ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XXIII, N 3, 8 SECTIO DDD 2010

Department of Endocrinology, Medical University of Lublin, Poland

ANDRZEJ NOWAKOWSKI, BEATA MATUSZEK

Acute complications of diabetes – the present state of knowledge. Part I. Diabetic ketoacidosis

Ostre powikłania cukrzycy – stan wiedzy. Cz. I . Cukrzycowa kwasica ketonowa

INTRODUCTION

Acute complications of diabetes comprise clinical conditions in the course of hyperglycemia: diabetic ketoacidosis (DKA), non-ketotic hyperosmolar hyperglycemia (HHNK syndrome), lactic acidosis (lactic coma) and hypoglycemia (hypoglycemic coma). The most commonly occurring acute complication of diabetes is DKA as a complication of mostly type 1 diabetes, sporadically type 2; less frequent is HHNK and very rare lactic acidosis. Hypoglycemic coma occurs rarely, more frequent are hypoglycemias as complications of treatment [1,4,6,10]. Mortality in acute complications of diabetes ranges at present from approximately 5% in DKA to approximately 15% in HHNK, in lactic acidosis it exceeds 50% . Before the discovery of insulin, mortality in DKA was 100%; it was significantly reduced together with progress in treatment and increasingly greater access to insulin preparations, although it still remains a serious, even life-threatening complication in the population of patients with diabetes [2,7,12].

EPIDEMIOLOGY

Epidemiological data concerning DKA indicate that this complication occurs with the frequency of 4.6–8.0 / 1000 people / year in the population of patients with diabetes. In children and adolescents at the first diagnosis of type 1 diabetes DKA occurs with the frequency of 25%–40%. Mortality in DKA according to the data of Chiasson et al. is from 4% to 10%, and according to Efstsathiou et al. it ranges from 5% to 15% depending on the clinical condition, complications and the place of hospitalization, reaching even 30% in intensive care units [1,2]. Epidemiological data concerning the HHNK syndrome are more varied and they are 5%–15% of all acute complications of diabetes in adult and child populations. The incidence of HHNK in diabetic adults is 17.5 cases / 100 000 people / year however, American data from the year 2003 give the incidence of < 1 case /1000 people / year in the population of people with diabetes, but aged > 60 years [3,7,11]. Interesting data concerning the

incidence of HHNK in children *de novo* diagnosed with type 2 diabetes were presented by Fourtner et al. in 2003 [3]. These authors observed the syndrome in approximately 4% of children and they associated the fact with an increasing trend in incidence of obesity among children. Lactic acidosis is a severe metabolic disorder which more commonly concerns older people and it occurs in 1% of general hospitalized population [6].

DIABETIC KETOACIDOSIS

D e f i n i t i o n . DKA is a state of acute and absolute insulin deficiency causing complex disturbances in metabolism of carbohydrates, fats, proteins, in water-electrolyte equilibrium and acid-base balance. This condition is characterized by hyperglycemia, ketonemia with ketonuria and metabolic acidosis.

P a t h o g e n e s i s . Important factors in DKA pathogenesis include: insulin deficiency, dehydration and electrolyte disturbances, an increase in the concentration of counter-regulating hormones against insulin, ketonemia and metabolic acidosis. Insulin deficiency decreases utilization of glucose in tissues, leading to hyperglycemia, glucosuria and osmotic dieresis. Moreover, it increases protein catabolism and disturbs fat metabolism. Disturbances in protein metabolism lead to hyperaminoacidemia, an increase in gluconeogenesis and hyperglycemia, and also to cellular dehydration and tissue hypoxia. An increase in lipolysis leads to hyperlipemia, hepatic ketogenesis, i.e. an increase in hepatic production of ketone bodies from free fatty acids (acetoacetic acid and β-hydroxybutyric acid), ketonemia and ketonuria, causing a reduction in alkaline reserve of the organism and development of metabolic acidosis. As a result, these metabolic disturbances lead to a complete clinical picture of diabetic ketoacidosis, and in the case of lack of proper treatment to development of hypovolemic shock, anuria, coma and a direct threat to life. An increase in the concentration of counter-regulating hormones, mainly glucagon and cortisol, aggravate already existing hyperglycemia through stimulation of gluconeogenesis and lipolysis. Growth hormone and katecholamines also participate in the last process.

