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CASE REPORT

Extreme hyperosmolarity and severe ketoacidosis in a child with type 1 diabetes mellitus at onset safely treated with current guidelines

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Background

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterized by the destruction of pancreatic beta cells by autoantibodies resulting in low or no production of endogenous insulin. The incidence of T1DM is extremely variable depending on the countries, and it is progressively growing [1]. Ketoacidosis (DKA) is present at diagnosis in 15–70% of patients affected by T1DM and is more frequent in children younger than 2 years of age, in case of delayed diagnosis, in some ethnic minorities and in children with poor access to medical care for socio-economic reasons [1]. DKA is defined by the presence of hyperglycaemia (blood glucose > 200 mg/dL), venous pH < 7.3 or serum bicarbonate < 15 mmol/L, ketonemia (blood β-hydroxybutyrate ≥ 3 mmol/L) or moderate or large ketonuria. Clinically, it shows through dehydration, tachycardia, tachypnea, sighing (Kussmaul) respiration, nausea, vomiting, abdominal pain and confusion state up to coma [1]. The hyperglycaemic hyperosmolar state (HHS) is an uncommon condition in children, and it usually occurs in an obese adolescent with type 2 diabetes mellitus (T2DM). Criteria to define HHS are hyperglycaemia (blood glucose > 600 mg/dL), venous pH > 7.25 (arterial pH > 7.3), bicarbonate > 15 mmol/L, small ketonuria and absent or mild ketonemia, serum osmolarity > 320 mOsm/kg, altered mental status and severe dehydration [1]. HHS rarely represents the onset manifestation of T1DM [2]. Some cases of T1DM with an initial manifestation of a mixed state with both conditions (DKA-HHS) are described in the literature [3].

We present the case of a child with T1DM onset and a mixed state of DKA and HHS, with severe DKA and extremely high blood glucose levels.

Case report

A 7-year-old male, Caucasian, was referred to our emergency department with a history of polyuria, polydipsia, polyphagia and severe weight loss (estimated about 20% of body weight) in the previous 2 weeks. The parents brought their child, without previous medical consult, when vomiting was overwhelming and level of consciousness severely impaired. Vomiting episodes and significant weakness had started 48 h before. Past medical history was negative. Furthermore, no family history for diabetes mellitus or other endocrine diseases were reported. At the emergency department, he showed poor clinical conditions, confusion, drowsiness, Glasgow coma scale 12, inelastic skin, dystrophic subcutaneous tissue, dry mucus membranes and capillary refill time 2 s. Weight was 19 kg (< 3rd percentile), height 120 cm (10th–25th percentile), body mass index 13.19 kg/m^2 (< 3rd percentile), body temperature 36.3 °C, heart rate 145 bpm, respiratory rate 40–45 breaths/min with Kussmaul breath, pulse oximetry 97% on room air and blood pressure 103/55 mmHg. Abdominal pain was present at physical examination. Pupils were isochoric and isocyclic normoreactive, no cranial nerves deficits were detected. The glucometer measured a blood glucose level above the instrument's sensitivity limit and β-hydroxybutyrate was 6 mmol/L. Laboratory results were as follows: blood glucose 2.604 mg/dL, sodium 124 mmol/L (theoretical corrected sodium: 193 mmol/L), effective osmolarity 393 mOsm/kg, venous pH 7.09, bicarbonate 9.1 mmol/L, creatinine 1.68 mg/dL, blood urea 116 mg/dL, potassium 5.3 mmol/L, chloride 83 mmol/L,

