

Hyperosmolar hyperglycaemic state (HHS) as the first manifestation of type 2 diabetes in a child

Stan hiperglikemiczno-hipermolalny jako pierwsza manifestacja cukrzycy typu 2 u dziecka

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Abstract

Hyperglycaemic hyperosmolar state (HHS) may occur in young patients with type 1 and type 2 diabetes and in infants with hyperglycaemia. Hyperglycaemic hyperosmolar state is characterised by extremely high glucose concentration, which, by increasing osmotic diuresis, intensifies dehydration. Hyperglycaemic hyperosmolar state criteria include the following: plasma glucose > 600 mg/dl, venous pH > 7.25, sodium bicarbonate > 15 mmol/l, slight ketonuria, plasma osmolality > 320 mOsm/kg, and impairment of consciousness (aggression, unconsciousness, convulsions). We describe the case of a 13-year-old patient with severe obesity (at presentation body mass > 120 kg, BMI > 40 kg/m²), who developed HHS (glycaemia 647 mg/dl, pH 7.18, pCO₂ 96.5 mmHg, BE – 5.0 mmol/l, HCO₃ 35.2 mmol/l; Na 167 mmol/l, plasma osmolality 370 mOsm/kg) in the course of pneumonia and newly diagnosed type 2 diabetes (HbA_{1c} 15.5%, C-peptide 2.63 ng/ml). In the follow-up, due to the hypoglycaemia, insulin was discontinued, metformin was administered at a dose of 2 g/day, with a further reduction to 500 mg/day, together with physical rehabilitation and a low-calorie diet. Weight reduction during 6 months of observation was approximately 37 kg. Due to breathing disorders occurring at night, the girl still needs breathing assistance (CPAP).

Key words:

hyperglycaemic hyperosmolar state, type 2 diabetes, obesity.

Streszczenie

Stan hiperglikemiczno-hiperosmolalny (HHS) może wystąpić u młodocianych pacjentów z cukrzycą typu 1 i 2 oraz u niemowląt z hiperglikemią. Charakteryzuje się wyjątkowo dużymi stężeniami glukozy, które poprzez zwiększenie diurezy osmotycznej nasilają odwodnienie. Kryteria HHS obejmują: stężenie glukozy w osoczu > 600 mg/dl, pH krwi żyłnej > 7,25, stężenie wodorowęglanu sodu > 15 mmol/l, brak ketonurii lub niewielką ketonurię, osmolalność w osoczu > 320 mOsm/kgH₂O, zaburzenia świadomości (agresja, utrata przytomności, drgawki). W pracy opisano przypadek 13-letniej pacjentki z ciężką otyłością (m.c. > 120 kg, BMI > 40 kg/m²), u której rozwinął się HHS (glikemia 647 mg/dl, pH 7,18, pCO₂ 96,5 mm Hg, BE – 5,0 mmol/l, HCO₃ 35,2 mmol/l, Na 167 mmol/l, osmolarność osocza 370 mOsm/kg) w przebiegu zapalenia płuc i nowo zdiagnozowanej cukrzycy typu 2 (HbA_{1c} 15,5%, peptyd C 2,63 ng/ml). W czasie leczenia wycofano się z insulinoterapii z powodu hipoglikemii, natomiast metforminę podawano początkowo w dawce 2 g/dobę, z dalszą redukcją do 500 mg/dobę, podjęto rehabilitację ruchową oraz utrzymywano dietę z ograniczeniem podaży kalorii. Zmniejszenie masy ciała podczas 6-miesięcznej obserwacji wynosiło około 37 kg. Z powodu zaburzeń oddychania występujących w nocy dziewczynka nadal potrzebuje wsparcia oddechowego (CPAP).

Słowa kluczowe:

stan hiperglikemiczno-hipermolalny, cukrzyca typu 2, otyłość.