C a u s e s . In cases of type 1 diabetes DKA is in 10% to 20% of cases connected with lack of or delay in diagnosis of diabetes. Bacterial infections, especially purulent, constitute from 40% to 50% of causes in type 2 diabetes, and in type 1 up to 20%. Pancreatitis should also be mentioned here together with viral infections (influenza and its complications, hepatitis).

Mistakes in insulin therapy, such as interruption in the use of insulin, missing one or several doses of insulin or oral medication, using insulin after expiry date or improperly stored (frozen) insulin and interruption in subcutaneous infusion of insulin (personal pump) due to technical problems constitute another group of causes of DKA.

Acute non-infectious diseases, such as myocardial infarction, cerebral stroke, the alimentary tract obstruction, hypertensive crisis and increased hyperthyroidism, are another group of causes. Other possible causes of DKA include pregnancy, injuries, surgical procedures in people with undiagnosed diabetes, alcohol and stress. It should also be emphasized that in a group of approximately 20% of cases the cause of acidosis remains unknown.

High risk factors in DKA include concomitant renal failure, myocardial infarction, cerebral stroke, pregnancy, old age and hyperglycemia > 600 mg/dl (>33.3 mmol/l).

Clinical picture. Major clinical symptoms in DKA are increased thirst and polyuria reaching 5–7 l/24 hours, loss of body mass linked to dehydration, nausea and vomiting, muscular weakness and cramps. Prodromal symptoms can include tiredness, disturbed vision, vertigo, disturbances in balance, difficulty in concentrating and increasing drowsiness. In the period of advanced acidosis hyperventilation develops with Kussmaul breath and the presence of acetone smell in exhaled air (the smell of fruit compote), chest pains aggravated during respiration may occur and also abdominal pains with marked muscular defence suggesting the so-called "acute abdomen" resulting from severe dehydration. Typically, hypotonia and tachycardia leading to hypovolemic shock appear. Leukocytosis, which is an expression of acidosis, not infection, is frequently observed. Worrying symptoms which may indicate poor prognosis include increasing drowsiness, dementia and coma, which occur in 10% of patients with DKA. Additionally, coma with lack of reactions to pain stimuli and removal of deep reflexes indicate bad prognosis [9,10]. Degrees of severity of DKA are presented in table 1.

Table 1. Degrees of severity of diabetic ketoacidosis

MILD DIABETIC KETOACIDOSIS
Conscious patient, glycemia > 250 mg/dl (> 14.0 mmol/l), ketonuria,
HCO_3^- 15–18 mmol/l, blood pH 7.25–7.3; anion gap >10
MODERATE DIABETIC KETOACIDOSIS
Patient with disturbed orientation,drowsiness, glycemia > 250 mg/dl (> 14.0 mmol/l), ketonuria,
HCO_3^- 10–15 mmol/l, blood pH 7.0–7.25; anion gap > 12
SEVERE DIABETIC KETOACIDOSIS (COMA)
Patient in coma, glycemia > 400 mg/dl (> 22.0 mmol/l), ketonuria,
HCO_3^- < 10 mmol/l, blood pH < 7.0; anion gap > 12

Diagnosis. The basis for diagnosis is hyperglycemia > 250 mg/dl (>13.9 mmol/l), ketonemia and /or ketonuria, blood pH < 7.3, bicarbonate content < 15 mmol/l and an anion gap > 10 [5].

Differential diagnosis. DKA should be differentiated from other diabetic comas, metabolic acidosis (uremic, hepatic), CNS disorders (cerebral stroke, tumours, inflammations), myocardial infarction, thyroid, adrenal, hypercalcemic crises, poisonings (glycol, methanol, salicylates), psychiatric disorders and starvation ketosis.

Treatment. The aim of treatment of DKA is to control water electrolyte disturbances, reduce hyperglycemia and return acid base balance. Additionally, the cause of the condition should be found and possibly eliminated, and preventive measures taken [5,8,9].