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total calcium 11 mg/dL, phosphate 6.8 mg/dL, magnesium 4 mg/dL and negative C-reactive protein (CRP). Blood count was: white blood cells 13.260/mmc, red blood cells 6,390,000/mmc, haemoglobin 13.3 gr/dL, haematocrit 45.9% and platelets 463,000/mmc. On the basis of laboratory results and clinical conditions and following Italian recommendations for the diagnosis and treatment of DKA (based on ISPAD guidelines) [1], rehydration therapy was started with 0.9% saline solution at 10 mL/kg for the first 1.5 h (overall 300 mL). Thereafter, regular insulin therapy was started at 0.05 unit/kg/h and rehydration was continued at maintenance dose of 1800 mL/24 h, assuming a 10% dehydration and taking into account the initial 300 mL rehydration. A 0.9% saline solution was infused for the first 8 h, then considering the high values of blood glucose (763 mg/dL), sodium (153 mmol/L, theoretical corrected sodium: 171 mmol/L) and effective osmolarity (340 mOsm/kg), saline solution was shifted at 0.45%. Subsequently, for blood glucose lowering below 250 mg/dL, the 0.45% saline solution was changed with a 0.45% saline + 5% glucose solution after 16 h from the access to the emergency department. For the whole duration of the rehydration, intravenous potassium supplementation with 40 mmol/L potassium chloride was added, after making sure that diuresis was preserved. During hospitalization, the clinical conditions of the child progressively improved, without any type of complications. Blood glucose normalization (109 mg/dL) and ketonemia negativisation were observed in 21 h after starting treatment. Intravenous rehydration therapy was suspended, and subcutaneous insulin infusion at 0.7 unit/kg/24 h was undertaken approximately 48 h from the access in emergency department. Signs and symptoms of cerebral oedema were never detected during the whole period of observation. The laboratory tests performed to complete the diagnosis were as follows: glycated haemoglobin (HbA1c) 12.4% (112 mmol/mol) (reference < 6%); fructosamine 924 micromol/L (reference 118–282 micromol/L); insulin 1.9 microU/mL (reference 1.9–23 microU/mL); C-peptide 0.1 ng/mL (reference 0.9–7.1 ng/mL); anti-glutamate decarboxylase antibody 15 U/mL (reference < 10 U/mL); anti-islet cell antibody, negative; anti-insulin antibody 0.8 U/mL (reference < 2.4 U/mL); thyroid-stimulating hormone (TSH) 0.23 microU/mL (reference 0.25–4.50 microU/mL); fT4 8.2 pg/mL (reference 5.5–12 pg/mL); anti-thyroperoxidase, negative; anti-thyroglobulin, negative; anti-IgA human tissue transglutaminase antibody, negative; and anti-IgG deamidated gliadin antibody, negative. After 12-day hospital admission, the child was discharged in good general clinical condition, with a weight of 20.6 kg, with basal–bolus insulin regimen and with adequate therapeutic and alimentary education. He is currently followed up regularly at the paediatric diabetic clinic of our department.

Discussion

The present report shows how a severe case of hyperglycaemia and DKA can be safely treated following current DKA treatment guidelines. Italian recommendations are basically the same as the ISPAD guidelines, which theoretically allow a uniform and safe treatment of all forms of DKA [1]. Our patient, despite severe DKA, displayed some feature of HHS: marked dehydration and extremely elevated blood glucose concentration associated with a severe clinical picture with a possibly life-threatening situation.

DKA and HHS are two medical emergencies that require timely and appropriate treatment. DKA is a complication of T1DM, whereas HHS is mostly associated with T2DM [1]. In the literature, cases of T1DM onset with HHS and cases of T1DM with an initial manifestation of a mixed state with both conditions (DKA-HHS) are reported [3]. Patients presenting the mixed DKA-HHS condition reported in anamnesis a high consumption of high carbohydrate drinks in the days prior to the onset (approximately 4–8 L/day). It has been hypothesized that the ingestion of high quantities of hyperosmolar liquids containing carbohydrates could make the initial hyperosmolar state worse [3]. In our case, a history of hyperosmolar drinks intake was not reported but at the arrival at the emergency department the child showed a condition of severe DKA and hyperglycaemia (blood glucose 2.604 mg/dL, pH 7.09, bicarbonate 9.1 mmol/L, β-hydroxybutyrate 6 mmol/L), with severe dehydration, severe hyperosmolarity (effective osmolarity 393 mOsm/kg) and acute prerenal failure (creatinine 1.68 mg/dL, blood urea 116 mg/dL). In our case, the mixed DKA-HHS presentation is likely to be due to an initial neglect of the symptoms, with consequent delay in access to the emergency department and therefore to the initiation of the appropriate treatment, which led the patient to a severe ketotic hyperglycaemia with elevated osmotic diuresis and consequent severe dehydration.

HHS, which is more common in adult patients, usually occurs over a longer time than DKA and is characterized by a gradual and prolonged onset of polyuria and polydipsia which leads to greater dehydration and a higher loss of electrolytes compared to DKA. The therapeutic approaches of DKA and HHS are similarly based on rehydration and gradual recovery of fluids and electrolyte losses, on the correction of hyperglycaemia and on the treatment of the triggering causes [1]. In HHS, the initial correction of dehydration is mandatory and the rate of fluid replacement should be performed more rapidly than in recommended for DKA [1]. In the literature, cases of children with severe hyperosmolarity in combination