The life-threatening hyperglycaemic hyperosmolar state (HHS) is characterised by very high glycaemia and hyperosmolality, with little or no acidosis. This is due to slowly increasing insulin deficiency, which is insufficient to cover the demand. Among the many possible reasons for the development of HHS, the most common are infections. Others include the use of certain drugs and psychoactive substances, non-compliance with therapy, and co-morbid diseases [1]. Hyperglycaemic-hyperosmolar state is believed to occur in approximately 1% of patients hospitalised for diabetes [2]. Most cases concern older people with type 2 diabetes. In the developmental population, HHS develops usually in the course of type 2 diabetes, but it can also occur in type 1 diabetes. It is believed to be associated with a delay in the diagnosis of these diseases. Mortality

in the course of HHS reaches 20–30%, and it is approximately 10-times higher than in diabetic ketoacidosis (DKA) [3, 4].

The clinical picture of HHS is dominated by significant dehydration and dyselectrolitaemia, gradually increasing polyuria, and polydipsia. Loss of fluid in the course of this syndrome is even twice as high as in DKA. The assessment of hydration of patients is hampered by obesity and hyperosmolality. In addition, hypernatraemia and hypertonicity prevent reduction of intravascular fluid volume, so the symptoms of dehydration are less visible. Preservation of circulatory efficiency happens at the expense of reducing intracellular space, which is particularly expressed within the central nervous system. The severity of the disturbances of consciousness may vary from lethargy to coma [1, 2].

The criteria for HHS include:

- plasma glucose concentration > 600 mg/dl (33.3 mmol/l),
- arterial pH > 7.30; venous pH > 7.25,
- serum bicarbonate > 15 mmol/l,
- small ketonuria, absent or small ketonaemia,
- effective serum osmolality > 320 mOsm/kg,
- change in consciousness (e.g. limited obtundation, combativeness) or seizures,
- significant dehydration.

We present a case of a teenager in whom the HHS was the first manifestation of type 2 diabetes, to underline the importance of early diagnosis and appropriate treatment of hyperglycaemic crisis in severely dehydrated children.

Table 1. Selection of initial laboratory test results

	Results	Normal range
hsCRP	97 ng/ml	0-5
procalcitonin	1.97 ng/ml	0–0.1
Na	167 mmol/l	135–145
K	4.2 mmol/l	3.8–5.0
Cl	112 mmol/l	98–107
Mg	2.98 mg/dl	1.7–2.2
phosphate	0.7 mg/dl	4.5–5.5
Ca	8.5 mg/dl	8.4–10.2
glucose	647 mg/dl	
HbA _{1c}	15.5%	5.4–6.2
ALAT	97 U/l	0–55
ASPAT	200 U/l	5–34
LDH	602 U/l	22–80
INR	1.2	0.9–1.3
total bilirubin	1.1 mg/dl	0.2–1.2
serum amylase	558 U/l	22–80
lipase	4701 U/l	7–60
creatinine kinase (CK)	313 U/l	29–168
serum creatinine	2.1 mg/dl	0.57–1.11
total cholesterol	72 mg/dl	< 190
HDL cholesterol	7 mg/dl	> 40

Case report

A 13-year-old girl with severe obesity (> 120 kg, 165.5 cm height, BMI > 40 kg/m²) was admitted to the district hospital in severe condition, with increased dyspnoea and consciousness disorders. In the physical examination considerable respiratory effort, numerous crackling over the lungs, tachycardia of 130 beats/min, tense abdomen and abdominal pain, enlarged liver, slight dehydration features, and elevated blood pressure of 140/90 mm Hg were found.

It was known that antibiotic therapy had been conducted for a week due to pneumonia with elevated body temperature; however, no significant improvement was observed. The parents reported that there had been incidents of involuntary daytime and night-time urination recently. Excessive weight gain in the child was observed from five years of age. Family history was not relevant, and parents and younger sister were healthy, with proper body mass.

In the additional tests performed, hyperglycaemia was found to be 647 mg/dl, acidosis pH 7.18, pCO₂ 96.5 mm Hg, pO₂ 43.2 mm Hg, BE 5.0 mmol/l, and HCO₃ 35.2 mmol/l. The sodium concentration was 167 mmol/l (corrected Na 178 mmol/l), and the serum osmolality was 370 mOsm/kg H₂O. Ketonuria was not found.