Hydration of the patient is achieved through infusion of 2l of 0.9% NaCl in the first two hours of treatment, another 2l are given during the next 2–4 hours, and in further treatment the infusion is continued at the rate of 250 ml/h until water electrolyte balance is achieved. In total, during 24 hours of treatment the patient should receive 5–6.5 l of fluid, but it should be stressed that the patient's condition must be taken into account, i.e. functioning of circulation, kidneys (hourly dieresis) and arterial pressure values. Before hydration of the patient is begun, effective plasma

molality and corrected (real) sodium concentration should be calculated. It is connected with the fact that during hyperglycemia sodium concentration is higher than laboratory indications and then infusions of 0.45% NaCl should be administered until proper natremia is achieved. In the case of existing hypernatremia with the values of Na > 150 mmol/l and effective plasma osmolality > 300 mOsm/kg H_2O, 0.45% NaCl solution should be infused as was mentioned above. Proper hydration can cause a decrease in glycemia even by 30%, but it does not exclude the application of the next stage of treatment, i.e. reduction in hyperglycemia involving insulin therapy.

Compensation of electrolyte deficiency. The greatest loss of electrolytes concerns potassium, sodium and chlorine. It is compensated for by administration of 0.9% NaCl correcting deficiency of mainly sodium and chlorine, and administration of potassium chloride (KCl) corrects deficiency of potassium. Supplementation of potassium is given depending on the concentration of potassium in blood serum. So KCl is not administered at the concentrations > 6 mmol/l, at the concentrations of 5–6 mmol/l we administer 5–10 mmol/h, at 4–5 mmol/l 10–15 mmol/h, at 3–4 mmol/l 15–20 mmol/h, below 3 mmol/l 25 mmol/h (1 ampoule of 10 ml KCl contains 40 mmol of potassium).

Insulin therapy is conducted using short-action insulin (Actrapid, Gensulin R, Humulin R, Polhumin R) in the form of intravenous infusion with an infusion pump. Appropriately 20 or 50 units of short-action insulin are added to 20 or 50 ml of 0.9% NaCl, obtaining 1 unit of insulin in 1 ml of solution, then insulin is administered at the dose of 0.1 unit/kg body mass/h. Insulin infusion is preceded by intravenous administration of a single dose of the so-called bolus of short-action insulin at the dose of 0.1 unit / kg body mass /h, that is from administration of 7–10 units. Then the rate of insulin infusion should be controlled and related to the present state of glycemia, and an hourly decrease in glycemia should not exceed 100 mg/dl (5.6 mmol/l). Glycemia must be decreased gradually in order to prevent blood osmolarity. When it reaches the value < 250 mg/dl (14.0 mmol/l) or the value of starting glycemia is reduced by half, the rate of insulin infusion is decreased by half and infusion of 5% glucose is added to the fluids to prevent possible hypoglycemia. The rate of insulin infusion should be adequate to present glycemia in order to ensure stable glycemia within the range of 120–140 mg/dl (6.7–7.8 mmol/l) and then intravenous insulin infusion should be replaced by subcutaneous insulin therapy, but only within 30–60 minutes after the first dose of subcutaneous insulin [13].

Controlling metabolic acidosis. In most cases, proper hydration, insulin therapy and compensation of electrolyte disturbances are sufficient to control ketoacidosis without the necessity of administration of bicarbonates. An indication for using bicarbonates is the situation when the value of arterial blood pH found in a patient with diabetic coma is less than 7.0 (< 6.9) or when ketoacidosis coincides with chronic renal failure. Then 8.4% sodium bicarbonate (1 ml = 1 mmol) is administered in the maximum dose of 1 mmol/kg of body mass, i.e. 50–100 ml in infusion of 0.9% NaCl or 5% glucose. A counterindication for administration of sodium bicarbonate is hypernatremia > 150 mmol/l, as it poses a risk of complications – pulmonary and/or cerebral edema [9].

Complications. Serious complications in DKA include: hypovolemic shock, pulmonary edema, cerebral edema, heart rhythm disturbances (ventricular), ARDS syndrome. Some complications can result from careless treatment, for example too rapid decrease in glycemia or inappropriate use of bicarbonates.

M o n i t o r i n g of treatment includes control of glycemia and diuresis every hour, control of Na and K electrolytes, fluid balance and state of consciousness every 2 hours. Gasometry should be checked every 4 hours, the presence of ketone bodies in urine every 8 hours. Additionally, arterial pressure, pulse, respiration rate and general condition of the patient should be continuously controlled. After successful management of DKA, the previously applied model of treatment (insulin therapy) should be resumed or modified [13,14].

