patient was much better 36 hours after admission with the blood glucose normalised and acidosis corrected. The patient was discharged from ICU to the paediatric ward three days after admission. He went into polyuric phase for five days. Serum sodium level was normal on Day 11 and CPK on Day 15. Insulin was off on Day 24. The creatinine that peaked at 417 umol/L, returned to normal on Day 36 of illness.

Other laboratory results showed insulin 28.1 uIU/ml (2.6-24.9 uIU/ml, paired plasma glucose 5.6 mmol/L); anti-islet cell antibody negative; C-peptide 0.12 nmol/L (0.27-1.27 nmol/L) and HbA1c 13.3% (4-6%). The lipid profile checked in the recovery phase was normal. Cardiac enzyme was normalised. Echocardiogram showed fraction shortening of 34% and ejection fraction of 52%. He was discharged with a prescription of 500 mg metformin two times per day with good blood glucose control (Haemstix 5 to 7 mmol/L, pre-feed). The schematic presentation for the clinic progress of the patient was shown in Figure 1.

Discussion

Childhood T2DM has increasing incidence in Hong Kong. Huen et al reported that the standardised age-adjusted incidence of T2DM was 2.1/100,000/year for 10-18-year age-group.[1] There is a significant increase in the incidence rate of T2DM with an increase of about 4.0 new cases/year for the paediatric population.[1] A serious complication of T2DM is HHS. It is estimated that 3.7% of newly diagnosed pediatric T2DM patients will have HHS.[2] The mortality rates in patients with HHS vary between 10%[3] and 37%.[4] It is thought that diagnosis delay may account for these mortalities.[3]

The American Diabetes Association has proposed the following criteria for the diagnosis of HHS: plasma glucose

>33 mmol/L, serum bicarbonate >15 mmol/L, no or small ketonuria <1.5 mmol/L, effective serum osmolality >320 mOsm/kg, and associated stupor or coma.[5] The clinical presentation of HHS could be explained by the pathophysiology of HHS. The hyperosmolality in HHS patients was accounted by the marked hyperglycaemia and severe fluid and electrolyte loss.

Hyperglycaemia was the result of deficit in insulin action with concomitant increase in action of counterregulatory hormones. The counterregulatory hormones stimulated glucose production in liver and reduced glucose utilisation in adipose tissue, muscle and liver. Compared with pathophysiology of DKA, patients with HHS had lower level of ketosis. This might be explained by insulin action in HHS patients was still adequate to suppress lipolysis but insufficient to facilitate glucose uptake by muscle, liver and adipose tissue.[4]

Dehydration and electrolyte loss were usually more severe in HHS than in DKA patient. The increase in osmolality preserved the intravascular volume made the dehydration less obvious.[4] Our patient had 15% dehydration, but his morbid obesity and hypernatraemic dehydration made the assessment of hydration status inaccurate. He had visited general practitioner twice, but no correct diagnosis was made. The insidious and subtle presentation made the diagnosis difficult and appropriate management delayed. What made the situation worse, our patient had drunk 5.8 litres of carbohydrate-rich, high sodium content drinks. The ingestion of carbohydrate-rich drinks worsened the osmotic diuresis. As more water than sodium was lost in the urine, resulting in hypernatraemia that was further exacerbated by high sodium intake. McDonnell et al reported similar cases in which five patients presented with newly diagnosed diabetes had complication of hyperosmolality and required intensive care and haemofiltration after taking large amount of carbohydrate fluid intake.[6]

Lawson Wilkins Paediatric Endocrine Society (LWPES) suggests that early insulin treatment is unnecessary and may increase mortality in HHS patient.[7] Unfortunately, in our patient, the diagnosis of HHS was delayed and the patient was managed as DKA at the initial stage. Early start of insulin caused a rapid drop in blood glucose. Hypovolaemic shock was the result of the osmotic shift from the intravascular space. In fact, this could be prevented if the diagnosis of HHS was considered earlier. Besides delayed administration of insulin, LWPES suggests that rates of fluid replacement in children should be more rapid than those recommended for DKA.[7] Canarie et al studied 20 HHS paediatric patients retrospectively. They found serious