Due to the deteriorating condition of the child and respiratory failure, the girl was referred for further treatment in the paediatric intensive care unit (PICU). The patient required mechanical ventilation.

On admission to the PICU, dehydration was found, auscultatory phenomena characteristic of pneumonia, and abdominal pain. The results of selected additional tests are given in Table I.

In urinalysis, no ketonuria or glucosuria were confirmed. However, in the following days of treatment, in diurnal urine (5280 l) 0.37 g/day of glucose and proteinuria (1.32 g/day) were found.

In imaging studies, pneumonia was confirmed in chest X-ray (slight inflammatory lesions and/or small amounts of diffuse fluid in the left pleural cavity), abdominal CT revealed liver steatosis and pancreatitis, whereas in MR of the brain numerous ischaemic changes and microcortures in the area of the temporo-parietal-occipital cortex were described.

In the girl the diagnosis of diabetes, most probably of type 2, was confirmed, complicated by HHS in the course of pneumonia, acute respiratory failure, and acute pancreatitis.

Noteworthy was the significant dyselectrolitaemia, definitely more extreme than usually found in ketoacidosis. The severe hypophosphatemia present in the patient could have led to rhabdomyolysis, which was manifested by increased CK activity (a further increase in CK activity to 1280 U/l was observed in the control examination).

Despite intensive insulin therapy and fluid therapy (on the first day 7100 ml, a furosemide-assisted diuresis – 4764 ml, fluid balance +1540 ml), in the first days of treatment the blood glucose levels were not normalised, patient was dehydrated, and heavy electrolyte disturbances were still present.

Moreover, antibiotic therapy was maintained. Due to the central venepuncture used and the risk of thrombosis, the girl received anticoagulant therapy. Because mechanical ventilation was used, she received sedation. In addition, due to anaemia, a transfusion of two units of red cell concentration (RCC) was made.

The patient was extubated on the 14th day of hospitalisation. After adjustment of ionic disturbances, glycaemia, and hydration, subcutaneous insulin therapy was implemented. There was also a gradual decline in insulin demand observed. Physical rehabilitation was started.

In the 20th day, the girl was transferred to our Department. Due to the numerous episodes of hypoglycaemia, insulin was discontinued while metformin was administered at a dose of 2 g/day. Physical rehabilitation was continued and her diet was maintained with limited caloric intake (1500 kcal/day). During the hospitalisation in our Department, normalisation of transaminases, amylase, and lipase activity as well as CRP were observed. The significantly lower percentage of HbA_{1c} (9.9%) resulted not only from near-normoglycaemia maintained during long hospitalisation, but also from the transfusion of RCC. In addition, the high concentration of C-peptide 4.23 ng/ml [N: 0.9–7.1] and the undetectable titre of antibodies against pancreatic islets' antigens (ICA, GAD, IA2) confirmed the diagnosis of type 2 diabetes.

The girl was discharged home in good condition after 28 days of treatment. At that time, she reduced her body mass by approximately 13 kg (including about 10 kg during her stay in PICU and about 3 kg in our Department). Figure 1 presents the assessment of body mass composition by bioimpedance method performed on the day of discharge.

Implemented intensive behavioural treatment resulted in reduction of body mass by 37 kg in seven months. The transaminase and CK activity normalised. The metabolic control of diabetes is optimal (HbA_{1c} 5.7%). The results of the assessment of body composition made during subsequent visits are