REFERENCES

1. Chiasson J.L., Aris-Jilwan N., Belanger R. et. al.: Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. CMAJ;168, 859, 2003.
2. Efstathiou S.P., Tsiakou A.G., Tsioulos D.I., et. al. : A mortality prediction model in diabetic ketoacidosis. Clin. Endocrinol.; 57,595, 2002.
3. Fourtner S.H., Weinzimer S.A., Murphy K.L. et. al.: Hyperglicemic hyperosmolar nonketotic (HHNK) syndrome in children. Proc. Endocr Soc. 85th Annual Meeting; Philadelphia June 22, 2003, abstract OR 42.
4. Karnafel W., Krzymineń J.: Ostre powikłania hiperglikemiczne. W: Cukrzyca. Kompendium. J. Sieradzki (red.).Wyd. Via Medica 2009.
5. Krentz A.J., Holt H.B.:Diabetic Ketoacidosis in Adults. In: Emergencies in Diabetes. Diagnosis, Management and Prevention. Ed. John Wiley & Sons,Ltd,2004,1-32.6.
6. Lalau J.D.: Lactic Acidosis in Diabetes. In: Emergencies in Diabetes. Diagnosis, Management and Prevention. Ed John Wiley & Sons,Ltd.2004,113.
7. Lober D.: Nonketotic hypertonicity in diabetes mellitus. Med.Clin.North.An.,79,39, 1995.
9. Savage M.W., Kilvert A.: ABCD guidelines for the management of hyperglycaemic emergencies in adults. Position Statement.Pract.Diab.Int.,23,227, 2006.
10. Sola E., Garzon S., Garcia-Torres S. et al.: Management of diabetic ketoacidosis in a teaching Hospital. Acta Diabetol.,43,127, 2006.
11. White N.H.: Management of Diabetic Ketoacidosis. Reviews in Endocrine & Metabolic Disorders;4,343, 2003.
12. Woerle H.J., Gerich J.E.: Hyperosmolar Non-ketotic Hyperglycaemia. In: Emergencies in Diabetes. Diagnosis, Management and Prevention. Ed John Wiley & Sons,Ltd., 55 2004.
13. Venkatraman R., Singhi S.C.: Hyperglycemic Hyperosmolar Nonketototic Syndrom. Indian J. Ped.,73,55, 2006.
14. Wierusz-Wysocka B., Zozulińska-Ziółkiewicz D.: Postępowanie w stanach nagłych i szczególnych u chorych na cukrzycę. Wyd. Via Medica 2009.
15. Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2010. Stanowisko Polskiego Towarzystwa Diabetologicznego. Diabet.Prakt., 11,supl.A,18 2010.

SUMMARY

Diabetic ketoacidosis (DKA) is the most common acute hyperglycemic complication, which poses problems mostly in type 1 diabetes, sporadically in type 2. The most frequent cause of developing

ketoacidosis in patients with type 1 diabetes is withdrawal of or missing an insulin dose or delayed diagnosis; in patients with type 2 diabetes it is severe infection or stress with accompanying relative insulin deficiency. The basis for diagnosis is hyperglycemia, ketonemia and/or ketonuria and features of metabolic acidosis. Mortality in the pathology reaches 5%. The study presents the current state of knowledge about DKA concerning epidemiology, pathogenesis, clinical picture and particularly current standards of treatment.

Keywords: diabetic ketoacidosis, type 1 diabetes, type 2 diabetes, epidemiology, pathogenesis, clinical picture, standards of treatment

STRESZCZENIE

Cukrzycowa kwasica ketonowa to najczęściej występujące ostre, hiperglikemiczne powikłanie, które komplikuje przebieg przede wszystkim cukrzycy typu 1, sporadycznie typu 2. Najczęstszą przyczyną wystąpienia kwasicy ketonowej u chorych na cukrzycę typu 1 jest odstawienie lub pominięcie dawki insuliny bądź opóźnione rozpoznanie, natomiast u chorych na cukrzycę typu 2 ciężka infekcja lub silny stres, w których przebiegu dochodzi do względnego niedoboru insuliny. Podstawą rozpoznania jest stwierdzenie hiperglikemii, ketonemii i/lub ketonurii i cech kwasicy metabolicznej. Śmiertelność tej patologii sięga 5%. Praca przedstawia stan wiedzy na temat DKA w zakresie epidemiologii, patogenezy, obrazu klinicznego, a szczególnie aktualnych standardów leczenia.

Słowa kluczowe: cukrzycowa kwasica ketonowa, cukrzyca typu 1, cukrzyca typu 2, epidemiologia, patogeneza, obraz kliniczny, standardy leczenia