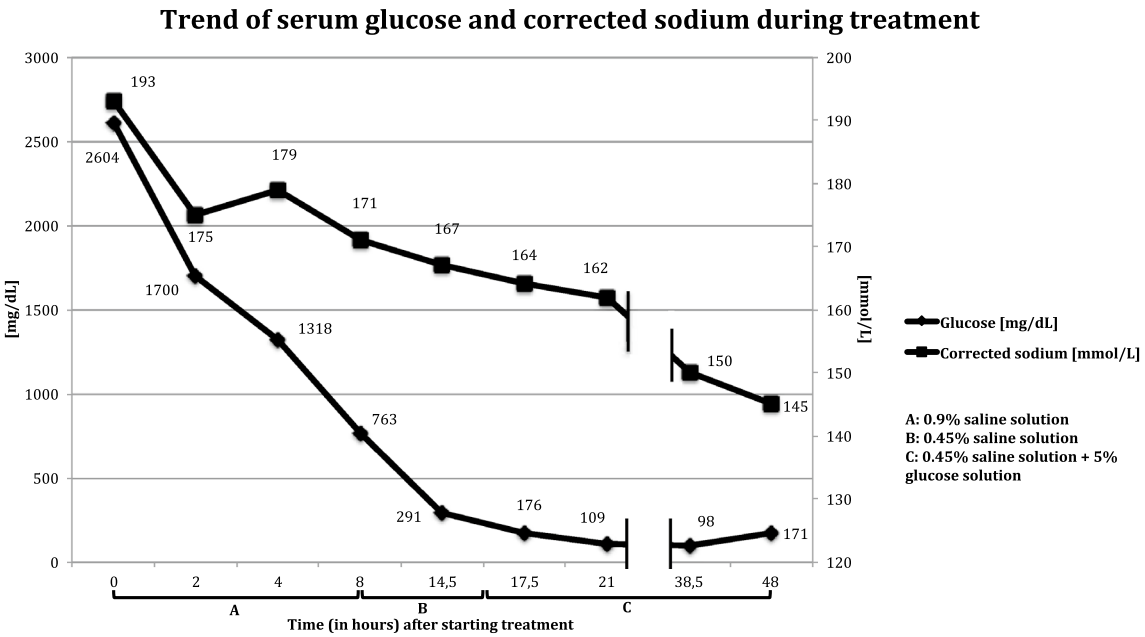

Fig. 1 Trend of serum glucose and corrected sodium during treatment

with ketoacidosis are reported, and the treatment must consider potential complications of both DKA and HHS (i.e. cerebral oedema or other central nervous system complications, rhabdomyolysis, venous thrombosis, malignant hyperthermia, severe hypophosphatemia) [1]. In these cases with a mixed DKA-HHS presentation, the therapeutic approach is guided by a careful monitoring of patient's circulatory state and of fluid and electrolytes balance [1, 3]. In our case, despite extremely high values of blood glucose, plasma osmolarity and sodium, we initially followed the guidelines of DKA treatment, to reduce the risk of cerebral oedema, which is the most significant cause of death in children with DKA [1]. Only after 8 h of 0.9% saline solution infusion, when blood glucose was 763 mg/dl and sodium concentration was still elevated (153 mEq/L, theoretical corrected sodium: 171 mEq/L), we preferred to switch to the infusion of a 0.45% saline solution, to keep the total volume of fluids infused within 24 h unchanged. In this way, we were able to achieve a normalization of blood glucose and β-hydroxybutyrate in about 21 h, and a progressive reduction of sodium values, with a gradual improvement of patient's clinical condition and recovery of oral hydration and nutrition, without complications (Fig. 1).

Whether intravenous fluid load contributes to brain injuries has been debated for decades [4]. At the time of our case, the paper by Kuppermann et al. [4] had not been published yet; therefore, we adopted the known slow rehydration protocol relying on the evidence that excessive fluid administration may result in rapid osmotic changes. Seizures and neurological damage are in fact known complications of hypernatriemia and/or its too quick reduction [5]. Based on our experience, for the management of a patient with a mixed DKA-HHS presentation, we believe it is important initially to strictly adhere to the guidelines of DKA treatment, without exceeding in the amount of fluids infused. Only after the initial improvement of biochemical parameters and clinical conditions and given the unique clinical and metabolic picture of our patient, we were forced to use a "hybrid" treatment using a 0.45% saline solution to try to solve the hypernatriemic state. We were able in this way to guarantee a slow but suitable rehydration, trying to reduce the risk of developing complications with possible short or long-term effects.

In their prospective, randomized trial, Kuppermann et al. [4] demonstrated that neither the rate of administration nor the sodium chloride content of intravenous fluids significantly influenced neurologic outcomes in children with diabetic ketoacidosis. On the other hand, we thought that in our case the change from 0.9 to 0.45% saline solution was mandatory by considering the hypernatriemic state and its related possible risks [5]. The positive clinical outcome seems to suggest that our therapeutic decisions were going in the right direction.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from the patient for being included in the study.

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