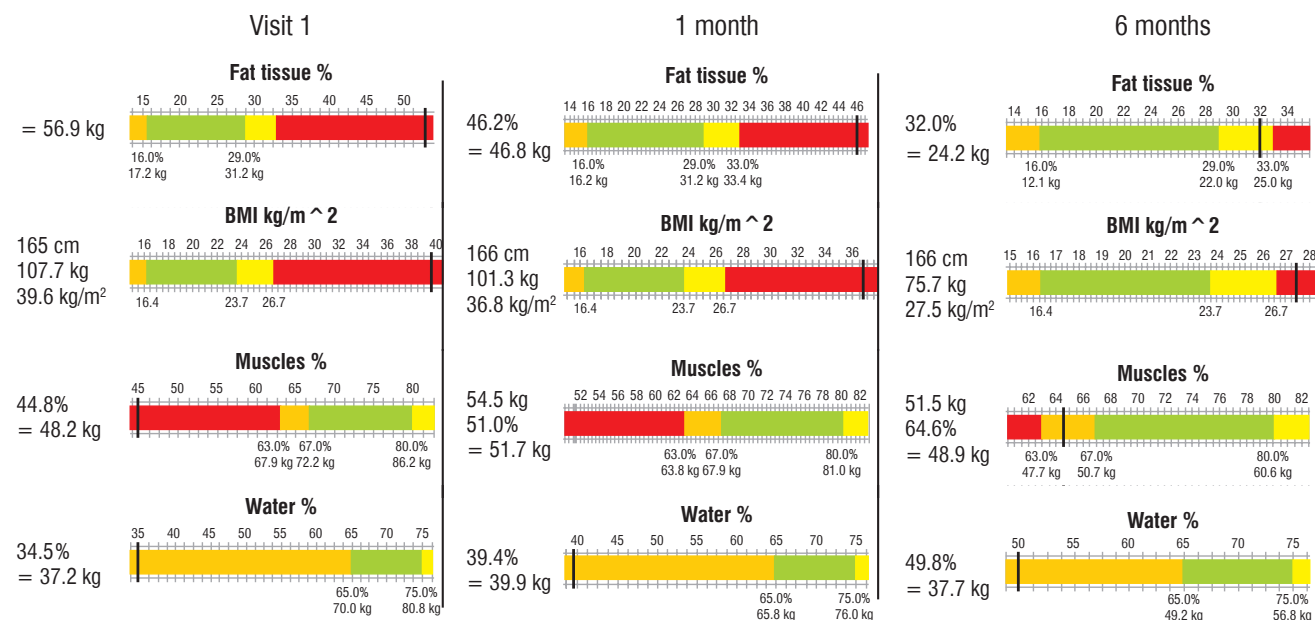


Figure 1. Body mass composition of the presented patient

presented in Figure 1. Due to breathing disorders occurring at night, the girl still needs breathing assistance (CPAP). The dose of metformin was reduced to 500 mg/day.

Discussion

Hyperosmolar hyperglycaemic state is a life-threatening condition manifested by marked elevation of blood glucose and hyperosmolality with little or no ketosis. Undiagnosed diabetes mellitus, most often type 2, with underlying infection is the most common cause of HHS, as it was in the presented case [1]. It is, however, still an unusual presentation of type 2 diabetes in children, found in 2% of cases, developing due to diagnosis delay, which also occurred in our patient [3–5]. Recent studies showed an increase of HHS prevalence in the paediatric population [6, 7]; it is therefore important to know how to diagnose and treat this condition.

According to ISPAD [1], the diagnostic criteria for HHS include the following: severe hyperglycaemia, which, together with hypernatraemia, results in hyperosmolality, near-normal pH with normal concentration of bicarbonates, as well as no ketonuria and mild ketonaemia. Altered consciousness or seizures are present in approximately 50% of cases.

The presented patient fulfilled most of the diagnostic criteria; however, a mild acidosis was stated with no ketonuria (pH 7.18). It was probably due to severe dehydration followed by hypoperfusion and lactic acidosis. Water deficit of approximately 100–200 ml/kg results of the massive losses due to the osmotic diuresis. In adult patients fluid deficiencies can reach over 12 litres [8, 9]. The fluid therapy conducted in our patients was intensive from the beginning – during the opening 24 hours of the treatment over seven litres of fluids were administered; however, fluid homeostasis was not achieved in the first few days. Moreover, creatinine and urea concentrations were elevated, all of which indicates severe dehydration.