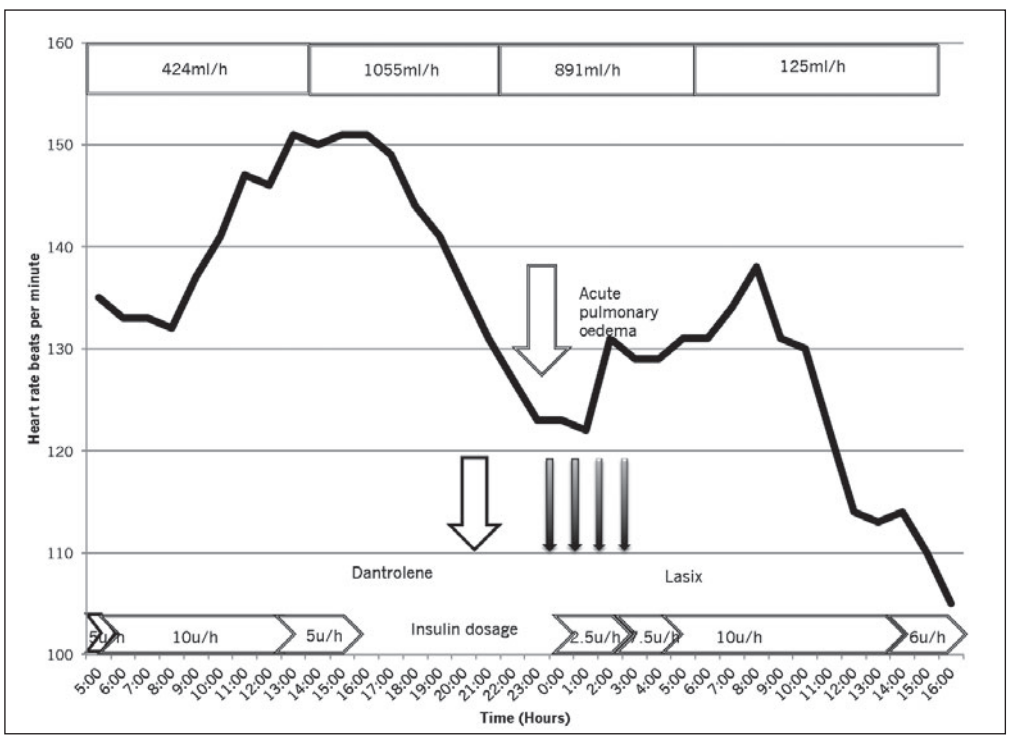

Figure 1 Clinical progress of the patient in the first 36 hours after admission.

complications were associated with irreversible shock over 24 hours of admission and less than 40 mL/kg of intravenous fluids being given over the first six hours of treatment.[3] Only 2500 mL (25 mL/kg) of intravenous fluid was given to our patient in the first 6 hours of treatment. This together with rapid extravascular fluid shifts due to rapid drop in plasma glucose as a result of early use of large dose of insulin, resulted in circulatory collapse and hypotension. Eventually, our patient had received nearly 19 litres of intravenous fluid within the first 24 hours of admission. Obviously cerebral oedema was the major concern, particularly in the fluid management of DKA patients. However, cerebral oedema is an uncommon complication in children with HHS. Vernon et al reported a 3-year-old child with HHS with extreme hyperosmolality. The intracranial pressure (ICP) of that child was monitored invasively. Though the serum osmolality dropped rapidly after fluid replacement, the ICP of that child was not elevated, and there was no complication of cerebral oedema.[8]

LWPES proposed that dantrolene should be initiated early for children who have fever associated with a rise in CPK.[7] Dantrolene, a diphenylhydantoin analog, is the drug of choice in the treatment of acute malignant hyperthermia crisis. In our patient, one bolus dantrolene was given in view of rising body temperature and increasing rhabdomyolysis. Administration of dantrolene led to defervescence and the level of muscle enzyme ceased to rise. The drug might stabilise the sarcoplasmic reticulum membrane and decrease the release of calcium from sarcoplasmic reticulum and prevents further rhabdomyolysis.[9]

With the emergence of T2DM associated with the current epidemic of childhood obesity, there is definite concern that the incidence of HHS will continue to rise. Adolescent with HHS seem to be very uncommon in Hong Kong. However, from personal communication, there were two more adolescents with HHS in 2012. Both of them died. Increase awareness and early recognition of the syndrome, more aggressive fluid therapy to replace the profound fluid depletion, delay and insidious start of insulin, as well as the use of dantrolene in cases with Malignant Hyperthermia-Like syndrome are all possible strategies in reducing morbidity and mortality associated with this syndrome.

Declaration of Interest

We declare that we have no conflict of interests.

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