As for severe dehydration occurring in all patients with HHS, fluid therapy seems to be most important, in order to expand the intra and extravascular volume and to restore normal renal perfusion. However, dehydration should be corrected gradually, to slowly reduce the serum sodium concentration (not more than 0.5 mmol/l/h) and serum osmolality (not more than 3 mOsm/kg H₂O/h). It is recommended that hypotonic fluids be administered until normal serum osmolality is reached, followed by a physiological saline. In the case of inadequate perfusion and haemodynamic insufficiency, infusion of isotonic NaCl is advised because isotonic fluids maintain the intravascular volume more effectively [1, 8, 9].

Correction of dehydration and hyperosmolality results in the decrease of blood glucose concentration. It is recommended to begin insulin administration at a dose of 0.025 to 0.05 U/kg/h once plasma glucose has reduced to less than 50 mg/dL (3 mmol/l) per hour with fluid alone. This should maintain the decline in blood glucose concentration by 50–75 mg/dl/h (3–4.5 mmol/l/h). In patients with more severe ketosis and acidosis, insulin therapy should be started earlier [1, 9].

In HHS severe electrolyte deficits are observed, particularly potassium, phosphate, and magnesium. They are considered to be more extreme than in diabetic ketoacidosis, so adequate replacement therapy should be initiated. Potassium supplementation should be started even if potassium concentrations are within the normal range and when normal renal function is established [10]. Electrolyte imbalance was observed in our patient, with severe depletion of phosphates. Severe hypophosphataemia may lead to rhabdomyolysis, and paralysis is an important predictor of the DKA-associated mortality [11]. It is recommended that hypophosphataemia is treated; however, one should be aware that such therapy may contribute to hypocalcaemia. Intravenous solutions of a 50 : 50 mixture of potassium phosphate and potassium chloride are used, resulting in adequate phosphate supplementation with low risk of clinically significant hypocalcaemia [10]. Also, large deficits of magnesium occur in HHS patients. Hypomagnesaemia may contribute to hypocalcaemia during therapy; therefore, supplementation should be considered in patients with hypomagnesaemia and hypocalcaemia (25 to 50 mg/kg of magnesium per dose, three to four doses given every four to six hours, with a maximum infusion rate of 150 mg/min and 2 g/h) [10].

Other complications of dyselectrolitaemia include thrombosis and haemolytic anaemia [10], which occurred also in the presented patient.

As in DKA, bicarbonates are contraindicated because they elevate the risk of hypokalaemia as well as reduce the oxygen supply to tissues [1].

It was unexpected to find only diminutive glucosuria in our patient because urinary glucose excretion (UGE) is supposed to increase with the rise in blood glucose level in a proportional manner. However, one must remember that insulin receptor is present in renal tubular cells, and insulin stimulates sodium reabsorption in renal proximal tubules. Thus, the renal threshold for glucose reabsorption is higher in individuals with type 2 diabetes mellitus because of the enhanced sodium-glucose cotransporter 2 (SGLT2) expression in the course of hyperinsulinaemia and insulin resistance; this was demonstrated in a recent study by Chen *et al.* in patients with prediabetes and newly diagnosed type 2 diabetes, where insulin levels and insulin resistance were negatively associated with UGE, independent of blood glucose [12]. Reduction in UGE may contribute to the progression of hyperglycaemia. Moreover, severe hypovolaemia is observed in HHS, which leads to a progressive decline in glomerular filtration rate and may affect reabsorption of different substances in renal tubules.

In contrast to adult patients, in whom comorbidities play a role in HHS development, in the paediatric population HHS appears to occur most often in obese but otherwise healthy children and adolescents, with type 2 diabetes diagnosed at HHS presentation. Therefore, HHS in the paediatric population may be considered as a consequence of severe obesity. Hence, with the increasing prevalence of obesity in children and adolescents, an increase in paediatric HHS frequency should be expected. As such, increased awareness of the occurrence of this life-threatening condition and its treatment is essential.

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